SPIKEVAX : Periodic safety update report assessment

19th June 2022 to 17th December 2022

This document consists of:

1. The PRAC assessment report of the SPIKEVAX periodic safety update report (PSUR) covering the period 19th June 2022 to 17th December 2022, and;
2. The SPIKEVAX PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMA/PRAC/294120/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010897/202212

Active substances: elasomeran (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5)

Period covered by the PSUR: 19/06/2022 To: 17/12/2022

RMP version number: 7.0

Centrally authorised Medicinal product: **For presentations: See Annex A**	**Marketing Authorisation Holder:**
Spikevax	Moderna Biotech Spain, S.L.

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	9 March 2023	9 March 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	8 May 2023	8 May 2023
☐	MS/PRAC members and MAH comments	7 June 2023	7 June 2023
☐	PRAC Rapporteur's updated assessment report following comments	22 June 2023	22 June 2023
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	6 July 2023	6 July 2023

Procedure resources	
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1. Background information on the procedure

This is the assessment of a PSUR submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for elasomeran (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5).

An update to the RMP resulting from data presented in the PSUR was submitted.

2. Assessment conclusions and actions

This report assessed the 4th Periodic Safety Update Report (PSUR) for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, summarising the safety information gathered during a 6-month reporting period from 19th June 2022 to the data-lock point (DLP) of 17th December 2022.

Elasomeran was first authorised in the EU through the centralised procedure on 6th January 2021. The European Union reference date (EURD) is 18th December 2020, which is also the International Birth Date (IBD), based on first approval in the USA. Elasomeran is currently authorised in the EU under the name Spikevax.

First authorisation for elasomeran/imelosomeran was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom (UK) on 12th August 2022, and elasomeran/davesomeran was granted Emergency Use Authorization (EUA) status by US Food and Drug Administration (US FDA) on 31st August 2022.

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA) based vaccine against the 2019 coronavirus (CoV; Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2]). Elasomeran is authorised in the European Union (EU) as a suspension for injection indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 months of age and older.

Elasomeran is formulated as a dispersion for injection to be supplied in multidose vial and dispersion for injection in pre-filled syringe and is administered intramuscularly (IM). Elasomeran/imelasomeran and elasomeran/davesomeran are formulated as dispersion for injection to be supplied in multidose vial and single use pre-filled syringe (for elasomeran/imelasomeran).

- Elasomeran 0.20 mg/mL dispersion for injection

Elasomeran is supplied as a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each. One dose (0.5 mL) contains 100 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran 0.10 mg/mL dispersion for injection and pre-filled syringe

Elasomeran is supplied as a multidose vial that contains 5 doses of 0.5 mL each or a maximum of 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 25 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 ml. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/imelasomeran is supplied as a multidose 2.5 mL vial (blue flip-off cap) that contains 5 doses of 0.5 mL each and a multidose 5 ml vial containing 10 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

• Elasomeran/imelasomeran 25 µg/25 µg dispersion for injection and pre-filled syringe

Elasomeran/imelasomeran is supplied as a single use pre-filled syringe which contains 1 dose of 0.5 mL. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 mL, for single use only. One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

• Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/davesomeran is supplied as a multidose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of davesomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

The dosage varies depending on the vaccine, and whether it is being used as part of a primary series vaccination or as a booster dose. Further, it varies with age and by whether persons are severely immunocompromised or not.

mRNA-1273 consists of an mRNA Drug Substance that is manufactured with LNPs composed of four lipids: heptadecan-9-yl 8- ((2-hydroxyethyl)(6-oxo-6-(undecyloxy) hexyl)amino) octanoate (SM-102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG).

At the time of the DLP of the 4th PSUR, elasomeran was authorised in 49 countries/regions for active immunisation of adults to prevent COVID-19 caused by SARS-CoV-2. Cumulatively, approximately 52,530 subjects were exposed in clinical trials. As of DLP of this report, a total of 912,827,813 doses of the vaccine had been administered worldwide.

Signals

No new important risks were identified from the signals presented in the PSUR.

During the reporting period, the following signals were assessed in separate procedures: 'heavy menstrual bleeding' (EPITT 19781), 'product label confusion leading to underdosing' (EPITT 19866) and 'pemphigus and bullous pemphigoid' (EPITT 19860)'. As an outcome of the assessment, section 4.8 of the SmPC was updated with 'heavy menstrual bleeding' with a frequency 'unknown'. The Package Leaflet was updated accordingly.

As per the request from the PRAC from a signal procedure (EPITT 19781) assessed in the previous reporting interval, the MAH presented an updated cumulative review on 'amenorrhea'. The PRAC considers that the data presented is insufficient to establish causal association between elasomeran and amenorrhea. No further actions beyond routine PV are considered warranted at this stage.

Adverse events of special interests (AESIs) and safety topics under monitoring (including Health authority requests)

For the topics: Acquired haemophilia, Autoimmune hepatitis, Thrombocytopenia with Thrombosis Syndrome (TTS), Guillain-Barre Syndrome (GBS), Acute Disseminated Encephalomyelitis (ADEM), Multisystem inflammatory syndrome (MIS), Single Organ Cutaneous Vasculitis (SOCV), Postural tachycardia syndrome (POTS) and Histiocytic necrotising lymphadenitis (HNL), the data presented did not change the current conclusions of no indication of a causal association with elasomeran.

The MAH's response to the RSI concerning the topic 'arrhythmia' raised a concern about the MAH's causality assessment of the arrhythmia cases presented in the PSUR. Therefore, the MAH is requested to present the topic in the next PSUR, with focus on reassessment of the serious cases of arrhythmia and cases reported with positive rechallenge.

Following review of additional data submitted by the MAH in response to the RSI, the PRAC considers that a causal association between hearing loss and Spikevax cannot currently be established. No further actions beyond routine pharmacovigilance are required.

No new and significant information was presented concerning overdose, off-label use, lack of efficacy/vaccine failure, use of bivalent vaccines, use in the elderly and in children. However, the MAH is requested to provide clarification concerning the presentation of paediatric cases with the next PSUR. Based on several discrepancies in the presentation of data, the MAH is once more reminded to be thorough in the preparation of data and text to be included in future PSURs, including specific arguments assigned to each causality assessment in all case reports.

Following a review of the data on mechanical urticaria, including the MAH responses to the RSI within this procedure, it is concluded that an association between Spikevax and mechanical urticaria is at least a reasonable possibility. The pattern of occurrence of mechanical urticaria is highly similar to urticaria; cases have primarily been observed after the booster administration with a delayed onset of up to 14 days after vaccination. It is recommended to update section 4.8 of the SmPC with the PT Mechanical urticaria with a frequency 'Unknown', and to update the Package Leaflet accordingly.

PSUR list of safety concerns

Important identified risks

During the reporting interval, the important identified risk 'anaphylaxis' was removed from the RMP. In line with the changes to the RMP, the MAH suggested to remove this risk from the PSUR. The PRAC did not endorse this. The MAH shall continue to present 'anaphylaxis' in section 16 of the PSUR and keep it in the PSUR list of safety concerns.

Based on the cumulative review, including literature and case reports, presented in the PSUR for the important identified risks myocarditis and pericarditis, an update to the warning in the SmPC and the Package Leaflet is considered warranted concerning the course and outcome of these conditions. Please refer to section 3 Recommendation of this report for the proposed wording.

Important potential risks

IgA nephropathy (IgAN): Based on the information provided by the MAH, the PRAC considers the available evidence on the potential association between IgAN and elasomeran-containing vaccines to be inconclusive. The MAH should therefore maintain IgAN as an important potential risk in the future PSURs.

Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD): Based on the cumulative evidence, this risk is refuted and no longer considered important in the context of the PSUR. It should therefore be removed from the PSUR list of safety concerns and an evaluation of new information on this topic in future PSURs is not required.

Missing information

Interaction with other vaccines: Based on the cumulative evidence, the knowledge gaps regarding this area of missing information have been filled and interaction with other vaccines has not been shown to constitute an important risk. Therefore, it is no longer considered important in the context of the PSUR. It should be removed from the PSUR list of safety concerns and an evaluation of new information on this topic in future PSURs is not required.

The following topics shall remain in the PSUR list of safety concerns and an evaluation of new information on these topics is required with future PSURs:

- Use in pregnancy and while breast-feeding
- Use in immunocompromised subjects
- Use in frail subjects with unstable health conditions and co-morbidities
- Use in subjects with autoimmune or inflammatory disorders

RMP

The MAH submitted an updated RMP version 7.0 with data lock point of 1st February 2023 and a final sign-off date of 21st February 2023 with this PSUR. Based on the cumulative evidence from relevant sources, the MAH proposed to remove a number of safety concerns from the RMP.

The PRAC considers removal of the following safety concerns from the RMP list of safety concerns to be acceptable:

- Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
- Interaction with other vaccines
- Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in subjects with autoimmune or inflammatory disorders

Regarding use in immunocompromised subjects, upon request within this procedure, the MAH provided further data supporting removal of the safety concern from the RMP. Overall, the PRAC consideres that there is sufficient evidence to conclude that the gaps in knowledge regarding the safety of Spikevax when used in immunocompromised individuals have been adequately filled and this can no longer be considered an area of missing information. Removal of 'use in immunocompromised subjects' from the RMP is therefore endorsed. Accordingly, an update of section 4.4 of the SmPC is required (see section 3 Recommendation of this report).

Regardless of the removal of the safety concern in the RMP, continued monitoring through routine pharmacovigilance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904 is warranted, as proposed by the MAH. Regarding the effectiveness in immunocompromised subjects, the studies P304 and P901 are ongoing and will remain in the pharmacovigilance plan.

Removal of the following safety concern in the RMP is currently not acceptable:

- Use in pregnancy and while breast-feeding

The revised RMP version 7.0 provided upon request for supplementary information within this procedure is acceptable.

The MAH should address the following with the responses to the request for supplemental information within variation EMEA/H/C/005791/II/0104/G:

- The MAH's should provide a consolidated version of the RMP to harmonise all the available information for the elasomeran, elasomeran/ imelasomeran, and elasomeran/davesomeran-containing vaccines.

Conclusion

No new significant information that would impact the benefit-risk balance was identified during the assessment of the data in this PSUR. In view of the data presented in the reviewed PSUR, the overall risk-benefit balance of elasomeran, elasomeran/ imelasomeran and elasomeran/davesomeran is therefore considered unchanged in the approved indication.

Given the extensive experience with elasomeran-containing vaccines gathered since its marketing authorisation in the EU on the 6th of January 2021 and lack of new safety issues identified during the assessment of the current PSUR, the PRAC recommends to change the frequency of PSUR submission for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran from 6 months to one year, at the first possibility.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran remains unchanged but recommends that the terms of the marketing authorisation should be varied as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Myocarditis

In view of the available evidence on myocarditis and pericarditis from the literature and spontaneous reports, the PRAC considers that new information on the course and outcome of myocarditis and pericarditis are identified. The PRAC concludes that the product information of products containing elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran should be amended accordingly.

Update of sections 4.4 and 4.8 of the SmPC to amend a warning regarding myocarditis and pericarditis. The Package leaflet is updated accordingly.

Use in immunocompromised subjects

In view of the available evidence on use in immunocompromised subjects from post-authorisation safety studies, literature and spontaneous reporting, the PRAC considers that use in immunocompromised subjects is no longer a safety concern. The PRAC concludes that the product information of products containing elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran should be amended accordingly.

Update of section 4.4 of the SmPC to amend a warning regarding use in immunocompromised subjects.

Mechanical urticaria

In view of the available evidence on mechanical urticaria from the literature and spontaneous reports, including cases with a plausible temporal relationship, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran and mechanical urticaria to be at least a reasonable possibility. The PRAC concludes that the product information of products containing elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran should be amended accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction mechanical urticaria with a frequency 'Unknown'. The Package leaflet is updated accordingly.

In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local

representatives in the Package Leaflet.

The following changes to the product information of medicinal products containing elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

The warning should be amended as follows:

The warning should be amended as follows:

Myocarditis and pericarditis

There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax.

These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often **in younger males, and more often** after the second dose compared to the first dose~~, and more often in younger males~~ (see section 4.8). ~~The risk profile appears to be similar for the second and the third dose.~~

Available data **indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.** ~~suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.~~

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The warning should be amended as follows:

Immunocompromised individuals

The efficacy ~~and safety~~ of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy~~. The efficacy of Spikevax~~ **and** may be lower ~~in immunocompromised individuals~~.

The recommendation to consider a third dose in severely immunocompromised individuals (see section 4.2) is based on limited serological evidence with patients who are immunocompromised after solid organ transplantation.

- Section 4.8

The following adverse reaction should be added under the SOC 'Skin and subcutaneous tissue disorders', with a frequency 'Unknown':

Mechanical urticaria

(...)

The description of the adverse reaction should be amended as follows

Myocarditis

The increased risk of myocarditis after vaccination with Spikevax is highest in younger males (see section

4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Spikevax. One study showed that in a period of 7 days after the second dose, there were about 1.316 (95% CI 1.299 – 1.333) extra cases of myocarditis in 12 to 29 year-old males per 10 000 compared to unexposed persons. In another study, in a period of 28 days after the second dose, there were 1.88 (95% CI 0.956 – 2.804) extra cases of myocarditis in 16 to 24 year-old males per 10 000 compared to unexposed persons. **In a follow up analysis, the risk of myocarditis after the third dose of Spikevax has shown to be lower than after the second dose.**

Package Leaflet

Section 2. What you need to know before you are given Spikevax

(...)

The warning should be amended as follows:

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Spikevax (see section 4).

These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often **in younger males, and more often** after the second dose compared to the first dose~~, and more often in younger males~~.

Most cases of myocarditis and pericarditis recover. Some cases required intensive care support and fatal cases have been seen.

Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before you are given Spikevax.

Section 4. Possible side effects

The following adverse reaction should be added under the 'Frequency unknown' section:

Rash elicited by external stimulus such as firm stroking, scratching, or pressure to the skin (mechanical urticaria).

4. Issues to be addressed in the next PSUR

The MAH should also address the following issues in the next PSUR:

IgA Nephropathy (IgAN)

A. The MAH is requested to maintain IgAN as an important potential risk in the future PSURs. It is therefore expected that the MAH will present new information on IgA nephropathy and risk characterisation in PSUR section 16.3 and 16.4, respectively. The MAH is also requested to include the following publication in the risk characterisation in the next PSUR:

- Ma Y, Xu G. New-onset IgA nephropathy following COVID-19 vaccination. QJM. 2023 Feb 14;116(1):26-39. doi: 10.1093/qjmed/hcac185.

B. According to the line listing of cases in the Appendix 11.17b to the PSUR, cases number [redacted]

[redacted], [redacted] and [redacted] are classified as WHO-UMC Causality Conditional "because the vaccine type was not specified". Since the vaccine type is now specified (in the Ota paper) the MAH is requested to confirm the origin of these 3 cases ([redacted], [redacted] and [redacted]) and to reclassify their causality status accordingly.

Multisystem inflammatory syndrome (MIS-C/MIS-A)

A. In the current PSUR (#4) the MAH states, that "Cumulatively, through 17 Dec 2022, a total of 166 cases (167 events) with MIS-related terms have been reported, with 159 serious cases (95.8%) and 143 cases medically confirmed. There were 7 cases (4.2%) with fatal outcomes."
However, in the previous PSUR (#3) it was stated that "Cumulatively, through 18 June 2022, a total of 401 cases (426 events) with MIS-related terms have been reported, with 354 cases medically confirmed. There were 139 cases (32.6%) with fatal outcomes. The MAH is requested with the next PSUR to explain the numerical incompatibility of the two statements.
B. The MAH is requested with the next PSUR to clarify how the case listing criteria differ between Appendix 11.15g: MIS During the Reporting Period BC Criteria Case Evaluations (All) (Booster) (elasomeran), and Appendix 11.15c: MIS During the Reporting Period - Case evaluations (All) (Booster) (elasomeran). Appendix 11.15g includes 3 cases, while appendix 11.15c lists 2 cases.
C. In the section Subpopulation Analysis of children < 18 years, a MIS-C suspected case is referenced by the MAH ([redacted] (WW Identifier [redacted]). However, this case is not included in the MAH's MIS data. The MAH is requested in the next PSUR to clarify why this case is not included in the MIS data, and the MAH is also requested to provide a detailed assessment of this case within the current procedure, and collect additional data if sufficient information is lacking.

Arrhythmias

A. The MAH is requested to re-evaluate cumulatively the WHO-UMC classification of all serious cases of Arrhythmias, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e., Possible vs Probable and Probable vs Certain), and to discuss the result in the context of the totality of evidence on the subject.
B. The MAH is requested to review and present all cumulative cases of arrhythmia with a positive rechallenge including an individually justified WHO-UMC causality categorisation.
C. The MAH is requested in future PSURs to specifically report on arrhythmia cases in vaccinees <18 years in the relevant subpopulation analysis.

Safety signals

In the future PSURs, the MAH is requested to reflect the PRAC recommendations in the summary of signals presented. Signals closed in previous reporting intervals should not be presented unless they were re-opened during the current interval. In that case, the reason for re-opening should be clearly stated.

Single organ cutaneous vasculitis (SOCV)

Cases of SOCV in patients after Bivalent booster dose of Moderna vaccine targeting SARS-CoV2 was reported in association with elasomeran/imelasomeran (n=2), but not in recipients of elasomeran/davesomeran (n=0). The information provided on the 2 cases did not allow for causality evaluation at this time. The MAH is requested to make an extra effort to gather further information concerning these two SOCV cases exposed to a Bivalent booster dose of Moderna vaccine targeting SARS-CoV2 and present status and updated information in the next PSUR.

Subpopulation analysis: children

A. The MAH reported on a 17-year-old serious case with febrile convulsion ([redacted]) in the presentation of the youngest babies/children (6 months to 5 years of age), which is inconsistent. Furthermore, this case is not included in the annex 11.26a and annex 11.26b (Use in Children (< 18

Years of Old): Serious Cases During the Reporting Period- Case Evaluations and Case Narratives (All) (elasomeran)). The MAH is requested to clarify this discrepancy within the next PSUR.

B. The following three serious cases of elasomeran/davesomeran ([redacted]) are not found in the appendix 11.26 (Use in children (<18 Years of Old): Serious cases during the reporting period). The MAH is requested to clarify this discrepancy within the next PSUR.
C. In the guidance of assessment and understanding of data the MAH is requested to specify within the next PSUR the MAH's definition of a noteworthy report, which has been used by the MAH as an argument to present cases.

Thrombosis with thrombocytopenia syndrome (TTS)

Cumulatively, 230 cases (250 events) of TTS and related preferred terms were identified for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. In total, 194 cases (84.3%) were medically confirmed, 224 cases (97.4%) were considered serious and 31 (13.5%) had a fatal outcome.

In the text, the MAH has written there was 230 cases, 224 events. The number of events is expected to be larger than number of cases; the number of events is 250 according to table 16.89, which seems more reasonable. The "224" events is expected to be a typo. The MAH is reminded to proof-read text and tables before submitting. If the discrepancy is not due to a type, the MAH is requested to provide further clarification.

Literature review

The MAH is requested to review their internal literature retrieval processes and to ensure that any publications published prior to the reporting interval, which have been missed in previous literature screenings, are included in relevant reviews in the next PSUR.

Chronic urticaria – literature

The publication by Drivenes et al (doi:10.1002/clt2.12206) is claimed by the MAH to be a Moderna clinical trial, and has not been further commented upon by the MAH. The MAH should comment upon this paper in the next PSUR, both on the content regarding Spikevax and occurrence of urticaria-related events, in particular the events concerning chronic urticaria, and to explain the stated relationship to a Moderna clinical trial.

The MAH is requested to comment upon the publication by Duperrex et al (doi:10.1001/jamanetworkopen.2022.54298) in the next PSUR.

If the literature review warrants further evaluation on the topic of chronic urticaria, the MAH should prepare and present an updated review on chronic urticaria, including a proposal for amendment of the Product Information if warranted.

RMP

The MAH should address the following with the responses to the request for supplemental information within variation EMEA/H/C/005791/II/0104/G:

- The MAH's should provide a consolidated version of the RMP to harmonise all the available information for the elasomeran, elasomeran/ imelasomeran, and elasomeran/davesomeran-containing vaccines.

5. PSUR frequency

☒Changes of PSUR frequency are proposed

Noting that the MAH has expressed a wish to stay aligned with the EURD, two additional 6-monthly PSURs (DLP June 2023 and DLP December 2023 respectively) will be submitted, then a first yearly PSUR (DLP December 2024), to be followed by further yearly PSURs.

Annex: updated PRAC Rapporteur assessment comments on PSUR and RMP

1. PSUR Data

1.1. Introduction

This is the periodic safety update single assessment (PSUSA) of the 4th periodic safety update report (PSUR) on elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran covering the period from 19 Jun 2022 to 17 Dec 2022.

Currently, the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates. The three previous PBRERs (PBRER#1, PBRER#2 and PBRER#3) submitted included single International Nonproprietary Name (INN) elasomeran, however, beginning with this PBRER#4, bivalent forms; elasomeran/imelasomeran, and elasomeran/davesomeran will also be included.

The international birth date (IBD) of elasomeran is 18 Dec 2020, the date of the first marketing approval in any country in the world. The product is currently authorized in 48 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First authorization approval for elasomeran/imelosomeran was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom (UK) on 12 Aug 2022, and elasomeran/davesomeran was granted Emergency Use Authorization (EUA) status by US Food and Drug Administration (US FDA) on 31 Aug 2022.

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has Anatomical Therapeutic Chemical (ATC) code: J07BX03.

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; SARS-CoV-2). As per Company Core Data Sheet (CCDS) (v15.0, dated 15 Nov 2022), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. Elasomeran/imelasomeran and elasomeran/davesomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

Elasomeran is Single-stranded, 5'-capped messenger Ribonucleic acid (RNA) (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the full-length Spike protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S-protein into a prefusion conformation (S-2P). The elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102); cholesterol; 1,2- distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1 monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). Imelasomeran contains mRNA, 5'-capped, encoding a full length, codon-optimized prefusion stabilized conformation variant (K983P and V984P) of the SARS-CoV-2 spike (S) glycoprotein (Omicron variant, B.1.1.529). Davesomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

Elasomeran, is formulated as a dispersion for injection to be supplied in multidose vial and dispersion for injection in pre-filled syringe and is administered intramuscularly (IM). Elasomeran/imelasomeran and elasomeran/davesomeran are formulated as dispersion for injection to be supplied in multidose vial and single use pre-filled syringe (for elasomeran/imelasomeran).

• Elasomeran 0.20 mg/mL dispersion for injection

Elasomeran is supplied as a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each. One dose (0.5 mL) contains 100 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

• Elasomeran 0.10 mg/mL dispersion for injection and pre-filled syringe

Elasomeran is supplied as a multidose vial that contains 5 doses of 0.5 mL each or a maximum of 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 25 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 ml. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

• Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/davesomeran **[it is assumed the MAH means imelasomeran]** is supplied as a multidose 2.5 mL vial (blue flip-off cap) that contains 5 doses of 0.5 mL each and a multidose 5 ml vial containing 10 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

• Elasomeran/imelasomeran 25 µg/25 µg dispersion for injection and pre-filled syringe

Elasomeran/davesomeran **[it is assumed the MAH means imelasomeran]** is supplied as a single use pre-filled syringe which contains 1 dose of 0.5 mL. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 mL, for single use only. One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

• Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/davesomeran is supplied as a multidose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of davesomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

Following are the dosages of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran:

Elasomeran posology for primary series, a third dose in severely immunocompromised and booster doses are provided in the below Table 1.1.

Table 1.1 Dosages and description for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran

Elasomeran 0.20 mg/mL concentration	*Primary series*	*Individuals 12 years of age and older* Elasomeran is administered as a course of 2 (two) 100 µg doses (0.5 mL each).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 through 11 years of age Elasomeran is administered as a course of 2 (two) 50 µg doses (0.25 mL each, containing 50 µg mRNA, which is half of the primary dose for individuals 12 years and older).	

	Third dose in severely immunocompromised	*Individuals 12 years of age and older* Elasomeran is administered as course of one dose of 0.5 mL, containing 100 µg mRNA.	A third dose may be given at least 28 days after the second dose.
		Children 6 through 11 years of age Elasomeran is administered as course of one dose of 0.25 mL, containing 50 µg mRNA	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran 0.25 mL, containing 50 µg mRNA	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Elasomeran 0.10 mg/mL concentration and 50 µg dispersion for injection in pre-filled syringe	*Primary series*[*]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of 2 (two) 50 µg doses (0.5 mL each, containing 50 µg mRNA).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age Elasomeran is administered as a course of 2 (two) 25 µg doses (0.25 mL each, containing 25 µg mRNA each, which is half of the primary dose for children 6 years through 11 years of age).	
	Third dose in severely immunocompromised[†]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of one dose of 0.5 mL, containing 50 µg mRNA.	A third dose may be given at least 28 days after the second dose.
		Children 6 months through 5 years of age Elasomeran is administered as a course of one (one) dose of 0.25 mL, containing 25 µg mRNA.	

	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran, 0.5 mL, containing 50 µg mRNA.	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 6 years through 11 years of age* Dose is administered as one dose of 0.25 mL containing 12.5 ug of elasomeran and 12.5 ug of imelasomeran.	There should be an interval of at least 3 months between administration of elasomeran/imelasomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/imelasomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.
		Individuals 12 years of age and older Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of imelsasomeran.	
Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 12 years of age and older* Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of davesomeran.	There should be an interval of at least 3 months between administration of elasomeran/davesomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/davesomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

*For primary series for individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.

†For the third dose in severely immunocompromised patients 12 years of age and older, the 0.2 mg/mL strength vial should be used.

‡ For details on the primary vaccination course for ages 12 and above, the 0.2 mg/mL strength vial should be used.

Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran may be used to boost adults who have received a primary series with elasomeran, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine.

The mRNA drug substance in mRNA-1273 is chemically similar to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs [1] [2]. This nucleoside is included in mRNA-1273 drug substance in place of the normal uridine base to minimize the indiscriminate recognition of the mRNA-1273 by pathogen-associated molecular pattern receptors (e.g., toll-like receptors) [3]. The cap structure used in the mRNA is identical to the natural mammalian Cap one structure [4,5] and is presented in Figure 1-1 below.

Figure 1-1 mRNA 1273 COVID-19 Vaccine Cap 1 mRNA structure

Abbreviations: mRNA, messenger RNA; PolyA, polyadenylated; UTR, untranslated region.

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, contain mRNA encapsulated in LNPs. The mRNA encodes for the full length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the spike protein and is immunogenic against the Wuhan-Hu-1 (D614) isolate and all key emerging variants tested, including B.1.1.7, B.1.351, BA.1 (Omicron variant B.1.1.529), BA.2, BA.4, and BA.5 (Omicron variants B.1.1.529.4 and B.1.1.529.5). After IM injection, cells at the injection site and the associated draining lymph nodes take up the LNP, effectively delivering the mRNA sequence into cells for translation into viral protein. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The expressed, membrane-bound spike protein of SARSCoV-2 is then recognized by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralizing antibodies, which may contribute to protection against COVID-19.

A modified, variant-matched bivalent COVID-19 mRNA vaccine has been developed that contains equal amounts of two mRNAs that encode for the Spike protein of the ancestral SARS-CoV-2 (Wuhan-Hu-1) and an antigenically divergent variant of concern (elasomeran/imelasomeran), each encapsulated into individual LNPs, and co-formulated into a single drug product (Spikevax bivalent). After delivery, both mRNAs are delivered to cells in the body where the two distinct spike protomers, each of which represents one of the three components of the spike trimer, are expressed. After expression these spike protomers assemble into the spike trimer and both homotrimers as well heterotrimers (mixed protomers from the Wuhan spike and the Variant spike), form. The inclusion of both the original and the variant spikes in the vaccine are intended to broaden immunity.

Below are the target variants for the various mRNA-1273 vaccines used in the clinical development program (See Table 1.2).

Table 1.2 Variants and WHO labels for mRNA-1273

Suffix	Variants
mRNA-1273.351	Beta
mRNA-1273.617.2	Delta
mRNA-1273.211	Bivalent: 1:1 ratio of prototype and beta (.351)
mRNA-1273.213	Bivalent: 1:1 ratio of beta (.351) and delta (.617)
mRNA-1273.214	Bivalent: 1:1 ratio of prototype and omicron BA.1 (.529)
mRNA-1273.222	Bivalent: 2 mRNAs: CS-023314 and CX-034476
mRNA-1273.529	Omicron BA.1

Note: The original 1273 vaccine, targeting the Wuhan strain is referred to as prototype.

The expressed Spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen

which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

Further details on mechanism of action, indications, pharmaceutical forms, and instructions for use are presented in the CCDS for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran (current v15 dated 15 Nov 2022) in Appendix 1 [of the PSUR].

Rapporteur assessment comment:

The MAH proposed changes to the product information in relation to the warning of myocarditis and pericarditis in SmPC section 4.4 and PIL section 2 as part of this PSUSA procedure. In addition, the MAH proposed changes to the RMP version 7 as part of this PSUSA procedure.

1.2. Worldwide marketing authorisation status

The International Birth date of elasomeran is 18 Dec 2020. The product is currently authorized in 48 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelosomeran was granted by the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by Food and Drug administration on 31 Aug 2022.

Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (⩾18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations (eg, immunocompromised) and/or as a booster dose, including authorization for two bivalent vaccines (elasomeran/imelosomeran and elasomeran/davesomeran) continue to expand.

Cumulative information on marketing authorizations in all countries and approval dates are provided in Appendix 11.1 [of the PSUR].

Rapporteur assessment comment:

The International Birth Date of elasomeran is 18 Dec 2020. The product is currently authorized in 48 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelosomeran was granted by the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by Food and Drug administration on 31 Aug 2022. The date of marketing authorization in the European Economic Area for the primary vaccination series in adults was 06 Jan 2021.

This section is endorsed.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

During the reporting period, the following safety-related actions were taken by ModernaTx, Inc.:

During the month of Sep 2022, ModernaTx, Inc. became aware of reports of medication errors that were indicating the occurrence of product confusion and product underdosing related to the administration of the bivalent vaccines, elasomeran/imelasomeran and elasomeran/davesomeran. Reports of accidental underdosing of the Spikevax bivalent booster vaccines, indicated that a 0.25 mL dose (equivalent to 25 µg) was administered instead of 0.5 mL (50 µg). In most cases, underdosing was due to dose confusion

since the booster dose volume for the original monovalent elasomeran vaccine used earlier in 2022 was 0.25 mL (equivalent to 50 µg).

The marketing authorization holder (MAH) conducted a signal evaluation of the potential signal of medication errors due to product confusion and/or product underdosing. The signal evaluation included a cumulative review of the MAH safety database with a data lock point (DLP) of 04 Oct 2022. Analysis of the data showed that medication error reports had been received at a higher proportion for individuals vaccinated with one of the authorized Spikevax bivalent vaccines (relative to elasomeran original).

Based on the findings of the safety assessment evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a Potential Risk (Not Important) and was classified as a Priority 1 Urgent (emerging) Safety Issue[1].

A communication letter was distributed to those countries where Spikevax bivalent was authorized, and additional informational material regarding dosing information was posted on the ModernaTx, Inc. website for easy access by providers and consumers.

The MAH will continue to monitor events for potential medication errors related to product confusion and/or product underdose using routine pharmacovigilance surveillance.

Rapporteur assessment comment:

During the reporting period, the MAH became aware of reports of medication errors that concerned product confusion and product underdosing related to the administration of the bivalent vaccines, elasomeran/imelasomeran and elasomeran/davesomeran. The MAH conducted a signal evaluation of this potential safety issue and classified it as a Potential Risk (Not Important). The MAH distributed a communication letter to those countries where the bivalent vaccine was authorized and posted additional information regarding dosing on its company website. The MAH will continue to monitor this potential safety issue by routine pharmacovigilance surveillance. Please refer to section 2.2. for MAH's signal evaluation and the Rapporteur's discussion of this potential safety issue.

This section is acknowledged.

1.3.2. Changes to reference safety information

The Reference Safety Information (RSI) for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in effect at the end of the reporting period (DLP 17 Dec 2022) and used for this report is the CCDS v15.0 (dated 15 Nov 2022). This CCDS was used to assess listedness of adverse reactions (ARs), risks in risk sections, and to support benefit-risk evaluation in this report. The RSI contains a complete review of the safety profile for the product. This document is provided in Appendix 1 [of the PSUR].

During this reporting period, the RSI (CCDS) was updated from v13.0 (dated 03 Jun 2022) to v14.0 (dated 18 Jul 2022) and then to v15.0 (dated 15 Nov 2022). The safety-related changes are summarized below in Table 4.1.

Table 4.1 CCDS safety-related changes during the reporting period

Version	Date	Summary of changes
14.0	18 Jul 2022	**Section 4.4, myocarditis:** Deleted last paragraph in line with EMEA/H/C/005791/II/57 (Adolescent booster). **Section 4.8, Table 1:** Added "acute and delayed urticaria" to Skin and subcutaneous tissue disorders SOC. Deleted "includes urticaria" from Immune system disorders SOC and adjusted related footnote.

15.0	15 Nov 2022	**Section 4.1**: Updated the indication to lower and include till 6 months of age and also add bivalent indication. **Section 4.2:** Posology updated to address all possible dosing methods across strength and vaccination type, including bivalents. Added infant and young children site for injection per EMA approval. **Section 4.4:** Updated myocarditis text per Pharmacovigilance recommendations. **Section 4.8:** Added little peds data per EMA approval of EMEA. Added bivalent BA.1 data per EMA.

EMA=European Medicines Agency, EMEA=Europe, Middle East, and Africa, SOC=System Organ Class

Rapporteur assessment comment:

MAH's RSI for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in effect at the end of the reporting period and used for the current PSUR is the CCDS v15.0. During the reporting period, the CCDS was updated from v13.0 (dated 03 Jun 2022) to v14.0 (dated 18 Jul 2022) and then to v15.0 (dated 15 Nov 2022).

The safety-related changes are summarized in the table above.

The Rapporteur notes that the EU product information for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran has been updated in the reporting period with the following safety relevant information:

An updated RMP version 4.0 was submitted in order to remove 'anaphylaxis' as an important identified risk and to remove 'interaction with other vaccines' as a safety concern. The Product Information was updated accordingly.

Sections 4.2 and 4.4 of the SmPC were updated to include a 50 µg booster dose for adolescents 12 to 18 years of age. The package leaflet was updated accordingly.

Section 4.5 of the SmPC was updated in order to indicate the possibility of co-administration with a high-dose quadrivalent influenza vaccine.

Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Package Leaflet were updated to reflect the extension of indication to include immunization of pediatric individuals from 6 months through 5 years of age.

Section 4.8 of the SmPC was updated to include 'Urticaria' as an adverse reaction, with the frequency 'Uncommon', as requested by the PRAC in the 13th Safety Summary Report (EMEA/H/C/005791/MEA/011.12). The Package Leaflet was updated accordingly.

Section 4.8 of the SmPC and section 4 of the PL were updated to include heavy menstrual bleeding as an adverse reaction in accordance with the signal recommendation.

This section is acknowledged.

1.3.3. Estimated exposure and use patterns

1.3.3.1. Exposure in Clinical Trials

Cumulative exposure in clinical trials

Cumulatively, 52,530 subjects have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA-1273.617.2, mRNA-1273.529), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its

variants mRNA-1283.211), in the mRNA clinical development program sponsored by ModernaTx, Inc. Out of the 52,530 subjects, 42,434 subjects were exposed to mRNA-1273 primary series. The total count of 52,530 represents unique subjects (Subjects enrolled in both trials P301 and P201 (Part C)/P205 or in both P204 and P306 and are only counted once in total).

Estimates of cumulative subject exposure, based upon actual exposure data from completed CTs and the enrolment/randomization schemes for ongoing trials is provided in Table 5.1. Further details on cumulative subject exposure categorized by age, gender, racial group and ethnicity is provided in Table 5.2, Table 5.3 [please see PSUR], Table 5.4 [please see PSUR] and Table 5.5 [please see PSUR], respectively.

Table 5.1 Estimated Cumulative Subject Exposure from Clinical Trials

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P201	Placebo	42[a]
mRNA-1273-P201	mRNA-1273	558[a]
mRNA-1273-P201	mRNA-1273 Booster	344
mRNA-1273-P201	mRNA-1273.351 Booster	40
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	20
mRNA-1273-P203	Placebo	1,144[a]
mRNA-1273-P203	mRNA-1273 100 ug	2,582[a]
mRNA-1273-P203	mRNA-1273 50 ug	52[a]
mRNA-1273-P203	EUA+mRNA-1273 Booster	154[a]
mRNA-1273-P203	Primary series+mRNA-1273 Booster	1,427
mRNA-1273-P204	Placebo	885[a]
mRNA-1273-P204	mRNA-1273	11,030[a]
mRNA-1273-P204	mRNA-1273 10 ug Booster	217
mRNA-1273-P204	mRNA-1273 25 ug Booster	2,886
mRNA-1273-P204	mRNA-1273 50 ug Booster	1
mRNA-1273-P204	mRNA-1273.214 10 ug Booster	2,309
mRNA-1273-P204	mRNA-1273.214 25 ug Booster	236
mRNA-1273-P204	mRNA-1273.214 50 ug Booster	1
mRNA-1273-P205	mRNA-1273 Booster	687[a]
mRNA-1273-P205	mRNA-1273.211 Booster	759[a]
mRNA-1273-P205	mRNA-1273.211	135[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product

	Booster+mRNA-1273.214 Booster	
mRNA-1273-P205	mRNA-1273.213 Booster	954[a]
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	511[a]
mRNA-1273-P205	mRNA-1273.529 Booster	508[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	1,157[a]
mRNA-1273-P206	mRNA-1273.214	12[a]
mRNA-1273-P301	Placebo	2,513[a]
mRNA-1273-P301	mRNA-1273	27,833[a]
mRNA-1273-P301	mRNA-1273 Booster	19,609
mRNA-1273-P304	mRNA-1273	81[a]
mRNA-1273-P304	EUA+mRNA-1273	71[a]
mRNA-1273-P304	EUA+mRNA-1273 Booster	82[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	87
mRNA-1273-P305	Overall (Trial is still Blinded)	3,548[a]
mRNA-1273-P306	mRNA-1273.214	188[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	5[a]
mRNA-1283-P101	mRNA-1273	22[a]
mRNA-1283-P201	Overall (Trial is still Blinded)	543[a]
mRNA-CRID-001	mRNA-1273	58[a]

[a]=These numbers were counted to get the total for each study.

Table 5.2 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Age[a]

Age Range	**mRNA-1273**									**mRNA-128**		**mRNA-CRID**	**Total**
	P201	**P203**	**P204**	**P205**	**P206**	**P301**	**P304**	**P305**	**P306**	**P101**	**P201**	**001**	
<2 years	0	0	2,828	0	12	0	0	0	166	0	0	0	**2,881[b]**

2 to <6 years	0	0	4,244	0	0	0	0	0	561	0	0	0	**4,333[b]**
6 to <12 years	0	0	4,843	0	0	0	0	0	0	0	0	0	**4,843**
12 to <16 years	0	2,936	0	0	0	0	0	0	0	0	0	0	**2,936**
16 to <18 years	0	996	0	0	0	0	0	1	0	0	0	0	**997**
18 to <65 years	508	0	0	3,858	0	22,826	184	2,350	0	27	447	55	**27,257[b]**
65 to <75 years	128	0	0	1,033	0	6,121	43	1,117	0	0	76	3	**7,692[b]**
75 to <85 years	21	0	0	235	0	1,309	7	75	0	0	16	0	**1,482[b]**
>=85 years	3	0	0	22	0	90	0	5	0	0	4	0	**109[b]**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Total	**660**	**3,932**	**11,915**	**5,148**	**12**	**30,346**	**234**	**3,548**	**727**	**27**	**543**	**58**	**52,530[b]**

[a]=Data from ongoing and completed trials till 17 Dec 2022.

[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.

Interval exposure in clinical trials

As requested by the Pharmacovigilance Risk Assessment Committee (PRAC), information pertaining to interval exposure in CTs has been added in this section.

During the reporting period, 2,663 subjects have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mrNA-1273.222, mRNA-1273.617.2, mRNA-1273.529) or placebo in the mRNA clinical development program sponsored by ModernaTx, Inc.

Further details on the clinical exposure during the reporting period is in Table 5.6.

Table 5.6 Estimated Subject Exposure from Clinical Trials during reporting period

Study ID	Vaccine Type	Total Subject Exposure during the reporting period
mRNA-1273-P201	Placebo	0[a]
mRNA-1273-P201	mRNA-1273	0[a]
mRNA-1273-P201	mRNA-1273 Booster	0

mRNA-1273-P201	mRNA-1273.351 Booster	0
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	0
mRNA-1273-P203	Placebo	0[a]
mRNA-1273-P203	mRNA-1273 100ug	0[a]
mRNA-1273-P203	mRNA-1273 50ug	48[a]
Study ID	**Vaccine Type**	**Total Subject Exposure during the reporting period**
mRNA-1273-P203	EUA+mRNA-1273 Booster	102[a]
mRNA-1273-P203	Primary series+mRNA-1273 Booster	40
mRNA-1273-P204	Placebo	0[a]
mRNA-1273-P204	mRNA-1273	1,082[a]
mRNA-1273-P204	mRNA-1273 10ug Booster	42
mRNA-1273-P204	mRNA-1273 25ug Booster	719
mRNA-1273-P204	mRNA-1273 50ug Booster	1
mRNA-1273-P204	mRNA-1273.214 10ug Booster	2,309
mRNA-1273-P204	mRNA-1273.214 25ug Booster	236
mRNA-1273-P204	mRNA-1273.214 50ug Booster	1
mRNA-1273-P205	mRNA-1273 Booster	0[a]
mRNA-1273-P205	mRNA-1273.211 Booster	0[a]
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	102[a]
mRNA-1273-P205	mRNA-1273.213 Booster	0[a]
mRNA-1273-P205	mRNA-1273.214 Booster	0[a]
mRNA-1273-P205	mRNA-1273.222 Booster	511[a]
mRNA-1273-P205	mRNA-1273.529 Booster	0[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	0[a]
mRNA-1273-P206	mRNA-1273.214	12[a]

Study ID	Vaccine Type	Total Subject Exposure during the reporting period
mRNA-1273-P301	Placebo	0[a]
mRNA-1273-P301	mRNA-1273	0[a]
mRNA-1273-P301	mRNA-1273 Booster	0
mRNA-1273-P304	mRNA-1273	0[a]
mRNA-1273-P304	EUA+mRNA-1273	0[a]
mRNA-1273-P304	EUA+mRNA-1273 Booster	21[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	13
mRNA-1273-P305	Overall (Trial is still Blinded)	0[a]
mRNA-1273-P306	mRNA-1273.214	188[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	0[a]
mRNA-1283-P101	mRNA-1273	0[a]
mRNA-1283-P201	Overall (Trial is still Blinded)	0[a]
mRNA-CRID-001	mRNA-1273	58[a]

[a]=To have the total for each study, these numbers were counted

1.3.3.2. Exposure from Marketing Experience

Cumulative Patient Exposure from Marketing Experience

Cumulatively, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries (a proportion of doses distributed have been subsequently donated via either bilateral agreements or collaborative efforts such as COVAX). Some countries rely on the assessment of the World Health Organization (WHO) rather than holding a country level approval. Therefore, the countries that have received elasomeran (91) exceed the number of countries where elasomeran has been approved (48 countries/regions or unions/areas). North America, Europe, and Asia accounted for approximately 89% of

elasomeran doses distributed (Table 5.8). Cumulatively, 208,489,076 (13.4%) doses had been distributed in lower-and middle-income countries.

A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the United Kingdom, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered (Table 5.9).

ModernaTx, Inc. internally tracks the number of doses of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran globally. Prior to Jul 2022, ModernaTx, Inc. estimated global doses administered based on review of health authority websites where estimates were posted. More recently, a large number of countries to which ModernaTx, Inc. distributed elasomeran, and elasomeran/imelasomeran and elasomeran/davesomeran did not publicly post data on doses administered with a lag time that was suitable to mandatory monthly safety reporting schedules required in some countries. Because there was concern that the approach of reviewing health authority websites was not sustainable with potentially progressive data degradation, the methods for estimation of administered doses were changed. Review of recent safety reports showed that the proportion of doses distributed globally that had been administered varied from 53% to 59% of the doses distributed. Based on this, the MAH estimated administered doses as 55% of country specific doses distributed plus an estimate of doses donated to COVAX. [Since Sep 2021, the number of donated doses distributed were estimated as 15% of the total distributed doses. Furthermore, a conservative estimate of 25% of the donated doses, were assumed to be administered]. The change in process to estimate administered doses was implemented from Jul 2022, after the previous PBRER report on Jun 2022. In this PBRER, doses administered in the review period are defined as the difference between the previous PBRER (PBRER#03) and the current PBRER (PBRER#04). Given this change in process, the region-specific interval administered doses are questionably interpretable and hence not presented in this report.

Table 5.7 Total doses distributed and administered for elasomeran and elasomeran/imelasomeran and elasomeran/davesomeran[a]

Region	Cumulative				Interval	
	Distributed	%[a]	Administered	%[a]	Distributed	%[a]
Total	**1,553,749,469**	**100.0**	**912,827,813**	**100.0**	**299,417,683**	**100.0**
North America	**631,787,740**	**40.7**	**347,483,257**	**38.1**	**114,869,440**	**38.4**
US	571,787,750	36.8	314,483,263	34.5	100,826,690	33.7
All Europe	**450,792,773**	**29.0**	**247,936,025**	**27.2**	**116,323,473**	**38.8**
European Economic Area	386,448,843	24.9	212,546,864	23.3	91,040,843	30.4
Asia	**326,051,716**	**21.0**	**179,328,444**	**19.6**	**47,233,330**	**15.8**
Middle East	**61,485,250**	**4.0**	**33,816,888**	**3.7**	**3,983,550**	**1.3**
Latin America	**32,461,600**	**2.1**	**17,853,880**	**2.0**	**11,871,410**	**4.0**
Oceania	**26,176,600**	**1.7**	**14,397,130**	**1.6**	**4,120,400**	**1.4**
Africa	**24,993,790**	**1.6**	**13,746,585**	**1.5**	**1,016,080**	**0.3**

International donations	-	-	**58,265,605**	**6.4**	-	-

[a]=The doses distributed and administered in US, European Economic Area are not mutually exclusive of North America, All Europe respectively. Therefore, their proportions are not included in the total number of doses.

Table 5.8 Doses distributed and administered for elasomeran[a]

Region	Cumulative				Interval	
	Distributed	**%[a]**	**Administered**	**%[a]**	**Distributed**	**%[a]**
Total	**1,315,589,716**	**100.0**	**772,908,958**	**100.0**	**63,269,010**	**100.0**
North America	**553,351,210**	**42.1**	**304,343,166**	**39.4**	**36,432,910**	**57.6**
US	505,350,070	38.4	277,942,539	36.0	34,389,010	54.4
All Europe	**340,925,400**	**25.9**	**187,508,970**	**24.3**	**7,956,700**	**12.6**
European Economic Area	301,338,500	22.9	165,736,175	21.4	5,930,500	9.4
Asia	**282,128,566**	**21.4**	**155,170,711**	**20.1**	**3,310,180**	**5.2**
Region	**Cumulative**				**Interval**	
	Distributed	**%[a]**	**Administered**	**%[a]**	**Distributed**	**%[a]**
Middle East	**22,660,640**	**1.7**	**12,463,352**	**1.6**	**16,50,400**	**2.6**
Latin America	**60,485,300**	**4.6**	**33,266,915**	**4.3**	**11,381,940**	**18.0**
Oceania	**23,676,600**	**1.8**	**13,022,130**	**1.7**	**1,620,400**	**2.6**
Africa	**32,362,000**	**2.5**	**17,799,100**	**2.3**	**916,480**	**1.4**
International donations	-	-	**49,334,614**	**6.4**	-	-

[a]=The doses distributed and administered in US, European Economic Area are not mutually exclusive of North America, All Europe respectively. Therefore, their proportions are not included in the total number of doses

Table 5.9 Spikevax bivalent doses distributed and estimated bivalent doses administered as of 17 Dec 2022[a]

Region	Product 214				Product 222			
	Distributed	**%[a]**	**Administered**	**%[a]**	**Distributed**	**%[a]**	**Administered**	**%[a]**
Total	**127,413,973**	**100.0**	**70,077,685**	**100.0**	**110,745,780**	**100.0**	**60,910,179**	**100.0**
North America	**10,521,450**	**8.3**	**5,786,798**	**8.3**	**67,915,080**	**61.3**	**37,353,294**	**61.3**
US	21,600	0.0	11,880	0.0	66,416,080	60.0	36,528,844	60.0
All Europe	**82,625,473**	**64.8**	**45,444,010**	**64.8**	**27,241,900**	**24.6**	**14,983,045**	**24.6**

European Economic Area	57,868,443	45.4	31,827,644	45.4	27,241,900	24.6	14,983,045	24.6
Asia	**29,334,350**	**23.0**	**16,133,893**	**23.0**	**14,588,800**	**13.2**	**8,023,840**	**13.2**
Latin America	**999,950**	**0.8**	**549,973**	**0.8**	-	-	-	-
Africa	**99,600**	**0.1**	**54,780**	**0.1**	-	-	-	-
Oceania	**2,500,000**	**2.0**	**1,375,000**	**2.0**	-	-	-	-
Middle East	**1,333,150**	**1.0**	**733,233**	**1.0**	**1,000,000**	**0.9**	**550,000**	**0.9**

North America: Canada and US

Europe: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Ukraine, Switzerland, UK

Asia: Bangladesh, Bhutan, Cambodia, Indonesia, Japan, Kyrgyzstan, Nepal, Pakistan, Philippines, Singapore, Taiwan, Tajikistan, Thailand, Turkmenistan, Uzbekistan, Vietnam, South Korea

Middle East: Israel, Kuwait, Qatar, Saudi Arabia, United Arab Emirates, Palestine

Latin America: Argentina, Bolivia, Chile, Colombia, Dominica, Grenada, Haiti, Mexico, Paraguay, Peru, St. Lucia, St. Vincent and the Grenadines

Oceania: Australia, Fiji, Vanuatu

Africa: Angola, Benin, Botswana, Brunei Darussalam, Burkina Faso, Central African Republic, Democratic Republic of Congo, Egypt, Guinea, Kenya, Nigeria, Rwanda, Sao Tome and Principe, Tanzania, Tunisia, Uganda, Zambia

[a] = The doses distributed and administered in US, European Economic Area are not mutually exclusive of North America, All Europe respectively. Therefore, their proportions are not included in the total number of doses.

Summaries of ModernaTx, Inc. distribution administered by country and distribution by lots/batches are included in Appendix 11.2 [of the PSUR].

Demographic characteristics of US recipients of all COVID-19 vaccine products for primary series are shown in Figure 5-1 [please see PSUR], data for booster doses are shown in Figure 5-2 [please see PSUR] and data for Bivalents are shown in Figure 5-3 [please see PSUR]. Because product specific demographic data (age, gender, and race/ethnicity) are not published by Center for Disease Control and Prevention (CDC) or international public HAs, figures presented in this section consider vaccinations targeting SARS-CoV-2 as a class. The proportion of vaccines administered was highest for those 50-64 years of age, female gender, and white race.

Available demographic characteristics of vaccine recipients (primary series boosters and bivalents) are shown for the European Economic Area (EEA) (PSUR Figure 5-4, Figure 5-5, Figure 5-6 and Figure 5-7) and Canada (PSUR Figure 5-8, Figure 5-9 and Figure 5-10). In the EEA, the highest proportion of vaccinated individuals were among 25-49 years of age for primary series and 60 years and older for booster doses. In Canada, the highest proportion of vaccinated individuals were among 18-29 years for primary series and 60-69 years for booster doses. Information on distribution by gender was not published by European Center for Disease Prevention and Control (ECDC) at the time that the data were accessed (https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html accessed 19 Jun 2022).

Interval Patient Exposure from Marketing Experience

In this reporting period (19 Jun 2022 to 17 Dec 2022), a total of 63,269,010 doses of elasomeran had been delivered and an estimated total of 110,037,791 doses had been administered. North America, Europe, and Latin America accounted for approximately 88% of elasomeran doses distributed (Table 5.7). During this reporting period, 12,622,400 (20%) elasomeran doses had been distributed in lower- and middle-income countries.

Traceability

Batch monitoring is performed using distribution data derived from the ModernaTx, Inc. supply chain and US manufacturing records. Patient level exposure for the EU is presented below by age. Subpopulation data across gender, race and ethnicity are not presently available.

As part of the EU Risk Management Plan (RMP) and Summary of Product Characteristics (SmPC), instructions have been provided with our product for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability. ModernaTx, Inc. has also developed Traceability and Vaccination Reminder cards.

The card is accessible electronically and though a Quick response (QR) code, on the applicant's website. The Traceability and Vaccination Reminder cards contain the following elements:

• Placeholder space for name of vaccine;

• Vaccine brand name and manufacturer name;

• Placeholder space for due date and actual date of first and second doses, and associated batch/lot number;

• Reminder to retain the card and bring to the appointment for the second dose of the vaccine.

• QR code that links to a website with additional information on product use; and

• Adverse event reporting information.

The vaccine carton labeling also contains a scannable 2D barcode that provides the batch/lot number and expiry date. In addition, ModernaTx, Inc. also provides stickers (two stickers per dose, containing printed batch/lot information, product identification, and 2D bar code) that encodes a unique identifier [serial number]) either in cartons or to be shipped along with each shipment, in the countries where this is required.

Rapporteur assessment comment:

The cumulative subject exposure in clinical trials is 52,530 persons. The interval subject exposure in clinical trials is 2,663 persons (including different vaccine variants and placebo).

The total cumulative exposure from marketing experience is estimated as 912,827,813 administered doses for elasomeran and elasomeran/imelasomeran and elasomeran/davesomeran. For elasomeran alone the cumulative number of administered doses is 772,908,958. For elasomeran/imelasomeran the estimated cumulative number of administered doses is 70,077,685. For elasomeran/davesomeran the estimated cumulative number of administered doses is 60,910,179.

The estimated interval exposure from marketing experience is 110,037,791 administered doses of elasomeran.

This section is acknowledged.

1.3.4. Data in summary tabulations

Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 was used for the coding of adverse events (AEs)/adverse drug reactions (ADRs) presented in this report. The line listings and summary tabulations are first arranged alphabetically by primary MedDRA System Organ Class (SOC) and then by the Preferred Term (PT).

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative (18 Dec 2020 to 17 Dec 2022) summary tabulation of Serious Adverse Events (SAEs) from Company-sponsored CTs is provided in Appendix 2 [of the PSUR]. The SAEs presented in this summary tabulation were derived from Company-sponsored interventional CTs. Inclusion requirement parameters for the incorporation of data from Company-sponsored CTs are that the SAE occurred during active treatment, the SAE originated from a clinical study with mRNA-1273, the event was assessed as serious, and the active treatment was mRNA-1273 or placebo.

Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

A cumulative (18 Dec 2020 to 17 Dec 2022) and interval (19 Jun 2022 to 17 Dec 2022) summary tabulation of ADRs (serious and non-serious) is provided in Appendix 3 [of the PSUR]. The ADRs presented in this tabulation were derived from spontaneous sources (healthcare professionals [HCPs], consumers, scientific literature, and regulatory authorities [RAs]) as well as serious ADRs from non-interventional studies and non-interventional solicited sources.

Rapporteur assessment comment:
No new important safety information is identified.
This section is acknowledged.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Summaries of significant findings from clinical trials in the reporting interval

Completed Clinical Trials

There was one ModernaTx, Inc. sponsored CT which was completed during the reporting period.

Study Protocol Number: mRNA-1273-P201

Study Title: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older.

Clinical Study report was finalized on 22 Aug 2022.

Summary:

Part A was the Blinded Phase, was a randomized, observer-blind, and placebo-controlled study, and evaluated the safety, reactogenicity, and immunogenicity of two dose levels (50 µg and 100 µg) of mRNA-1273 vaccine, each administered as two doses 28 days apart, in adult participants at least 18 years of age, grouped into two cohorts (≥ 18 to < 55 years old and ≥ 55 years old). Following authorization of a COVID-19 vaccine under EUA, the study was amended to provide transition to Part B,

the Open-label Interventional Phase.

Part B was designed to offer participants who received placebo in Part A of the study. This was an option to receive two injections of open-label mRNA-1273 (100 µg) and participants who received one or two doses of 50 µg or 100 µg mRNA-1273 in Part A of this study the option to receive a single booster dose of 50 µg mRNA-1273.

Part C: A proof-of-concept, was the open-label interventional part of the study to evaluate a single booster dose of mRNA-1273.351 (50 µg or 20 µg) or mRNA-1273/mRNA-1273.351 mixture (50 µg total). Part C was prompted by the need to proactively prepare for vaccination strategies that induce broader protection against variants of concern such as the SARS-CoV-2 Beta (B.1.351) variant.

The mRNA-1273-P201 Primary Analysis (Day 57) clinical study report (CSR), dated 22 Aug 2022, provides the primary analysis of safety and immunogenicity data through Day 57 of Part A (database lock 05 Nov 2020) and includes a complete description of the study investigational plan and methodology. The mRNA-1273-P201 CSR Addendum 1 (End of Part A), dated 13 Aug 2021, provides updated safety and immunogenicity data through the Program Data Vector (database lock 10 Jun 2021). The mRNA-1273-P201 CSR Addendum 2 (Part B), dated 24 May 2022, provides safety and immunogenicity results for Part B (database lock 23 Nov 2021). The mRNA-1273-P201 CSR Addendum 3 (Part C) dated 22 Aug 2022 provides safety and immunogenicity results for Part C (database lock 23 Nov 2021) and is considered the last study report for P201 marking the completion of the study.

Study Conclusions: All booster vaccines demonstrated no unexpected reactogenicity or safety results. Findings were similar to those of Part A and Part B, thereby further supporting the acceptable benefit-risk profile of the booster vaccination with monovalent and bivalent variant vaccines.

Rapporteur assessment comment:

The MAH reports that there was one company sponsored CT which was completed during the reporting period. For this study the MAH concludes that all booster vaccines demonstrated no unexpected reactogenicity or safety results.

This section is acknowledged.

Ongoing Clinical Trials

There was a total of 11 ModernaTx, Inc. sponsored CTs ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P305, mRNA-1283-P101, mRNA-1283-P201, mRNA-1273-P206, mRNA-1273-P306, and mRNA-CRID-001), during the current reporting period. Of these 11 ongoing CTs, three trials (Protocol mRNA-1283-P101, Protocol mRNA-1283-P201 and Protocol mRNA-CRID-001) included an additional mRNA-1273 treatment arm. Cumulative exposure split by studies has been presented in Table 7.1.

There was no clinically important information that arose from ongoing CT during the reporting period.

Table 7.1 Summary of Cumulative Subject Exposure by Study

Study ID	Total subjects exposed
mRNA-1273-P203	3,932
mRNA-1273-P204	11,915
mRNA-1273-P205	5,148
mRNA-1273-P206	12
mRNA-1273-P301	30,346
mRNA-1273-P304	234

mRNA-1273-P305	3,548
mRNA-1273-P306	727
mRNA-1283-P101	27
mRNA-1283-P201	543
mRNA-CRID-001	58

Refer to PSUR Appendix 5 for further details of all the ongoing and completed studies during the reporting period.

Rapporteur assessment comment:

The MAH reports that there were 11 company sponsored CTs which were ongoing during the reporting period. The MAH reports that there was no clinically important information that arose from these studies during the reporting period.

This section is acknowledged.

Long-term Follow-up

Patients completing CTs mRNA-1273-P101 (Division of Microbiology and Infectious Diseases [DMID] 20-0003), mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P903, and mRNA-1273-P904 are followed up for longterm safety. The clinical development program has a safety follow-up period of 12 months in all the above listed studies except in the Phase 3 study mRNA-1273-P301 where subjects will be followed up for 24 months.

In the Phase 3 Study mRNA-1273-P301, the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) which is 183 days (range: 1 to 218 days), or approximately 6 months. The follow-up time is through Day 209 for the Phase 1 study mRNA-1273-P101 (DMID 20-0003) and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.

As of the DLP of this PBRER, there have been no significant safety findings in the ongoing studies nor in the completed studies mRNA-1273-P201 and mRNA-1273-P101 (DMID 20-0003) studies, which are being assessed to characterize the long-term safety of mRNA-1273/mRNA-1273.214/mRNA-1273.222.

Rapporteur assessment comment:

The MAH reports that as of the DLP there were no significant safety findings identified from the CTs that investigate the long-term safety of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

This section is acknowledged.

1.3.5.2. Findings from non-interventional studies

The following non-interventional studies were ongoing during the reporting period:

mRNA-1273-P902

Title: Moderna mRNA-1273 Observational Pregnancy Outcome Study

Status: Enrolment for this prospective pregnancy registry began in Oct 2021. Although data collection is ongoing and remains a commitment, enrolment has proceeded slowly, and the study has been replaced in

the EU-RMP by ongoing study mRNA-1273-P905 and planned study mRNA-1273-P919, a US administrative claims-based study of pregnancy safety. It is expected that study mRNA-1273-P902 will be terminated upon approval of the study protocol and initiation of data management for study mRNA-1273-P919. At this time, no safety findings have yet been identified.

mRNA-1273-P903

Title: Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity.

Status: This is a retrospective observational cohort study which uses secondary, de-identified individual level medical and pharmacy claims data provided by HealthVerity. Analyzes are ongoing for study, which includes components of active vaccine surveillance via a historically controlled comparator and signal refinement using a SCRI design. The main results of preliminary signal refinement analyzes discussed in Interim Report#7 (Oct 2022) are presented here. The final report will be prepared by 30 Jun 2023.

Results: There were 140,122,236 individuals identified in the HealthVerity database at any time between 01 Dec 2017 and 10 Dec 2020. Of these individuals, 108.8 million were enrolled in a health plan providing information on enrolment during the same time frame. We excluded 134,778 individuals will missing information on sex, 6,096 individuals with missing information on age, and 15,157,248 individuals without continuous enrolment for at least 365 days at any time during the study period before sampling 50,015,708 individuals to mirror the distribution of the 2019 US census age and sex distribution. Of these individuals, 38,686,912 were at least 18 years of age and 11,328,796 were under 18 years of age.

To form the pre-COVID and COVID era cohorts, 50,015,708 individuals meeting study entry criteria were sampled to mirror the distribution of the 2019 US census age and sex distribution. Of these individuals, 38,686,912 were at least 18 years of age and 11,328,796 were under 18 years of age. Among the historical comparator populations, there were 908,741 and 894,045 immunocompromised adults and 33,640 and 35,011 immunocompromised pediatric individuals in the pre-COVID and COVID eras, respectively. Among females of childbearing age (12-55 years) in the historical populations, after applying study inclusion criteria, there were 91,122 and 65,519 pregnant women in the pre-COVID and COVID eras, respectively. Within the pre-COVID comparator population, 3,104,556 adults and 1,570,161 pediatric individuals were vaccinated for influenza.

There were 22,589,594 adults and 119,401 pediatric patients vaccinated with elasomeran who met study entry criteria through 25 Apr 2022. Among these individuals, 64.3% of adults and 55.6% of pediatric patients received a second dose. Among individuals who received a second dose, 23.9% of adults and 26.6% of pediatric patients also received a third dose. There were 622,568 immunocompromised adults who were vaccinated with elasomeran, of which 65.8% received a second dose; 35.7% of immunocompromised adults with a second dose also received a third dose. Slightly more immunocompromised adults received a non- elasomeran COVID-19 vaccine during follow-up than the general population (2.1% vs. 1.6%). There were 33,639 pregnant women 12-55 years who received elasomeran and met study entry criteria to be included in the pregnancy-specific analyzes, and 61% received a second dose of elasomeran. Of these, 4.1% also received a third dose.

PSUR Table 8.1 indicates the specific populations by Adverse Events of Special Interest (AESI) that met the threshold for both signal refinement (observed expected [O/E] analyzes) and signal evaluation (SCRI analyzes) in this interim report.

Myocarditis

Interpretation of analyzes of myocarditis is similar to that shared in Interim Report 6 (IR6), where 1,636 cases of myocarditis were identified using claims through 25 Apr 2022; most (68.9%) cases occurred after the second dose of elasomeran. Dose-agnostic, dose 1 and dose 2-specific SCRI analyzes produced

findings comparable to the previous interim report, where the event rate ratio (ERR) was greater following the second dose compared to the first dose among adults overall and among both males and females 18-29 years. Event rate ratios following dose 3 were attenuated compared to IR6.

Consistent with IR6, there was not a sufficient number of myocarditis events among the pediatric population to conduct SCRI analyzes.

Pericarditis

Interpretation of analyzes of pericarditis has also not changed substantially from IR6, where 3,175 cases of pericarditis occurred through 25 Apr 2022; most (69%) cases were identified after the second dose of elasomeran. Observed ERRs were largely consistent with IR6 following dose-agnostic, dose 1, and dose 2-specific SCRI analyzes, where the ERR was greater following the second dose compared to the first dose among adults overall and among both males and females 18-29 years. The ERR for young adult females was increased, however this was estimated from only 6 events in the risk (n=4) and control (n=2) windows. Unlike IR6, in both the adult population and males overall, a slight attenuation in the ERR was observed in dose 3 analyzes compared to dose 2 in the current analyzes.

Consistent with IR6, there was not a sufficient number of pericarditis events among the pediatric population to conduct SCRI analyzes.

Other AESIs

In the current interim report, anosmia/ageusia, anaphylaxis, arrhythmia, chilblain-like lesions, cerebral venous sinus thrombosis, coagulation disorders, erythema multiforme, narcolepsy/cataplexy, seizures/convulsions, single organ cutaneous vasculitis, and thrombosis with thrombocytopenia met pre-specified thresholds for execution of SCRI analyzes in at least one subgroup. Results from the signal detection (unadjusted historical IRR comparison) and preliminary refinement (O/E) stages of analyzes were similar to those presented in the last interim report, with the exception of immune thrombocytopenia which no longer met the threshold for O/E analyzes and Bell's palsy which no longer met the threshold for SCRI analyzes. Given the results of IR6, SCRI analyzes were conducted for immune thrombocytopenia regardless, however insufficient case counts were available to support SCRI for Bell's palsy.

Anosmia, ageusia

There were 18,721 cases observed among adults through 25 Apr 2022, compared to 16,202 in IR6. Among adults (overall ERR 1.04, 95% CI 0.89–1.22), dose 3 ERRs were elevated among males 18-29 years and ≥75 years, noting that these estimates were imprecise. Dose 3 results among other age and sex strata were largely consistent with the dose-agnostic and dose 1 or 2 specific analyzes. SCRI analyzes among pediatric patients were conducted for previous interim reports and will be included in the final report.

Anaphylaxis

There were 4,764 cases observed among adults through 25 Apr 2022, compared to 3,781 in IR6. Following dose-agnostic SCRI analyzes, increased risks were observed among all adult and females age strata. Similar findings were seen following dose 1-specific results. Following dose 2 and dose 3-specific analyzes, increased risks were observed among several age and sex strata, although generally attenuated compared to dose-agnostic and dose 1 estimates.

Among pediatric patients, there were 35 cases, compared to 30 in IR6. Results of dose-agnostic SCRI analysis among the pediatric population were generally consistent with IR6, except among pediatric patients and female pediatrics overall where elevated ERRs were newly observed. This is consistent with the known safety profile of elasomeran.

Arrhythmia

Among adults, neither signal refinement nor evaluation were conducted as there were no increased rates of arrhythmia observed after any dose of elasomeran compared to historical rates.

There were 155 cases observed among pediatric patients, compared to 121 in IR6. Results from signal refinement in IR6 newly met the threshold for SCRI analyzes, for which increased risk of arrhythmia was observed in dose-agnostic, dose 1 and dose 2 SCRI analyzes among male pediatric patients, albeit among a small number of patients producing imprecise estimates. Dose 3 SCRI were not performed because the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report.

Bell's palsy

There were 7,927 cases observed among adults through 25 Apr 2022, compared to 6,341 in IR6. Rates of Bell's palsy were not elevated following any dose of elasomeran among adults.

There were 14 cases observed among pediatric patients, compared to 12 in IR6. Results from signal refinement in IR6 newly met the threshold for SCRI analyzes for Bell's palsy, however the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report. Bell' s palsy will continue to be monitored for IR8 as cases accrue.

Chilblain-like lesions

There were 1,353 cases observed among adults through 25 Apr 2022, compared to 969 in IR6. Compared to IR5, results from dose-agnostic and dose 1 and 2-specific analyzes were slightly attenuated, though increased risk was still observed across multiple age and sex subgroups. With the exception of overall females and females 40-64 years, no elevated ERRs were observed in dose 3 SCRI analyzes.

Cases will continue to be monitored among the pediatric population with SCRI analyzes expected to be included in the final report.

Cerebral venous sinus thrombosis

There were 360 cases observed among adults through 25 Apr 2022, compared to 272 in IR6. Results of SCRI analyzes of Central Venous Sinus Thrombosis (CVST) were consistent with IR6 with elevated ERRs observed among adults ≥75 years. There were only 14 events in the dose 3-specific analysis to draw meaningful conclusions. Results from two sensitivity analyses requiring claims for imaging 14 days before or after the CVST event and applying a washout period for CVST utilizing all available data resulted in no observed increased risk in any subgroup.

Only 2 cases observed among pediatric patients through 25 Apr 2022, consistent with IR6.

Coagulation disorders

Among adults, there were 112,178 cases observed through 25 Apr 2022, compared to 87,962 in IR6. Consistent with IR6, the rates of coagulation disorders following elasomeran vaccination were not elevated after any dose.

Among pediatric patients, 56 cases were observed, compared to 44 in IR6. Dose-agnostic and dose 1-specific SCRI analyzes resulted in elevated ERRs among overall pediatric and female pediatric patients, which were attenuated when compared to IR6. Clinician review of the specific events included within the composite definition of coagulation disorders in IR6 suggested that the observed events may be reflective of erroneous lab values secondary to other diagnoses or medications or of unclear clinical significance, leading to an overestimation in the risk of clinically relevant coagulation disorders. Dose 3 SCRI were not performed because the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report.

Erythema multiforme

There were 1,239 cases observed among adults through 25 Apr 2022, compared to 1,023 in IR6. Newly reported SCRI analyzes among adults resulted in elevated ERRs among young women 30-39 years in dose-agnostic, dose 1, and dose 2-specific analyzes. Older males had elevated ERRs in dose 2-specific analyzes, while elevated ERRs were observed among young adults aged 18-29 years in dose 3-specific analyzes, although both estimates may be imprecise due to low sample size.

There were 38 cases observed among pediatric patients, compared to 29 in IR6. Consistent with IR6, there was no elevated risk of erythema multiforme in the dose-agnostic analysis. There was not a sufficient number of events (≥10) to perform dose specific SCRI analyzes for this report.

Immune thrombocytopenia

There were 3,474 cases observed among adults through 25 Apr 2022, compared to 2,765 in IR6. Consistent with IR6, ERRs were attenuated, and slightly elevated, in the dose-agnostic and dose specific analyzes across age and sex subgroups. Additional sensitivity analysis excluding all cases using all prior available data resulted in elevated ERRs only among adults 50-64 years, which was not previously observed.

Among pediatric patients, there were 5 cases through 25 Apr 2022, compared to 4 in IR6. Results from signal refinement in IR6 met the threshold for SCRI analyzes for ITP among paediatrics <12 years, however the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report. Immune thrombocytopenia will continue to be monitored for IR8 as cases accrue.

Narcolepsy/cataplexy

There were 3,207 cases observed among adults through 25 Apr 2022, compared to 2,555 in IR6. SCRI analyzes were largely consistent with IR6, identifying an increased risk of narcolepsy/cataplexy among adults ≥75 years. Among immunocompromised adults, an elevated ERR in the dose-agnostic SCRI was newly observed among males 50-64 years, although among only 2 events in the control window. Sensitivity analyzes requiring a washout of narcolepsy/cataplexy utilizing all available data resulted in slightly elevated ERRs that were attenuated when compared to the primary analyzes.

Among pediatric patients, neither signal refinement nor evaluation were conducted as there were no increased rates of narcolepsy/cataplexy observed after any dose of elasomeran compared to historical rates.

Seizures/convulsions

There were 51,673 cases observed among adults through 25 Apr 2022, compared to 41,356 in IR6. Among adults, neither signal refinement nor evaluation were conducted as there were no increased rates of seizures/convulsions observed after any dose of elasomeran compared to historical rates.

There were 184 cases observed among pediatric patients, compared to 151 in IR6. Newly included dose-agnostic and dose 1-specific SCRI analyzes found an increased risk of seizures/convulsions among pediatrics overall and within several age and sex-specific strata. Elevated ERRs were observed following dose 2, however there is greater uncertainty around these estimates given there were only 11 events. There was insufficient sample size to conduct dose 3-specific SCRI analyses in the pediatric population.

Single organ cutaneous vasculitis

There were 3,141 cases observed among adults through 25 Apr 2022, compared to 2,517 in IR6. Newly included SCRI analyzes resulted in elevated ERRs within dose-agnostic, dose 1, and dose 2-specific SCRI analyzes among adults 18-29 years. Within the dose 3-specific analysis, an increased risk of single organ cutaneous vasculitis was observed among adults aged 50-64 years, though estimates may be imprecise given the sample size.

There were 9 cases observed among pediatric patients, compared to 8 in IR6. Consistent with IR6, Single Organ Cutaneous Vasculitis (SOCV) met the threshold for SCRI analyzes, however there were insufficient sample sizes to conduct SCRI analyzes among pediatric patients. SOCV will continue to be monitored within the pediatric population as events accrue.

Thrombosis with thrombocytopenia

There were 112,663 cases observed among adults through 25 Apr 2022, compared to 88,357 in IR6. Among adults, neither signal refinement nor evaluation were conducted as there were no increased rates of thrombosis with thrombocytopenia observed after any dose of elasomeran compared to historical rates.

In pediatric patients, 59 cases were observed, compared to 47 in IR6. Consistent with IR6, no increased risk of thrombosis with thrombocytopenia was observed in dose-agnostic and dose 1 SCRI analyzes. Due to insufficient sample size, dose 2 and 3-specific SCRI analyzes were not included in this report but will continue to be monitored.

AESI for which SCRI analyzes have not yet been performed

The AESI that met thresholds for observed versus expected analyzes from the last interim report consistently met those thresholds with the updated data in this interim report, with the exception of immune thrombocytopenia. Additionally, following preliminary, unadjusted signal detection, thresholds for O/E analyzes were met in at least 1 adult or pediatric population comparison for the following AESI: acute aseptic arthritis, acute respiratory distress syndrome (ARDS), and acute myocardial infarction. Acute respiratory distress syndrome and type 1 diabetes both had higher than expected observed events in their respective risk windows following elasomeran vaccination among pediatric patients, newly meeting the threshold for self-controlled analyzes. Protocol annexes describing the approach for these self-controlled analyzes will be submitted, with the results from those analyzes reported in the next interim report.

Discussion

Interim results of this post-marketing safety study describe the absolute and relative incidence rates of 43 pre-specified AESI among adult and pediatric patients across three time-specific cohorts (pre-COVID, COVID era, and post-EUA elasomeran vaccination era).

Consistent with the previous interim report, AESI with elevated incidence rates among adults with at least 1 dose of elasomeran were identified for anaphylaxis, anosmia/ageusia, cerebral venous sinus thrombosis, chilblain-like lesions, erythema multiforme, immune thrombocytopenia, myocarditis, pericarditis, and narcolepsy/cataplexy. Sensitivity analyzes for narcolepsy/cataplexy and ITP resulted in slightly elevated ERRs that were attenuated compared to primary analyzes, and sensitivity analyzes for CVST resulted in no elevated ERRs. Results from the self-controlled analysis for arrhythmia, SOCV, and seizures/convulsions are newly included in this interim report. Within the adult population, no AESI newly met the threshold for self-controlled analyzes.

Among pediatric patients, elevated rates among those who received at least one dose of the elasomeran vaccine was consistent with IR6. Interpretation of these analyses should consider that all use as of the DLP was off-label administration of adult dosage in the United States. Unlike IR6, acute kidney injury met the threshold for SCRI analyzes as part of this report, similar to IR5 where these estimates were first reported, and are expected to be included in the final report. Upon further refinement via O/E analysis, ARDS and type 1 diabetes mellitus (DM) met the criteria for a selfcontrolled analysis. A protocol annex will be submitted detailing the approach to further evaluate these potential findings. Results from the self-controlled analysis for ARDS and type 1 DM in pediatric patients will be presented in IR8.

Results evaluating the risk of pregnancy-related AESI (gestational diabetes, preeclampsia, preterm labor, spontaneous abortion, and stillbirth) found no elevated risks, consistent with IR6 after all doses of elasomeran.

Additional analyzes in forthcoming reports will characterize and refine the observed signals. The subsequent IR8 will include results for additional SCRI analyzes identified in this report.

mRNA-1273-P904

Title: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe.

Summary: A preliminary screening stage analyzes for selected databases in this observational study using large administrative databases in Denmark, Norway, Italy, Spain and the UK was presented in Interim Report 3 on 30 Sep 2022. the number of eligible elasomeran recipients with at least one dose of elasomeran was 563,998 in Denmark, 428,779 in Italy, 532,797 in Norway, and 587,436 in Spain.

Rates of several AESIs were lower than expected in Italy, subject to further investigation and quality control.

Results of the signal detection, available from the Italy/ARS database, identified the following AESIs as fulfilling pre-specified criteria for additional signal evaluation based on at least one analysis performed: Diabetes type 1, (Idiopathic) Thrombocytopenia , Microangiopathy, Heart failure, Stress-induced cardiomyopathy, Coronary artery disease (CAD), Arrhythmia, Myocarditis, Pericarditis, Cerebrovascular disease, Deep vein thrombosis, Splanchnic vein thrombosis, Coagulation disorders, Acute liver injury, Acute kidney injury, Generalized convulsions, ARDS, Anaphylaxis, and Death of any cause. No signal evaluation was undertaken, and signal detection was not conducted in other databases.

The results reported here should be considered preliminary and are not interpretable as indicative of any changes to the current benefit-risk profile of elasomeran. Results inclusive of all participating countries and all study objectives will be presented and interpreted in the Final Study Report.

mRNA-1273-P905

Title: Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries.

Summary: For this observational cohort study carried using large administrative databases in Denmark, Norway, Italy, Spain and the UK, with feasibility counts were described in the Sep 2022 interim study update. At this time, no safety findings have yet been identified given the early stage of the study.

mRNA-1273-P911

Title: Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA).

Summary: The overarching goal of this study is to characterize presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (elasomeran). A first interim feasibility report was completed 31 Oct 2022. At this time, no safety findings have yet been identified given the early stage of the study.

In addition, the following studies are planned as of the DLP of this PBRER. No safety findings have yet been identified given the early stage of these studies:

mRNA-1273-P910

Title: Natural History of Vaccine-Associated Myocarditis

Summary: The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and Spikevax bivalent vaccination. A statistical analysis plan is currently in development.

mRNA-1273-P915

Title: Survey on acute phase safety for persons with underlying diseases with high risk

Status: The overarching goal of this post-marketing surveillance (PMS) activity to confirm the incidence of hypersensitivity reactions including shock and anaphylaxis observed after vaccination with this drug and to explore risk factors in persons with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A protocol is currently under review.

mRNA-1273-P916

Title: Survey on Shock and Anaphylaxis for Persons with Underlying Diseases with High Risk

Status: The overarching goal of this PMS activity is to identify the incidence of specified AEs in the acute phase observed after vaccination in subjects with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A protocol is currently under review.

mRNA-1273-P917

Title: Survey on non-acute phase safety for persons with underlying diseases

Status: The overarching goal of this PMS activity is to identify hypotheses for the safety evaluation of this product by confirming the occurrence status of non-acute hospitalization-associated serious events observed after vaccination in persons with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A protocol is currently under review.

mRNA-1273-P918

Title: General Use Results Survey: Spikevax Intramuscular Injection (Previously COVID-19 Vaccine Moderna Intramuscular Injection) During the Early Phase of Treatment With Novel Corona Vaccine, Follow-up of Key Survey Participants.

Summary: The overarching goal of this PMS activity is to follow-up subjects who are vaccinated early after the marketing approval of this product in Japan for 11 months from the day after the day following the last day of the last vaccination with this drug as the primary immunization (the last day of the observation period in the health status investigation of preceding vaccinees) to 12 months after the last vaccination with this drug as the primary immunization, and to collect information on SAEs observed during the follow-up period and COVID-19.

mRNA-1273-P919

Title: An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to SPIKEVAX During Pregnancy

Status: This observational PMS study will evaluate the risk of adverse pregnancy and infant outcomes following maternal exposure to elasomeran during pregnancy. A statistical analysis plan is currently under review.

mRNA-1273-P920

Title: Post-marketing safety of an Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine in the United States

Status: The overarching aim of this study is to characterize the safety of the Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine as used in routine clinical practice. A statistical analysis plan is currently under review.

mRNA-1273-P921

Title: Evaluation of Post-marketing safety of Spikevax (elasomeran) in the Kingdom of Saudi Arabia

Status: The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and Spikevax bivalent vaccination. A protocol is currently under review.

mRNA-1273-P923

Title: Post-marketing safety of Spikevax vaccine in South Korea

Status: The overarching aim of the study is to characterize the safety of the elasomeran vaccine (primary series and booster) as used in the routine clinical practice in Korea. A protocol is currently in development for a retrospective database study supporting this aim.

mRNA-1273-P924

Title: Post-marketing Surveillance: Use-Result Surveillance with Spikevax Bivalent.

Status: This PMS activity aims to evaluate safety of elasomeran elasomeran/imelasomeran (SARS-CoV-2 mRNA vaccine)] and elasomeran/davesomeran in Korea. A protocol has been recently approved for execution of the survey.

Rapporteur assessment comment:

The MAH reported status from PASS included in the EU RMP and presented post-marketing surveillance (PMS) activites in countries outside the EU. Most PMS activities are in an early stage and no safety data has been analysed yet.

No new safety information that has not been assessed in other procedures has been presented.

The provided information is acknowledged.

1.3.5.3. Other clinical trials and sources

Rapporteur assessment comment:

The MAH reported information from several investigator-sponsored studies and licensing partner studies. No significant safety findings had been identified.

The information provided is acknowledged.

1.3.5.4. Medication errors

Please, refer to the PSUR section 16.3.6.7.1 and to appendix 11.20 in the PSUR for complete information on medication errors presented by the MAH.

Summary of results

During this reporting period, there were 4,931 cases with 7,383 medication error events, and 4,373 of the cases (88.7%) were medically confirmed. There were 1,644 cases (33.3%) reported in males and 1,963 cases (39.8%) reported in females; gender information was not provided in 1,324 cases (26.9%).

The majority of cases were received directly by the MAH as spontaneous reports from the public (4,038; 81.9%). Most cases reporting medication errors were received from the United States (2,912; 59.1%), with the regions reporting the next highest volumes being much smaller at 490 (9.9%) from Latin America and 437 from Australia (8.9%).

Of the events with a known dose number, the greatest portion of events occurred after the 2nd dose (799; 10.8%). 4,749 events (64.3%) were associated with an unknown dose number (see PSUR Table 16.128).

In this reporting period, the MedDRA PTs of Expired product administered (2,393; 32.4%), and Product storage error (1,494; 20.2%) are among the most frequently reported medication errors (see PSUR Table 16.129). The events included in this analysis that were coded to product administered to patient of inappropriate age (215; 2.9%) or inappropriate schedule of product administration (745; 10.1%) may or may not represent true medication errors as there was not enough information in the report to determine whether these instances were intentionally administered outside of labelled product use guidance. Overall, there were fewer medication error events from this review period and the last review period.

During the reporting period, there were 1361 cases (4,665 events) of medication error reported with an associated AE. The most frequent AE reported were COVID 19 (289; 6.2%), Pyrexia (180; 3.9%) (see PSUR Table 16.130).

Medication Errors Involving elasomeran/imelasomeran

During this reporting period, the MAH became aware of reports of medication errors related to product confusion between elasomeran booster and elasomeran/davesomeran booster (mainly in the United States) and accidental underdosing of the elasomeran/imelasomeran and elasomeran/davesomeran boosters in the rest of the world. Instances of accidental underdosing typically were due to administration of a 0.25 mL dose (equivalent to 25 µg) instead of 0.5 mL (50 µg) per product label for the bivalent boosters. The volumes drawn for bivalent boosters were confused with the volume to be drawn for the elasomeran booster used earlier in 2022 (0.25 mL, equivalent to 50 µg).

Based on the findings of the safety assessment evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a potential risk and was classified as Priority 1 (Urgent (emerging) Safety Issues: Issues which have a significant impact on the product's benefit-risk profile, and which require the most rapid communication and implementation) and that risk minimization measures needed to be implemented in agreement with the respective HAs in the countries where the bivalent vaccines have been authorized. Therefore, safety letters from the MAH have been disseminated worldwide regarding the issue.

Therefore, communication letters have been disseminated worldwide regarding the issue.

During this reporting period, and cumulatively, there were 622 cases (1,106 events) reporting medication errors in elasomeran/imelasomeran. There were 79 cases (12.7%) reported in males and 129 cases (20.7%) reported in females; gender information was not provided in 414 cases (66.6%). The majority of cases were reported through spontaneous reports (589; 94.7%), and most cases were received from the UK (249; 40%).

The most frequent medication error event reported was unspecified Product storage error (267; 24.1%) (see PSUR Table 16.142).

During the reporting period, there were 49 cases (165 events) of medication error reported with an associated AE in elasomeran/imelasomeran. There were 15 cases (30.6%) in males, 32 cases in females (65.3%); 2 cases (4.1%) were missing gender information. The most frequent AEs reported was Headache (10; 6.1%). (see PSUR Table 16.143).

Medication Errors Involving elasomeran/davesomeran

During this reporting period, and cumulatively, there were 1,583 cases (2,505 events) reporting medication errors in elasomeran/davesomeran. There were 439 cases (27.7%) reported in males and 523 cases (33%) reported in females; gender information was not provided in 621 cases (39.2%). All cases were reported through spontaneous reports (1,583; 100%), and most cases were received from the United States (1,375; 86.9%).

The most frequent medication error events reported were Product temperature excursion issue (597; 23.8%), and Poor-quality product administered (512; 20.4%) (see PSUR Table 16.144).

During the reporting period, there were 60 cases (193 events) of medication error reported with an associated AE in elasomeran/davesomeran. There were 12 cases (20%) in males, 44 cases in females (73.3%), and 4 cases (6.7%) had missing gender information. The most frequent AEs reported was Pain in extremity (12; 6.2%) (see PSUR Table 16.145).

Discussion

Review of the data does not suggest any identifiable patterns or trends in the reports of medication errors received by the MAH, including those reports concerning patients who received doses of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccine beyond the primary series or any interchange of other COVID-19 vaccine products. For more details about interaction with other vaccines/heterologous vaccines, please refer to Section 16.3.6.7.4 in the PSUR. During this reporting period, the MAH became aware of reports of medication errors related to product confusion between elasomeran booster and elasomeran/davesomeran and accidental underdosing of the elasomeran/imelasomeran and elasomeran/davesomeran boosters. The MAH considered that this was a potential risk and classified as Priority 1 Safety Issues. Therefore, safety letters from the MAH have been disseminated worldwide regarding the issue. However, there seemed no difference for bivalent boosters and original booster for the nature of reported medication errors and importantly associated AEs in general. AEs associated with reported medication errors were usually known to the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran safety profile, and no events were associated with significant harm to the patient due to the medication error. There were no significant changes in the frequencies and types of medication error events in general from this review period and the last review period.

Conclusion

After careful review of all new safety data received during the review period and cumulatively for medications errors, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. Medication errors reported to ModernaTx, Inc. will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

During the reporting period, the MAH raised a signal concerning bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) and product label confusion leading to underdosing. For more information concerning the signal, please refer to section 2.2.2.4 of this AR.

Apart from that, no new and significant safety information was identified from the review of medication error cases presented by the MAH. The number of medication error cases received by the MAH in the current interval has decreased compared to the previous interval (4,931 vs 11,251). The pattern of medication errors reported in the current interval is similar to the pattern observed previously.

Endorsed.

1.3.5.5. Literature

A global literature search and analysis was performed utilizing Embase®, Medline® and PubMed databases for abstracts for the reporting period 19 Jun 2022 to 17 Dec 2022. The literature search was performed for the publications related to elasomeran and for publications related to the class mRNA COVID-19 vaccines. The product search terms included elasomeran, mRNA-1273, Moderna COVID-19 Vaccine, SPIKEVAX, CX-024414, TAK-919, SPIKEVAX pre-filled syringe, SPIKEVAX Bivalent Original/Omicron BA.4-5, SPIKEVAX bivalent Original/Omicron BA.1. Find the complete global literature search strategy used for Medline and Embase search under PSUR Appendix 12.1a and search strategy used for PubMed under PSUR Appendix 12.1b.

A local literature search was performed for ModernaTx, Inc. vaccine approved countries for the journals which were not indexed in Medline or Embase using product names as key search terms. Please find the journal list under PSUR Appendix 12.1c. Literature search strategy for medical topics can be found under PSUR Appendix 12.1d.

During the reporting period, there were a total of 24,239 abstracts retrieved and upon removal of duplicates 19,365 abstracts were reviewed (full text reviewed as required) from the global search. There were 6,730 local journal searches performed, and 236 abstracts were reviewed. From all the searches performed, three (3) articles were identified with relevant new safety information and are summarized below: For more detailed information and full text articles please refer to PSUR Appendix 12.2.

A Disproportionality Analysis for Association of Systemic Capillary Leak Syndrome with COVID-19 Vaccination Using the World Health Organization Pharmacovigilance Database [6]

Park J et al. performed a disproportionality analysis using VigiBase data to investigate the association between different types of COVID-19 vaccines and systemic CLS (SCLS). Cases with MedDRA PT of SCLS associated with BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 vaccines were extracted. From VigiBase, 48 cases after BNT162b2, 12 cases after mRNA-1273, and 41 cases after ChAdOx1 nCoV-19 were obtained for SCLS. Disproportionality was evaluated by calculating the information component or reporting odds ratio (ROR) using the entire database and also a viral vaccines data subset. The ChAdOx1 nCoV-19 vaccine showed a significantly positive association with SCLS by IC025 of 0.71 (95% CI, 0.24–1.12) and ROR025 of 1.68 (95% CI, 1.23–2.29) using the entire database as the comparator. Additionally, a disproportionality analysis was performed for the data reported by physicians and other healthcare professionals, to minimize reporting bias. The authors noted a significant potential signal of disproportionality of SCLS in ChAdOx1 nCoV-1 when using the entire database (IC025 = 0.42, ROR025 = 1.12) and when using all viral vaccines (IC025 = 0.36, ROR025 = 1.22) as comparators. On the contrary, no significant potential signal of disproportionality for SCLS was noted for the two mRNA-based vaccines when applied comparators were the entire database (IC025 = −0.36, ROR025 = 0.65) and all viral vaccines (IC025 = −0.44, ROR025 = 0.71). The author concluded that there was no potential safety signal for developing SCLS noted with mRNA COVID-19 vaccines but, suggested extensive research for establishing diagnostic criteria for SCLS and elucidating the causal relationship between SCLS and the COVID-19 vaccines.

Breast Cancer Screening and Axillary Adenopathy in the Era of COVID-19 Vaccination [7]

The authors present two cases of women recently vaccinated with elasomeran who were subsequently studied with mammography for breast cancer screening. Both women had mammographic evidence of lymphadenopathy, which the authors report may occur in 2.4 to 35% of women and may persist as long as 43 weeks, with higher incidence following mRNA than vector vaccines. On biopsy, one patient was found to have benign reactive lymphadenopathy; the other patient, in contrast, was found to have metastatic adenocarcinoma. As many as 1% of breast cancers may present as isolated axillary lymphadenopathy. The authors review professional societies' evolving recommendations and summarize

that: women with a personal history of breast cancer should receive vaccination on the contralateral side to the breast cancer; screening mammography should not be delayed following COVID-19 vaccination; isolated unilateral axillary lymphadenopathy ipsilateral to the side of recent COVID-19 vaccination without other suspicious imaging findings may be considered Breast Imaging-Reporting and Data System (BI-RADS) category 2 (benign) without follow-up imaging or BI-RADS category 3 (probably benign) with follow-up imaging in greater than 12 weeks if increased clinical concern; and more cautious management, including possible biopsy, should be undertaken for patients with concurrent suspicious imaging findings, with adenopathy contralateral to the site of vaccination, or for patients with high risk or with a personal history of breast cancer.

Retinal Vascular Occlusion after COVID-19 Vaccination: More Coincidence than Causal Relationship? Data from a Retrospective Multicenter Study [8]

Feltgen N et al. conducted a retrospective multicenter study using data from the German Retina Society which invited 50 retina clinics to participate in an investigation of retinal vascular occlusive disease (RVOD) and a potential association with vaccination against SARS-CoV-2. The study period was 01 Jun 2021 to 31 Jul 2021 (2 months,) a time of widespread vaccination in Germany. Data from patients with central and branch retinal vein occlusion (CRVO and BRVO), central and branch retinal artery occlusion (CRAO and BRAO), and anterior ischemic optic neuropathy were retrospectively collected according to a defined protocol. The study participants were randomly selected from residents' registration offices (City of Mainz and District of Mainz- Bingen, Germany,) and at the initial examination the overall participation rate was 55.5 percent. This study took a mixed-methods approach to ensure the highest probability of detecting any association between RVOD and COVID-19 vaccination. In case-by-case analysis, a total of 508 patients were included. Three hundred and twenty-one study participants (76.2%) were vaccinated at least once before the RVOD onset, and 221 patients received BNT162b2 (BioNTech/Pfizer), followed by 57 ChadOx1 (AstraZeneca [AZ]), 21 mRNA-1273 (ModernaTx, Inc.), 11 Ad26.COV2.S (Johnson & Johnson) and 11 received an unknown vaccine. The other 89 patients had not received a COVID-19 vaccine. Seventy patients (21.8% of the vaccinated patients) were vaccinated within 2 weeks of RVOD onset, 85 (26.5%) had received in 2-4 weeks, 44 had received (13.7%) between 4 and 6 weeks, and 122 participants had received (38.0%) more than 6 weeks before RVOD onset. When examining the time-dependent distribution between vaccinations and RVOD, the author observed no events within the first 4 weeks after SARS-CoV-2 vaccination, regardless of the disease or vaccine administered. No clear relationship between vaccination and RVOD was found from this data. In the case-control analysis, a comparative analysis was performed between the patients with RVOD and healthy controls from the general population recruited by the Gutenberg Health Study (GHS). The author compared the probability of being vaccinated in the previous four weeks between RVOD patients and the population-based GHS sample. In the unadjusted conditional logistic regression analysis, there was noted one significant association: a lower risk for CRAO after vaccination. The case-control study integrating population-based data from the GHS found no evidence of an increased risk after COVID-19 vaccination within the last four weeks. Further adjustment with the most complete data on diabetes, obesity, arterial hypertension, smoking, and the use of anticoagulation did not alter this finding. There was no significant temporal shift forward found when comparing the vaccination time point between the cases and controls. In this retrospective multicenter study on RVOD onset and COVID-19 vaccination status, the author found no increased risk of retinal vascular occlusion.

Rapporteur assessment comment:

The MAH reported to have identified 3 papers with relevant new safety information. The results were summarized by the MAH. The papers concerned Systemic Capillary Leak Syndrome, where no association was identified with mRNA vaccines targeting SARS-CoV-2, Breast Cancer Screening and Axillary Adenopathy, where two cases were identified however no direct evaluation of a potential association with

Moderna vaccination was presented, and Retinal Vascular Occlusion, where no increased risk of retinal vascular occlusion was identified in association with mRNA-1273 vaccination.

Endorsed.

1.3.5.6. Other periodic reports

No other PBRERs have been written during the reporting period for elasomeran, elasomeran/imelosomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

According to the MAH, no other periodic reports have been presented for Moderna vaccines targeting SARS-CoV2.

Endorsed.

1.3.6. Late-breaking information

The MAH states: There were no potentially important safety, efficacy and effectiveness findings that arose during the preparation of this report after the DLP.

Rapporteur assessment comment:

The MAH has not identified any late-breaking information after DLP.

Endorsed.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 16.1 provides the Summary of Safety Concerns as per RMP v3.0 approved on 01 Mar 2022 in place at the beginning of the reporting period.

Table 16.1 Summary of Safety Concerns valid at the beginning of the reporting period (as per RMP v3.0 approved on 01 Mar 2022)

Important identified risks	• Anaphylaxis • Myocarditis • Pericarditis
Important potential risks	• Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease

Missing information	• Use in pregnancy and while breast-feeding • Long-term safety • Use in immunocompromised subjects • Interaction with other vaccines • Use in frail subjects with unstable health conditions and comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders.

During the reporting period, the elasomeran RMP v3.0 was updated to v4.0 approved on 23 Jun 2022 to remove 'anaphylaxis' as an important identified risk and reclassify it as an identified risk (not important). While anaphylaxis, remains as an identified risk for the product, as with any other biologicals, it does not have a considerable impact on the benefit-risk balance of the vaccine. Furter v4.0 was updated to v4.1 to include the data on individuals 6 months of age and older and v4.1 was later updated to v4.2 (approved on 01 Sep 2022) to include elasomeran/imelasomeran as a new medicinal product to the RMP and to add the INN elasomeran/imelasomeran with no additional changes to the list of safety concerns. RMP v4.2 was updated to v4.5 (not approved and information consolidated with v6.3) to include elasomeran booster dose for children 6 to 12 years of age. Using RMP v4.2, a new version was updated to v5.0 (approved on 06 Oct 2022) to reclassify category 2 studies within the Pharmacovigilance Plan (PV) (mRNA-1273-P301, mRNA-1273-P203 and mRNA-1273-P204) to category 3 studies related to the application to move the conditional marketing authorization for elasomeran to a full marketing authorization. Later RMP v4.2 and v5.0 merged with the addition of elasomeran/davesomeran indication and other changes to create v6.0 (not approved – information merged into v6.3) with no additional changes to the list of safety concerns. Further RMP v4.1, v4.5 and v6.0 merged to create v6.1 (not approved information merged into v6.3) with updated indication to include individuals 6 months of age and older for elasomeran original, updated the indication for elasomeran/imelasomeran for use in individuals 6 years of age and older, updated the indication for elasomeran/davesomeran for use in individuals 12 years of age and older. Lastly, RMP v6.1 was updated to create v6.3 (approved on 15 Dec 2022) to update indication and posology for all the 3 products and product details to include the 0.10 mg/mL dispersion for injection supplied as a multidose vial and associated strengths and posology with no additional changes to the list of safety concerns.

Table 16.2 Summary of Safety Concerns valid at the end of the reporting period (as per RMP v6.3 approved 15 Dec 2022)

Important identified risks	• Myocarditis • Pericarditis
Important potential risks	• Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease
Missing information	• Use in pregnancy and while breast-feeding • Long-term safety • Use in immunocompromised subjects • Interaction with other vaccines • Use in frail subjects with unstable health conditions and comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders.

Rapporteur assessment comment:

During the reporting interval the RMP was updated from version 3.0 to version 6.3. With regards to the summary of safety concerns, this resulted in the removal of 'anaphylaxis' as an important identified risk and the reclassification of it as an identified risk (not important). This section is acknowledged.

Please be informed that an RMP version 7.0 was submitted for assessment with the current PSUR (please see AR section 3 Update of the Risk Management Plan).

In addition to the RMP safety concerns the PSUR summary of safety concerns also contains IgA Nephropathy. This PSUR safety concern is assessed in AR section 2.3.2.

2.2. Signal evaluation

2.2.1. Overview of signals: new, ongoing or closed

Validated signals during the reporting period

ModernaTx, Inc. has an established signal management process that includes signal detection, validation, prioritization, and assessment. During signal detection, data sources are screened for new safety information related to elasomeran. Following initial review of available data, a determination is made on the basis of the nature and the quality of the new information whether the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis, at which point those topics are referred for further evaluation and are considered as "validated signals." Potential signals may be identified from any data source, including but not limited to safety data from ModernaTx, Inc.-sponsored CTs, non-interventional studies, spontaneous AE reports, published literature, regulatory safety surveillance databases (e.g., Eudravigilance, vaccine adverse event reporting system [VAERS]), and communications from external sources, including regulatory agencies, and (if applicable) business partners. As part of the ModernaTx, Inc.'s routine pharmacovigilance activities, weekly to monthly signal detection analyzes are performed on the following data sources: ModernaTx, Inc. global pharmacovigilance database (Argus platform) using a defined signal detection methodology (both qualitative and quantitative aggregated analyzes), signals of disproportionate reporting from regulatory databases (e.g., Eudravigilance, VAERs), published literature that involves targeted keyword searches in widely recognized databases (i.e., Medline, Embase), health authority websites screening, review of publicly available competitors' labels, as well as social media.

This routine aggregate review also includes O/E analyzes, which are performed as described in Appendix 11.3 [of the PSUR].

During the reporting period of this PBRER, 3 signals were closed and refuted, 1 signal was closed and categorized as a Potential Risk (not important), 2 signals were ongoing and lastly 1 signal of "Capillary Leak Syndrome (CLS) (Re-evaluation)" was closed as a refuted signal before the reporting period of this PBRER, but not presented in PBRER#3, is presented here for completeness. The list of ongoing/closed signals is presented in Table 15.1 below [the more detailed table 20.1 from appendix 4.1 has been presented instead] and detailed presentation of all signals is included in Appendix 4.1 [of the PSUR].

Table 20.1 Tabular summary of safety signals new, ongoing or closed during the reporting interval [from appendix 4.1 of the PSUR]

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source of trigger of signal	Reason for Evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
IgA nephropathy *	08 Jul 2022	Closed	22 Jul 2022	Health Authority Request EudraVigilance /EVDAS Spontaneous Reports	MAH considered IgA nephropathy as a validated signal following review of PRAC PSUR assessment report of covering period from 30 Jun 2021 to 31 Dec 2021, highlighting the fact that IgA nephropathy was delineated from other renal PTs, both in disproportionality analyzes as well as in case reviews, although cumulative evidence is not sufficient to warrant amendment of the product information. Following MAH assessment based on the review of all available sources, no cases of IgA nephropathy were reported in the CT setting. Analysis from the Company GSDB retrieved 54 cases (including 34 de novo IgA cases and 20 IgA flare cases), of which 27 cases were literature reports. All but one flare cases resolved or were resolving at time of reporting. Review of the literature indicated that post-vaccination IgA nephropathy's clinical signs, symptoms and treatment were similar to those of "typical" IgA nephropathy, and no pathognomonic signs or symptoms that link IgA nephropathy to vaccination were found. The European Renal Association and the European Vasculitis Society raised in Mar 2022 the reassuring recommendation that patients with immune-mediated kidney diseases should follow national guidance on vaccination. In conclusion MAH considered IgA nephropathy in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed, the very low reporting rate (< 1 case per 10 million doses administered) and lack of pathophysiological mechanism. MAH did not plan to update the product information and/or RMP, including relevant risk minimization measures. IgA nephropathy will continue to be monitored through routine PV surveillance.	Signal Evaluation Report	Routine Pharmacovigilance
Heavy menstrual bleeding (re-evaluation)	13 Jun 2022	Closed	22 Aug 2022	Health Authority Request	A signal of heavy menstrual bleeding (HMB) was evaluated as a refuted signal in Mar 2022 (EPITT No 19780). A new signal for HMB was opened based on PRAC Signal AR (dated 13 Jun 2022) requesting an updated cumulative review following its conclusion that the current evidence was insufficient to warrant an update to the product information. Following re-assessment based on the review of all available sources, non-clinical data showed no elasomeran -related effects or changes in mating, fertility and ovarian/uterine examinations. From a focused review of the 915 serious cases, vast majority of cases were unassessable due to the extremely limited data (87.1%) and 39.5% had plausible alternate explanations for HMB. The O/E analysis did not provide observed counts higher than expected when assuming 25% of cases were reported. Literature search results did not provide evidence of a causal association between mRNA vaccines or elasomeran and HMB and published studies were lacking comparisons with unvaccinated subjects. In conclusion, HMB is a common gynecologic problem affecting 1 out of	RTQ	Routine Pharmacovigilance

					every 4-5 women. Considering the subjectivity of HMB definition, the challenge of missing information when analyzing spontaneous reports, and the lack of evidence across data sources, MAH considered HMB in association with elasomeran as a refuted signal. MAH did not plan changes in clinical trial conduct, labeling, other RSI or the RMP. HMB will continue to be monitored through routine PV surveillance.		
Myocarditis and pericarditis (re-evaluation)	09 Sep 2022	Closed	20 Oct 2022	Health Authority Request Spontaneous Reports	A signal of myocarditis and pericarditis was evaluated as an important identified risk in Jun 2021, then myocarditis and pericarditis frequency of occurrence was further characterized as "Very rare" in Dec 2021. Upon a health authority request from TGA, a follow-up signal for myocarditis and pericarditis was opened to re-evaluate the risk (e.g. severity, demographics, booster doses) as the data is accruing. Cumulative review of data as of 18 Sep 2022, confirmed that the important identified risk of myocarditis and pericarditis was adequately characterized in current MAH CCDS; no changes in terms of demographic characteristics, severity (including fatal outcomes) nor clinical presentation were identified. This follow-up signal was therefore considered as a refuted signal, with no further changes planned in the CCDS and/or RMP.	Signal Evaluation Report	Routine Pharmacovigilance
Product label confusion leading to underdosing of Bivalent vaccines	03 Oct 2022	Closed	13 Oct 2022	Health Authority Request Spontaneous Reports	Since Sep 2022, reports of product label confusion that led in many cases to accidental underdosing related to the administration of ModernaTx, Inc. Spikevax bivalent products (elasomeran/imelasomeran and elasomeran/davesomeran) were received from various sources, including quality complaints,	Other (Signal evaluation report executive summary)	Other (Communication Letter to HCP, including

(elasomeran /imelasomeran and elasomeran/ davesomeran)				Routine Signal Detection Other (Product Quality Complaints, Requests for clarification from HCPs (Canada, Germany))	regulatory agencies, spontaneous reports and HCP inquiries. Analysis of the MAH GSDB revealed a disproportionate reporting of the Product label confusion and Underdose PTs with both the ModernaTx, Inc. Bivalent vaccines as compared to the monovalent vaccine. Most of the reports described prescribers' confusion regarding the actual volume to administer, without an identifiable patient, and no AEs or prescribers' administering 0.25 mL instead of 0.5 mL, leading to underdosing the patients. Following investigation of the possible root causes, MAH considered Product label confusion leading to underdosing as a potential risk (not important). Marketing authorization Holder implemented preventive actions in agreement with national HAs, including the distribution of a communication letter with educational tools to clearly identify each presentation and appropriate dosing information, and updates to the ModernaTx, Inc's website.		educational tools) Other (Updates to Moderna's website)
Capillary Leak Syndrome (Re-evaluation)**	13 Jan 2022	Closed	09 Mar 2022	Health Authority Request	A signal of CLS was evaluated as a refuted signal in Nov 2021 (EPITT ref. No. 19743). A new signal was opened based on PRAC Signal AR (dated 13 Jan 2022) requesting an updated cumulative review of CLS, including a separate discussion on cases with a medical history of CLS, and considering the publication from the EuréClark StudyGroup [41]. Based on the updated review of the reported cases with CLS related terms, as of 31 Dec 2021, a total of 9 cases (11 events) of were reported, with 7 (77.8%) cases medically confirmed.	Signal Evaluation Report RTQ	Routine Pharmacovigilance

					Analysis of the data reported in the MAH GSDB continues to provide support for a lack of a causal association between CLS and elasomeran. Cumulatively, the reporting rate of CLS for elasomeran is substantially lower than one report per million doses. Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considered that CLS observed following immunization with elasomeran, was not a safety issue of concern. CLS is a refuted signal and no changes to the CCDS or the RMP is warranted. CLS will continue to be monitored through routine PV surveillance.		
Pemphigus and pemphigoid***	05 Dec 2022	Ongoing	NA	Health Authority Request EudraVigilance /EVDAS Literature Article	MAH considered pemphigus and pemphigoid as a validated signal following receipt of PRAC's signal assessment report (EPITT No. 19860) requesting MAH for elasomeran (Moderna Biotech Spain S.L.) to perform a cumulative review of all cases of pemphigus and pemphigoid from all sources, including available data from CTs, scientific and post-marketing exposure. Data should be presented separately for new onset cases and for cases reporting flare-up and/or aggravation. MAH responses to a list of questions (e.g WHO-UMC causality assessment; potential reporting patterns (gender, age, TTO), risk factors, seriousness, treatment of ADR and outcome; tabular presentation of cases; literature review regarding plausibility and MoH; overview of PT Dermatitis bullous and other related terms within HLT Bullous conditions for identification of pemphigus/pemphigoid cases; O/E analyzes with a risk window of 28 days) including the need for potential amendment to the product	Signal Evaluation Report RTQ	Evaluation ongoing

					information and/or RMP should be provided by 09 Feb 2023.		
Amenorrhea (re-evaluation)***	13 Jun 2022	Ongoing	Pending	Health Authority Request	A signal of amenorrhea was evaluated as a refuted signal in Mar 2022 (EPITT No 19781). A new signal for amenorrhea was opened based on PRAC Signal AR (dated 13 Jun 2022) where PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present and agreed that the MAH of COVD-19 mRNA vaccine (nucleoside modified) elasomeran, should provide an updated cumulative review of amenorrhea events post-vaccination in the PSUR with the DLP of 17 Dec 2022.	PBRER/PSUR/MSSR RTQ	Evaluation Ongoing

*In addition to the RMP safety concerns, IgA nephropathy was included as an important potential risk in PSUR, as an outcome of the previous PSUSA procedure EMEA/H/C/PSUSA/00010897/202112
**Signal of CLS was closed before the reporting period of this PBRER but has been presented in PBRER#4 for completeness.
***Both the Signals were closed and refuted by the MAH after the DLP, but the PRAC assessment is pending. Once the assessment is completed by PRAC, detailed evaluation reports will be appended in PBRER#5.

Rapporteur assessment comment:

The MAH reports that there were seven signals that were closed or ongoing during the reporting period. It is noted that the information presented in the above table was not updated with PRAC recommendations. The following information was missing:

-IgA nephropathy: following the assessment of PSUR#2, the PRAC recommended that IgA nephropathy shall be added to the list of safety concerns as an important potential risk in the PSUR (PSUSA no.: EMEA/H/C/PSUSA/00010897/202112). Consequently, the risk should be followed in sections 16.3 and 16.4 in the PSUR. From the above table, it seems that the MAH reopened the signal on 08/07/2022 and closed it on 22/07/2022. The MAH did not state the reason for reopening the signal. The data submitted on IgA nephropathy is presented in AR section 2.3.2 New information on important potential risks.

-Heavy menstrual bleeding: based on the data assessed in the stand-alone signal procedure (EPITT 19780), the PRAC recommended that 'heavy menstrual bleeding' should be added to section 4.8 of the SmPC.

-CLS: based on the data assessed in the stand-alone signal procedure (EPITT 19743), the PRAC recommended update of section 4.4 of the SmPC with a warning concerning CLS (flareup). The signal was closed in the previous reporting interval and hence should not have been included in the above table.

-Amenorhea: the signal assessed in a separate procedure (EPITT 19781) was closed as per the PRAC recommendation dated 10/06/2022, with the recommendation for a followup in the current PSUR.

In the future PSURs, the MAH is requested to reflect the PRAC recommendations in the summary of signals presented. Signals closed in previous reporting intervals should not be presented unless they were reopened during the current interval. In that case the reason for reopening should be clearly stated.

The signal on pemphigus and pemphigoid was assessed in a separate signal procedure (EPITT no.: 19860). During the preliminary assessment of the current PSUR, the PRAC concluded that available evidence was insufficient to demonstrate an association between pemphigoid/pemphigus and Spikevax (dated 14/04/2023). The signal was closed with a followup in the PSUR.

The signal evaluations of these signals will be discussed in the corresponding sections later in this report.

2.2.2. Signal Evaluation

A summary of the results of evaluations of validated signals that were evaluated/re-evaluated and closed (rejected/refuted or considered to be potential or identified risks following evaluation) during the reporting interval is provided below.

Four signals were closed during the reporting period. Based on a scientific evaluation of the available information, three of the closed signals were refuted [IgA nephropathy, Heavy menstrual bleeding (re-evaluation), and Myocarditis and pericarditis (re-evaluation)], and one signal [Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran)] was categorized as a Potential Risk (not important). Two validated signals [Amenorrhea (re-evaluated) and Pemphigus and pemphigoid] were ongoing at the DLP of the reporting period. In addition, one validated signal [CLS (Re-evaluation)], which was closed as a Refuted Signal before the reporting period of this PBRER, but not presented in PBRER#3, is presented here for completeness.

2.2.2.1. IgA Nephropathy

[As per outcome of PSUSA#2, IgA Nephropathy was added as an important potential risk to the PSUR safety concerns. The data submitted on IgA nephropathy is presented and assessed in AR section 2.3.2 New information on important potential risks.]

2.2.2.2. Heavy menstrual bleeding (re-evaluation)

Table 16.3 Heavy menstrual bleeding (re-evaluation)

Signal evaluation criteria	Summary
Source	Heavy Menstrual Bleeding (HMB) was evaluated as a signal based on a trigger from PRAC (EPITT No. 19780) and was refuted as a signal on 30 Mar 2022. A new signal for HMB (re-evaluation) was opened and validated (by default) based on the communication received from PRAC on 13 Jun 2022.
Background	As of 09 Mar 2022, more than 50,000 reports of menstrual changes or unexpected vaginal bleeding following COVID-19 vaccination have been reported through the yellow card surveillance. Similar reports received by the US VAERS. Overall, to date there is no definitive evidence to demonstrate an association between menstrual disorder and vaccination. The basic biology of the menstrual cycle is a complex, coordinated sequence of events. Normal variations exist within women over the lifespan. Menstrual cycle features such as volume, pain and PMS symptoms are subjective 1,2 and data are necessarily collected, in healthcare as well as research, by self-report. Menstrual disorders are very common, as perturbed by environmental factors such as stress, extreme exercise, eating disorders, obesity, and infection. Hypothetical Biological Mechanisms: The relationship between HMB and elasomeran is unclear. Some hypothetical biological mechanisms in the literature include immune response leading to changes in hormones driving the menstrual cycle and endometrial inflammatory response mediated by immune cells in the lining of the uterus and alterations in coagulation system, which is critical component of the endometrial function at menstruation. ACE-2 receptors have been found on the ovarian and endometrial tissue and hence vaccination can hypothetically affect ovarian hormone production and/or the endometrium response at menses.

Methodology	The assessment of HMB in association with the use of elasomeran in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources is described below. • Clinical Trial Data: Two clinical studies (mRNA-1273-P301 and mRNA-1273-P203) sponsored by ModernaTx, Inc. were reviewed using the following MedDRA v 23.0 preferred terms, "Menorrhagia", "Polymenorrhagia", "Menometrorrhagia", "Polymenorrhea", and "Vaginal hemorrhage". • External Databases: VAERS and EudraVigilance Data Analysis System (EVDAS) were reviewed for the PTs: Heavy menstrual bleeding, Menometrorrhagia, and Polymenorrhagia. • Non-clinical: Developmental and reproductive toxicity (DART) studies in pregnant and lactating female Sprague Dawley rats were performed to assess the potential effects of elasomeran on fertility and pre and postnatal. • Review of the Pharmacovigilance Database: Post-marketing data for validated signal of heavy menstrual bleeding events were retrieved from the Company safety database using the following three MedDRA preferred terms: "Heavy menstrual bleeding", "Menometrorrhagia", and "Polymenorrhagia" with a DLP of 18 Jun 2022, using MedDRa version 24.1. • Clinical literature search review: A focused literature search and review was performed using PubMed and Google Scholar databases. Multiple search strategies were used to identify articles related to HMB and COVID-19 vaccines.
Results	Clinical Trial Data: *mRNA-1273-P203 Study with data cut-off of 31 Jan 2022:* In study mRNA-1273-P203, three participants were identified who reported the Treatment Emergent Adverse Events (TEAE) of HMB via unsolicited reporting. All three cases were in the mRNA-1273 arm and two of the three participants had a medical history or use of concomitant medication that provided a plausible alternate explanation for the HMB. The median age of the 3 cases was 13 years (range 13-15). All three cases were considered non-serious, two had recovered and all three cases were assessed as not related to mRNA-1273 by the principal investigator. *mRNA-1273-P301 with data cut-off date of 05 Apr 2022*: In study mRNA-1273-P301, the MAH performed an updated cumulative review using data from Part A, Part B and Part C. Of the 13,252 female participants who received mRNA-1273 primary series in Part A or Part B, 67 female participants were identified using the HMB-specific PTs. They reported the treatment-emergent adverse event of heavy menstrual bleeding via unsolicited reporting. When restricted to female participants of reproductive age (18-55 years), 58 of the 7421 female participants, reported HMB. The

	median age was 44 (range 20-54), 6.9% were postmenopausal, ~76% had other risk factors for HMB, majority of events were non-serious, and recovered or recovering and 8.6% of cases were assessed as related by the principal investigator. External Databases: • VAERS: following are the EB05 observed for these PTs. No Disproportionality was observed: • Heavy menstrual bleeding (EB05: 0.795; N= 2,416) • Menometrorrhagia (EB05: 0.737; N=50) • Polymenorrhagia (EB05: 0.469; N=2) • EVDAS: Disproportionality was observed in the EVDAS database. The ROR for each PT is listed below: • Heavy menstrual bleeding (ROR: 3.76; N=5,242) • Menometrorrhagia (ROR: 2.96; N=219) • Polymenorrhagia (ROR: 1.54; N=6) Non-Clinical Data: No elasomeran-related effects or changes in mating and fertility and ovarian/uterine examinations were observed. Epidemiological studies: Using the spontaneous reported data (DLP of 18 Jun 2022), and the background incidence rate estimated by [9] the observed to expected analyzes was performed. In the observed to expected analysis, there were 5,727 cases of HMB cumulatively (reporting rate of 28.3 per 100,000 person-years). Overall incidence described in Stalhman et al, 2017 was 1009 per 1,00,000 person-year, corresponding to the 204,485 cases expected. The rate ratio was 0.03 (95% CI 0.03, 0.03). Considering demographic subgroups, the rate ratio for all age and gender strata were <= 0.5. Currently, the Observed expected analysis does not support an association between HMB and elasomeran. The sensitivity analysis (assuming 25% and 50% capture of the observed cases) does not change this interpretation). Review of the Pharmacovigilance Database: Cumulatively, as of 18 June 2022, the search criteria yielded a total of 5,791 cases with 6,291 events of which 999 events were serious. Of the 5,791 cases, 1,118 (19.3%) were serious, 647 (11.2%) were medically confirmed and none had a fatal outcome. Cumulatively, majority of the reported events (84.1%; 5,121) were non-serious. Of the 5,791 case reports, 91 cases required hospitalization with no reported intervention. As expected, most cases (84.8%; 4,908) were among women of reproductive age, specifically 18-49 years of age. Only 0.52% (30/5,791) of the total reports received were among adolescents 12-17 years of age. The mean age was 36.7 years, and the median age was 37.0 years (range 0.0 to 81.0). Cumulatively, 96.6% (5,594) of the reports were from regulatory authorities and 3.4% (197) were spontaneously reported to the MAH. Most of the cases were received from the EEA (4,122; 71.2%) and UK (1,088; 18.8%). Cumulatively, when the dose number immediately preceding the event was known, more events were reported after Dose 1 (24.4%) than Dose 2 (20.2%), Dose 3 (8.8%) or Dose 4 (<0.1%). This should be interpreted with caution as the dose number was unknown in almost half (46.6%) of the reported events; and the global vaccine administration/exposure

	data are limited for the various doses. When time to onset and dose number was known, the average Time to Onset (TTO) was 15.3 days (SD: 83.5) and the median TTO was 6.0 days. Cumulative data does not present clustering of cases by dose and TTO; however, it is difficult to interpret the TTO without putting it into context of the menstrual cycle including what phase of menstrual cycle vaccination occurred. **Serious Events of Heavy Menstrual Bleeding:** Cumulatively, there have been 999 serious events of heavy menstrual bleeding-specific PTs reported by 915 serious cases of which 83 cases were medically confirmed, and none had a fatal outcome. Distribution by age, gender, source, and region of origin is similar to the cumulative distribution presented above. Of the 915 serious case reports, 91 (9.9%) cases reported hospitalization with no reported intervention. According to the WHO- Uppsala Monitoring Center (UMC) causality assessment of the 885 serious cases, none was assessed as "Certain or Probable"; although there were case reports with elements of positive rechallenge causality was deemed "Possible" because of the lack of clear biological plausibility, natural background variation in menstrual cycle, lack of evidence of a full resolution of HMB prior to subsequent vaccination in most of the case reports, and incomplete and insufficient information needed to perform a comprehensive case and causality assessment to determine the presence or absence of other plausible alternate explanation(s) for HMB. 8.5% (75) of the 885 cases were assessed as "Possible", 4.4% (39) cases as "Unlikely" and 87.1% (771) were "Unassessable" **Confounders for Heavy Menstrual Bleeding**: Overall, 39.5% (350/885) of the cases had at least one confounder and 47.3% (419/885) had extremely limited information and so the lack or presence of a confounder could not be determined. Given that HMB has many causes, the list of confounders was extensive and included: 1) age >=45 or <18; 2) coagulopathy such as immune thrombocytopenia, von Willebrand's disease, heparin, hemorrhagic diathesis, thrombocytopenia, anticoagulants; 3) infections such as confirmed or suspected COVID-19, endometritis; 4) endocrine causes such as hypothyroidism, Polycystic ovary syndrome, obesity, autoimmune thyroiditis, DM, overweight, autoimmune hypothyroidism, type 1 DM, type 2 DM, Basedow's disease, hyperthyroidism, hyperprolactinemia, pituitary tumor, thyroiditis, breastfeeding, menopausal symptoms indicating perimenopausal status; 5) hormonal therapy such as contraception, hormone replacement therapy, tamoxifen; 6) history of abnormal menses such as HMB; and 7) structural causes such as uterine leiomyoma, adenomyosis, uterine polyp, uterine disorder, endometriosis. **All case reports of rechallenge of heavy menstrual bleeding with subsequent vaccination**: In summary, of the 1,501 (25% [1501/5791]) unique cases reviewed (all cases that reported at least 3 doses of a COVID-19 vaccine, cases coded as positive rechallenge in the database, serious cases), 69 (4.6% [69/1501]) had evidence of recurrence of HMB after subsequent vaccination. However, in the setting of natural variation in the menstrual cycle, high background incidence of HMB, and lack of evidence of a full resolution of HMB prior to subsequent vaccination for most of the cases, it is very difficult to assess whether recurrence of HMB with the subsequent vaccination is truly a positive rechallenge using spontaneous passive reports that have incomplete data regarding gynecological history including baseline menstrual cycle characteristics, medical history, concomitant medications, diagnostic evaluation and results, treatment, and clinical course. Clinical literature search review: A recent systematic literature review by [10] evaluated

Signal evaluation criteria	**Summary**

	14 studies published from Mar 2020 to May 2022; these studies included a total of 78,138 vaccinated female participants and determined that 52% participants reported some form of menstrual change after vaccination. In this analysis, menorrhagia, metrorrhagia, and polymenorrhea were the most commonly observed menstrual change following vaccination and overall, the incidence rate of menstrual abnormalities varied widely from 0.83% to 90.9% across different studies evaluating all types of COVID-19 vaccine. As the authors pointed out, all of the studies were limited by lack of comparator groups and the heterogeneity in cohorts limits the generalizability of the results. These studies cannot establish a causal relationship and support the need for well-designed prospective and longitudinal studies such as ongoing prospective cohort studies that are designed to study heavy menstrual as an outcome after SARS-CoV-2 vaccination (e.g., National Institutes of Health funded studies conducted by Boston University, Harvard Medical School, John's Hopkins University, Michigan State University, and Oregon Health and Science University) (Available at https://www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation). Overall, the literature search does not support a causal link between HMB and COVID-19 vaccines, including elasomeran.
Discussion	This validated signal of HMB was re-evaluated in the context of PRAC request received on 13 Jun 2022. The Global Safety Database (GSDB) was queried including validated, clinical, and spontaneous worldwide cases received from all sources (HCP, regulators, literature, and consumers) reported from the mRNA-1273 vaccine (Moderna COVID-19 vaccine). Overall, the observed to expected ratios for HMB using post-marketing data and expected rates from Europe and the United States do not provide evidence of an association of HMB with elasomeran. The reporting rate was 28.3 per 100,000 person-years. The observed number of cases was lower than the expected number of cases with a rate ratio of 0.03 (95% CI 0.03, 0.03). Among women of reproductive age, all the events and a vast majority (91.4%) of the events of HMB in the P203 and P301 CTs, respectively were non-serious and majority had medical history or concomitant medications that provided alternate explanations for HMB. However, information regarding participants baseline menstrual cycle characteristics are not collected in any of the ongoing ModernaTx, Inc. sponsored CTs and in the setting of expected normal variation of menstrual cycles, it is difficult to interpret data regarding HMB in CT participants without knowledge of baseline menstrual characteristics especially given the lack of a placebo group. There is a geographic disproportion in the origin of reports of heavy menstrual period with majority of reports originating from EEA (71.2%) and UK (18.8%). Of the 915 serious cases reporting HMB, none were assessed as "Certain" or "Probable"; majority of the cases had limited data and missing critical. Consistent with the Netherlands Pharmacovigilance Center Lareb report, evaluation of recurrence of HMB after subsequent vaccination was challenging, and only a small number of reports had sufficient information to make an assessment. Of the 784 cases reporting at least three doses of COVID-19 vaccine, a small percentage (4.8%) reported recurrence of HMB, however in the setting of natural variation in the menstrual cycle, high background incidence of HMB as well as lack of evidence of a full resolution of HMB prior to subsequent vaccination, the data do not support the suggestion that HMB with the subsequent vaccination is truly a positive rechallenge particularly given the incomplete data from spontaneous passive

Signal evaluation criteria	**Summary**

	reports. A focused literature search and review did not provide evidence for causal association between COVID-19 vaccines and HMB. The majority of the studies are cross-sectional and collected information on menstrual irregularities, using unvalidated questionnaires. It was difficult to interpret the results from these studies given that HMB is common and may be caused by a multitude of reasons. Although there have been reports of heavy menstrual bleeding after COVID-19 vaccination, it is important to note that normal variations exist within women over the lifespan and menstrual disturbances are common. Additionally, menstrual cycle features (such as bleeding volume) are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification. Patient self-reports, however, can be inaccurate indicators of the quantity of blood loss. Furthermore, there is no clear biological plausibility; theoretical hypotheses proposed include immune response leading to changes in hormones driving the menstrual cycle and endometrial inflammatory response mediated by immune cells in the lining of uterus. However, to date there is no definitive evidence to demonstrate any causal association between menstrual disorders and vaccination. Furthermore, the published data are not able to determine the frequency with which people experience HMB following elasomeran or determine whether there is a link between elasomeran and HMB; studies were limited due to lack of unvaccinated control group, recruitment of participants retrospectively, use of unvalidated questionnaires, selection, and recall bias. Despite the limitations, findings from these studies were reassuring, the reported changes were small compared to natural variation and quickly reverse. There is also no clear biological plausibility linking elasomeran and HMB; all cases reviewed (clinical trial and post-marketing data) were only temporally associated with elasomeran and a vast majority of them had medical conditions or were on concomitant medications that provided other plausible alternate explanations. Last, the number of reports of menstrual disorders and vaginal bleeding is low in relation to both how common menstrual disorders are and the number of people who have received COVID-19 vaccines to date (as of 18 Jun 2022, worldwide 1,252,320,706 elasomeran doses were distributed and 662,871,167 elasomeran were administered). Of these, 184,939,184 [27.9% of all doses] doses were administered in the women of childbearing potential [12-49 years]). Thus, there is insufficient information to establish a causal relationship between the administration of elasomeran and the development of HMB.
Conclusion	Overall, based on the analysis of all available safety data as of 18 Jun 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran and the development of HMB. No new or emerging safety issue of concern was identified. This health authority validated signal is refuted and no change to the RSI, labeling or RMP is required. The benefit-risk profile of elasomeran continues to be positive and the MAH will continue to monitor events for HMB through routine pharmacovigilance activities.

Rapporteur assessment comment:

The signal on heavy menstrual bleeding was raised in January 2022 and assessed in a separate procedure (EPITT 19780). The signal procedure was concluded during the reporting period of the current PSUR (27 October 2022). "Heavy menstrual bleeding" was recommended by the PRAC to be added to the SmPC section 4.8, with a frequency 'unknown', and correspondingly in the PIL.

In the current PSUR, the MAH included cumulative data on the topic received through 18-Jun-2022, which corresponds to the DLP for the data presented in the above-mentioned signal procedure. No new data was thus presented in the current PSUR that would warrant reassessment of heavy menstrual bleeding.

It is noted that the PRAC recommendation concerning the signal on heavy menstrual bleeding is not reflected in the MAH's signal overview and that the signal has a status 'refuted'. The MAH is again reminded to present signal status in accordance with PRAC recommendations and not only with MAH initial conclusions.

The MAH concluded that they would continue monitoring heavy menstrual bleeding via routine pharmacovigilance. This is endorsed.

2.2.2.3. Myocarditis and pericarditis (re-evaluation)

Table 16.4 Myocarditis and pericarditis (re-evaluation)

Signal evaluation criteria	Summary
Source	Following a request from the Australian's health authority Therapeutics Goods Administration (TGA) to include additional information related to myocarditis and pericarditis in their Package Insert for the elasomeran vaccines, a follow-up signal evaluation was opened to re-evaluate the characterization of the risk of myocarditis/ pericarditis regarding the following: • Have the demographic characteristics of cases of myocarditis/ pericarditis changed or not from the established safety profile. • Has the severity of the cases of myocarditis/ pericarditis changed or not from the established safety profile (e.g., regarding fatal outcomes for reported cases). • Has the clinical presentation of myocarditis/ pericarditis changed or not from the established safety profile (atypical symptoms [e.g., fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough].
Background	After receiving the request from TGA, the Safety and Risk Management Team (SRMT) met on 20 Sep 2022, and concluded: • Important information is missing in the case report provided by the agency, including patient's medical history as well as results for any laboratory test conducted including those for the purpose of identifying any possible viral/bacterial/fungi etiology of the myocarditis. Information related to the first emergency department (ED) visit is also missing and can provide important information. Additionally, there are important confounders in this report that could had contribute to the fatal outcome of this patient. A causal relationship cannot be excluded due to missing information. • The proposed TGA labeling changes will be considered a local Australian variation and do not merit change to the elasomeran CCDS. • The SRMT reviewed and provided edits/comments on the labeling changes proposed by the TGA, which were submitted to the agency. • Independently, the SRMT and labeling committee will review the CCDS to consider any appropriate changes (e.g., update regarding risk with booster doses).
Methodology	The re-evaluation of cases of myocarditis and pericarditis in association with the use of elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran in all patients exposed was performed using the Company's GSDB, and literature. • Review of the Pharmacovigilance Database: The MAH's GSDB was queried as of 18 Sep 2022, for valid case reports of myocarditis and pericarditis received from HCP, HA, consumers, and literature, worldwide, for elasomeran, and for both bivalent vaccines [elasomeran/imelasomeran or elasomeran/davesomeran] using the non-infectious myocarditis/pericarditis MedDRA narrow standardized MedDRA query (SMQ) that contains the following PTs: Autoimmune myocarditis, Autoimmune pericarditis, Carditis, Chronic myocarditis, Eosinophilic myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis, Myocarditis, Myopericarditis, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, and Pleuropericarditis. • Clinical literature search review: Combinations of "Myocarditis/ Pericarditis" AND at least one of mRNA-1273 OR Moderna COVID vaccine OR COVID vaccine OR COVID-19 vaccine OR COVID OR SARS-CoV-2.

Results	Review of the Pharmacovigilance Database: **Have the demographic characteristics of cases of myocarditis/ pericarditis changed from the established safety profile?** • Cumulatively, through 18 Sep 2022, a total of 6,469 cases (6,856 events) reporting myocarditis and/or pericarditis have been received. • Majority of cases involved males (4,292; 66.3%) compared to females (2,031; 31.4%); 146 reports (2.3%) did not include gender data. • Mean age of the patients was 37.3 years (SD 16.6), with a median age of 33 years (min: 7 /max: 94); 639 cases did not report age. • Cumulatively, there were 3,409 cases (52.6%) reporting myocarditis and pericarditis events in patients in the 18 to 39-years-old population group, with 2,572 (75.4%) of those cases occurring in males. • Events continued to occur most frequently after the 2nd dose (1,974; 28.8%). • Regardless of dose number, the greatest proportion of events had an onset of less than 7 days from the time of vaccination (2,381; 65.5%), inclusive of 421 events following a third/booster dose (includes reported 3rd and 4th doses). • The median TTO from most recent dose was 3 days (min: 0/ max: 384). Conclusion: The demographic characteristics of cases of myocarditis/ pericarditis have not changed from the established safety profile. **Has the Severity of the cases of myocarditis/ pericarditis changed from the established safety profile (e.g., regarding fatal outcomes for reported cases)?** • Cumulative, as of 18 Sep 2002, there have been 76 cases (1.2% of all reported myocarditis/pericarditis cases) with fatal outcomes. • There were 69 cases with fatal events of myocarditis and/or pericarditis *excluding seven level 5 (Unlikely) cases according to the Brighton Collaboration case definition. No temporal changes in frequencies were observed. • 3 cases included both myocarditis and pericarditis, or myopericarditis, events • 7 cases involved only pericarditis • 55 cases involved only myocarditis • 4 cases of carditis • 59 medically confirmed cases. • Gender: 49 Males (71.0%), 19 Females (27.5%), 1 Unknown (1.4%) • Age: 19 to 94 (Median: 57 year/ Mean: 55 years) • Median TTO is 5 days (min:0/max:150) • Majority of reports after Dose 2 (26; 40%) Conclusion: The number of reported cases with fatal reports has been constant with some small increases at times when the MAH has received bolus of retrospective reports from different countries. **Has the clinical presentation of myocarditis/ pericarditis changed from the established safety profile (atypical symptoms [e.g., fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough])?**
	Out of the 4,164 cases of Myocarditis/ Myopericarditis reported as of 18 Aug 2022: • There are 3,602 cases (85.5%) of Myocarditis/ Myopericarditis without any of the additional PTs included in the report • There are 562 (13.4%) cases reporting both Myocarditis/ Myopericarditis and at least one of the additional PTs • There are no cases reporting ONLY additional PTs. Conclusion: None of those additional PT was present alone in any of the fatal cases. They were always associated with chest pain, dyspnoea, headaches, etc., which is in agreement with the literature, that has reported that the most commonly reported symptoms of myocarditis are chest pain, fever, dyspnoea, and headaches, followed by chills, and fatigue. Clinical literature search review: No new articles were identified that will support any changes to the safety profile of mRNA-1273 for reports of myocarditis/ pericarditis.

Discussion	The MAH conducted a signal evaluation of the validated signal of re-evaluation of characterization of the risk of myocarditis/ pericarditis after elasomeran vaccines exposure, following a request from TGA to include additional information related to myocarditis and pericarditis in their Package insert (PI). The signal evaluation included a cumulative review of the MAH safety database with a DLP of 18 Sep 2022. Analysis of the data showed that this was a refuted signal based on: • The demographic characteristics of cases of myocarditis/pericarditis have not changed from the established safety profile. • The severity of the cases of myocarditis/ pericarditis has not changed from the established safety profile (e.g., regarding fatal outcomes for reported cases). • The clinical presentation of myocarditis/ pericarditis has not changed from the established safety profile (atypical symptoms [e.g., fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough]).
Conclusion	Based on the findings of the safety assessment regarding a re-evaluation of characterization of the risk of myocarditis/ pericarditis after elasomeran vaccines exposure, the MAH considered that this signal was refuted. Based upon the signal assessment, the changes included in the Australian Package Insert will constitute a local label variation. Therefore, no update of the CCDS is required. The MAH will continue to monitor events of myocarditis and pericarditis using enhanced and routine pharmacovigilance surveillance.

Rapporteur assessment comment:

This signal evaluation follows a request from the Australian health authority.

The overall demographic characteristics of cases of myocarditis/pericarditis are as previously concluded. Predominantly younger males aged 18-39 are affected, TTO commonly within 7 days and by now mostly after 1st and 2nd dose. According to literature presented elsewhere in the AR, it is indicated that the risk is higher after 3rd dose than after 1st but not as high as after 2nd dose.

For the age group of children younger than 12 years of age, the incidence has changed. Previously there have not been any cases reported for this group. In the new review period there are reported 11 cases in this group, demographically 10 of the 11 cases are from Taiwan.

Also, among fatal cases, males are overrepresented, the median age is somewhat higher, TTO approximately unchanged, and regarding diagnosis most cases involved myocarditis.

Regarding outcome, the presented literature introduces negative health outcomes following myocarditis/pericarditis after vaccination. This concerns problems with daily activities, pain and anxiousness/depression, symptoms that are present at least 90 days after onset of myocarditis/pericarditis.

Based on the signal assessment the MAH concluded that no update of the CCDS were required and the changes included in the Australian Package Insert constituted a local label variation.

For further evaluation of new information on the important identified risks myocarditis and pericarditis, including suggested changes to the EU Product Informtion, please see the AR section 2.3.1.

2.2.2.4. Product label confusion leading to underdosing of Bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran)

Table 16.5 Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran)

Signal evaluation criteria	Summary
Source	During the month of Sep 2022, ModernaTx, Inc. became aware of reports of medication errors that were indicating the occurrence of product confusion and product underdosing related to the administration of the bivalent vaccines, elasomeran/imelasomeran and elasomeran/davesomeran. The information came from different sources: From Pharmacovigilance: • ModernaTx, Inc. was notified by MHRA that it has been receiving reports associated with underdosing on individuals receiving the bivalent vaccine • Request from Germany to provide guidance to practitioners who have been calling regarding underdosing of individuals and whether they need to be re-vaccinated • Information from Canada indicating "The vial doesn't say Booster" • From Quality: • ModernaTx, Inc. Quality has received a number of complaints regarding misdosing which is being attributed to the Bivalent labeling. Specifically, the reporters are stating that the label indicates both .25 mL and .50 mL and that it's not clear what the dose should be.
Background	Two different issues were identified according to the countries where the bivalent vaccines are authorized, but all going back to labeling and product confusion. In the United States, • The volume of a booster dose of Moderna COVID-19 Vaccine or elasomeran (COVID-19 Vaccine, mRNA) depends on the presentation • Multiple-dose vial of elasomeran with a red cap and a label with a light blue border - Booster Dose is 0.25 mL • Multiple-dose vial of Moderna COVID-19 Vaccine with a dark blue cap and a label with a purple border - Booster Dose is 0.5 mL. • Adults available Booster dose vials (Original and Bivalent) are multiple-dose vial with a dark blue cap and a label with a purple border or a gray border - Booster Dose is 0.5 mL - Product Confusion • The Bivalent Booster container labeling includes 2 different dosing indications – 0.5 mL or 0.25 mL based on age - Underdose • The 0.25 mL is included for future authorization of the pediatric population • In Europe, Canada and the Rest of the World • elasomeran/imelasomeran launch packaging was prepared in the Spring of 2022, using the WHO nomenclature in effect at that time: 0 (Zero)/O (Omicron). • There is no indication that this is a Booster dose on the carton or vial itself - Product Confusion • There is no mention of dose on the carton or vial itself- Underdose • There are two different vial size (2.5 mL and 5 mL) with no indication of the dose - Product Confusion
Methodology	The assessment of product confusion/ product underdose in association with the use of elasomeran/imelasomeran or elasomeran/davesomeran in all patients exposed was performed using the Company's GSDB. The methods of evaluation used in the analyzed data is described below. There is no clinical data related to use of the bivalent vaccines at the lower dose reported for the underdose cases (0.25 ug instead of 0.5 ug). <u>Review of the Pharmacovigilance Database:</u> A cumulative search in GSDB, through 04 Oct 2022 using the family names mRNA 1273 BIVALENT and mRNA 1273 BIVALENT .222 was conducted using the following search strategies: • Product confusion errors and issues • Family name: mRNA 1273 BIVALENT and mRNA 1273 BIVALENT .222 • High Level Term (HLT): Product confusion errors and issues

	• Underdose • Family Name: mRNA-1273 BIVALENT, mRNA-1273 BIVALENT .222 • PT: Accidental underdose, Incorrect dose administered, Underdose • SMQ Medication errors • Family Name: mRNA-1273 BIVALENT, mRNA-1273 BIVALENT .222 • SMQ Medication errors: Broad.
Results	Review of the Pharmacovigilance Database: **Product confusion errors and issues** • There were 70 cases (71 Events) identified • 66 Medically Confirmed (94.3%) /4 Not Medically Confirmed (5.7%). MC cases were reported mainly by healthcare professionals (Pharmacist, nurses and physicians). • 71.4% of the cases (50) are invalid cases and 28.6% of the cases (20) are valid. The cases are invalid as no patient is involved. • 21.4% of the cases (16) were reported for Batch 200002A. All these cases were reported from the same facility in the UK • Most of the cases from UK reported the following PTs "Accidental underdose, No adverse event, Product label confusion". • Example of reports: "Nurse gave 0.25 mL instead of the 0.5 mL of Spikevax bivalent booster" "It is really confusing on the package that it does not say bivalent" • Proportional Fraction Reporting Ratio of bivalent vs monovalent= 402.62. Interpretation: The PT Product label confusion is reported 402 times higher for bivalent than for monovalent. **Underdose** • There were 327 cases (327 Events) identified using this search strategy • 317 Medically Confirmed (96.9%)/10 Not Medically Confirmed (3.1%). MC cases were reported mainly by healthcare professionals (Pharmacist, nurses and physicians). • 11.9% of the cases (39) are invalid cases and 88.1% of the cases (288) are valid. The cases are invalid as no patient is involved. • 29.4% of the cases (96) were reported for Batch 2000011A. All these cases were reported from the same facility in the UK • Example of reports: "Nurse reported that they had administered autumn Spikevax bivalent dose 0.25 ml instead of full 0.5 ml to patient over 80 (high risk patient). The patient was vaccinated a day prior to this report and no guidance was provided by their HAs regarding dosage errors. • Proportional Fraction Reporting Ratio* (PT Accidental underdose, underdose and incorrect dose administered bivalent vs monovalent) of bivalent vs monovalent= 45.84 Interpretation: These 3 PTs are reported 45.84 times higher for bivalent than for monovalent. **SMQ Medication errors** • There were 502 cases (628 Events) with 3 serious cases – SAE did not include an underdose PT or a product label confusion issue. • 454 Medically Confirmed (90.4%) / 48 Not Medically Confirmed (9.621.7% of the cases (104) are invalid cases and 77.5% of the cases (389) are valid. The cases are invalid as
	no patient is involved. • Proportional Fraction Reporting Ratio (SMQ Medication errors) of bivalent vs monovalent= 5.25 ***Interpretation***: Medication errors in general are reported 5 times higher for bivalent than for monovalent.

Discussion	The MAH conducted a signal evaluation of the potential signal of medication errors due to product confusion and/or product underdosing. The signal evaluation included a cumulative review of the MAH safety database with a DLP of 04 Oct 2022. Analysis of the data showed that medications error reports have been received at a higher proportion for individuals vaccinated with one of the authorized Spikevax bivalent vaccines (relative to elasomeran Original). As of the DLP, the majority of the reports do not contain an ADR that can be classified as heat, alcohol, running and massage to the patient, but it may be too early to detect reported impact (lack of effect and breakthrough COVID-19 infections) of an underdose -Lack of efficacy/ Vaccine Failure. The majority of the reports are associated with label/ packaging confusion/ lack of adequate information in both the carton and the vial label, and the identified medication errors issues affect both elasomeran/imelosomeran, and (with a higher reporting ratio) elasomeran/davesomeran. Given that there are no clinical data related to the use of the bivalent vaccines at a lower dose than the one indicated, no recommendations regarding revaccination of individuals who received an underdose can be provided to HAs.
Conclusion	Based on the findings of the safety assessment evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a Potential Risk (Not Important) and was classified as Priority 1 (Urgent (emerging) Safety Issues: Issues which have a significant impact on the product's benefit-risk profile, and which require the most rapid communication and implementation) and that risk minimization measures needed to be implemented in agreement with the respective HAs in the countries where the bivalent vaccines have been authorized. The MAH will continue to monitor events for potential medication errors related to product confusion and/or product underdose using routine pharmacovigilance surveillance.

Rapporteur assessment comment:

The signal 'Product label confusion leading to underdosing' concerning bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) was raised by the MAH based on medication error reports received from several sources. Due to the difference in dose volume between the monovalent and the bivalent booster (0.25 mL vs 0.5 mL), some of the recipients of the bivalent vaccines might have received only half of the recommended dose.

Cumulatively, the MAH identified 70 cases from the HLT 'Product confusion errors and issues', including 50 cases that did not fulfill requirements for valid ICSRs (no patient reported). Of the 20 valid cases, the majority (16) were reported from the same facility in the UK. In addition, the MAH received 327 cases of underdose, including 96 cases reported from the same facility in the UK.

The MAH did not state whether any cases of vaccination failure were reported among the patients who received only half of the recommended booster dose. The MAH stated it might be too early to detect an impact of the underdosing, such as lack of vaccine effect.

The MAH closed the signal with the conclusion that 'Product label confusion leading to underdosing' should be classified as an identified risk, not important.

The MAH reported the issue to EMA as an ESI (EPITT no.: 19866). Following circulation of the ESI, the member states were advised to check the educational tools they are using in their vaccination sites and decide whether an update of the national procedures/instructions is warranted.

Endorsed.

2.2.2.5. Capillary Leak Syndrome (Re-evaluation)

Table 16.6 Capillary Leak Syndrome (Re-evaluation)

Signal evaluation criteria	Summary
Source	There were multiple triggers for the evaluation of this topic in 2021 as well as in 2022. According to these multiple requests, ModernaTx, Inc. had to perform a cumulative review of CLS following elasomeran and new information if any identified form the cases. The detailed request on the source, can be found under Appendix 4.2e [of the PSUR].
Background	Having considered the available evidence from the ongoing monitoring of this safety topic in the MSSRs and the new case reports from a national database in Italy, the PRAC has recommended that the MAH of elasomeran (Moderna Biotech Spain, S.L) should provide an updated analysis of the association between elasomeran and CLS from all available sources. Based on the review, the MAH should consider whether any precautionary measures are
	considered warranted including an update of the product information and/or the RMP. If warranted, relevant changes to the product information and/or the RMP wording should be submitted. Capillary Leak Syndrome also named Systemic Capillary Leak Syndrome (SCLS) and Clarkson disease is very rare and serious (potentially lethal) [11]. The frequency of episodes can vary widely between patients, with intervals ranging from days to years [11]. The majority of patients have a detectable monoclonal protein in the serum, although the importance of the monoclonal protein in the disease pathogenesis is unclear [11]. Systemic Capillary Leak Syndrome is a diagnosis of exclusion and is often confused with sepsis, angioedema, or anaphylactic shock. Capillary Leak Syndrome are mostly due to viral infections, malignant hematological diseases, inflammatory diseases, treatments such as chemotherapies/anti-tumoral therapies and therapeutic growth factors [12], [13], [14]. The pathophysiology is not fully known, especially on the transient aspect, and it involves a multifactorial endothelial disruption for which mechanisms are still unclear. Damage to endothelial cells causes extravasation of plasma and proteins from the capillaries to the interstitial space, resulting in diffuse edema (mainly in the arms and legs), hypotension, hypoalbuminemia and hemoconcentration [14,15]. A new article was published in Feb 2022 from the EurêClark registry 1, which is an international study group, that gather observations of Monoclonal Gammopathy associated Systemic Capillary Leak Syndrome and prospectively monitor attacks, preventive treatments, complications and outcome of patients. The article mentioned by the PRAC discuss recent reports of first episodes and relapses of Clarkson's disease after receiving any of the COVID-19 vaccines, as well as after infection with SARS-CoV-2. One of the most important points of this article is the burden that the COVID-19 pandemic has brought to patient with Clarkson disease. As the authors mentioned in their article, COVID-19 infection seems to induce very frequently a relapse of Clarkson disease. Another important point noted by the authors was the lack of response to treatment with Intravenous Immunoglobulin (IVIg) to patients infected with COVID-19, including those that may had been asymptomatic, when compared to those that may had experienced a flare temporarily related to the administration to one of the COVID-19 vaccines. The evidence provided in this article only shows that rare disorders like SCLS during conditions like the one we are living today, in which just with elasomeran, as of 31 Dec 2021, more than 500 million people have been vaccinated, continuous surveillance activities need to maintain evaluating the information to becomes available in order to assess any possible associations.
Methodology	The re-assessment of CLS in association with the use of elasomeran in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources is described below: • Clinical Trial Data: PTs Capillary Leak Syndrome and Capillary permeability increased in P301 study. • Review of the Pharmacovigilance Database: 2021-Post-marketing data for potential signal of CLS events were retrieved from the Company safety database using the following MedDRA preferred terms: "Capillary Leak Syndrome and Capillary Permeability Increase" with a DLP of 31 Oct 2021. The term Capillary Leak Syndrome and Capillary Permeability Increase was searched using MedDRA version 24.0. Cases from all sources and relevant literature were reviewed.

	2022-The Company GSDB was queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 Dec 2020 to 31 Dec 2021, worldwide, reported for the elasomeran vaccine (Moderna COVID-19 vaccine Moderna) using the following PTs: Capillary leak syndrome, Capillary permeability increased, and Clarkson disease/syndrome. • Clinical literature search review: A cumulative literature search in PubMed as of 11 Nov 2021 was performed using the following search criteria: (("capillary leak syndrome" [Title/Abstract] OR "capillary permeability increased" [Title/Abstract]) AND "Spikevax"[Title/Abstract]) OR "mRNA-1273" [Title/Abstract] OR ("Moderna"[All Fields] AND "covid19 vaccine"[Title/Abstract])
Results	Clinical Trial Data: No cases with PTs Capillary Leak Syndrome and Capillary permeability increased in P301 study were reported. External Databases: Re-evaluation of information in VAERS as of Dec 2021 did not show disproportionate reporting of events using EB05 > 2 Epidemiological studies: Since SCLS was first characterized in 1960, <500 cases have been described in the medical literature [11]. The typical presentation of CLS associates diffuse severe edema, hypovolemia, hemoconcentration, and hypoalbuminemia [16]. However, this condition is likely under-diagnosed, with possible misclassification as hypotension, edema and/or non-sepsis cardioshock. Formal estimates of incidence are unavailable; however, some sources describe a background rate of one per million, which was applied to estimate expected rates. Six events of CLS and three events of capillary permeability increased (9 events in 8 cases) have been observed (reporting rate 0.05 per 100,000 person-years), which was below the ~16 cases that would be expected for an event occurring at an incidence of 1 per million person-years. Based on the small number of reports to date, stratified analysis is currently largely uninterpretable. Age and age by gender stratified results lack precision, however the occurrence of 1 case in men and 3 cases in women aged 40-49 could be attributable to either chance given small numbers or an increased reporting rate. Review of the Pharmacovigilance Database: 2021: Cumulatively search as of 31 Oct 2021, retrieved 8 cases that were reviewed, and a causality assessment was provided utilizing the WHO-UMC standardized case causality assessment [17]. The majority of cases (7/8) were received from regulatory authorities, and most originated from the EEA (75%), especially 4 cases came from Italy, 1 from Germany, 1 from Spain and 2 from the USA. The majority were in women, 6 cases vs. 2 cases in men. The median age was 46 years-old, the mean was 49 (range from 37 to 64 years). When known (unknown for 4 events), all events of CLS were reported after Dose 2, with a TTO in average of 6.0 days (SD 6.5) and a median of 3.0 days (0 min /14 max). Cases were equally distributed among older ages 40-49 and 50-64 years with 1 case under the age of 40 years. The events duration was in average 4.4 days (SD 5.3) with a median of 4.1 days (0-13). 2022- Cumulatively, through 31 Dec 2021, a total of 9 cases (11 events) of CLS related terms have been reported, with 7 (77.8%) cases medically confirmed. There were 8 serious cases with 1 case with a fatal outcome. The majority of the reports were in females 7 (77.8%) and in patients >50 years of age. Out of the 9 cases, two cases were considered to be a duplicate, i.e., in reference to the same individual ([redacted] [reported in a literature article], and [redacted] [reported by a consumer]), a 46-year-old female with previous medical history of CLS. Based on the updated review of the reported cases with CLS related terms, there were 2 reports that fulfill the Clarkson criteria to be considered confirmed cases of CLS. Both cases were considered possible according to the WHO causality assessment. Both reports will be discussed under ITEM 3 as both reports had previous history of CLS. There were 6 reports that were unassessable according to the Clarkson criteria due to the completed lack of laboratory information; and there was one report that was not considered a case of CLS based on the information provided in the report. According to the WHO causality assessment, there were 2 reports considered possible based on a temporal association as well as some laboratory documentation provided; there were 2 reports considered conditional due to only having some information available in the reports but important information missing; there were 3 reports unassessable due to the

	very little information available; and there were two reports that were considered unlikely related to the vaccine due to some other risk factors and confounders that provided a more plausible explanation for the occurrence of the events. There were two reports of patients identified as having a previous medical history of CLS that experienced a flare of CLS temporarily associated with the administration of elasomeran. Clinical literature search review: Summary: A cumulative search as of 11 Nov 2021 retrieved 361 articles. One article in Jun 2021 describing 3 cases following COVID-19 vaccines: Jansen, Pfizer and elasomeran Articles on Vaxzevria. There was a small number of articles describing CLS and mRNA vaccine and none of these shown any direct temporal association with mRNA vaccines against COVID-19 disease. There are not pathognomonic findings to link vaccine to these AEs. Conclusion: Literature search results did not provide evidence of causal association between mRNA vaccines or elasomeran and CLS.
Discussion	CLS is a serious, well characterized disease. Although rare it is gaining more attention. It is acknowledged that there are no formal estimates of incidence for CLS; thus, it cannot be concluded that observed rate varies from the expected. A cumulative search of GSDB as of 31 Oct 2021, was performed for individuals with medical history of CLS. The search retrieved 8 individuals, after reviewing these 8 cases, 6 were considered CLS. In summary, out of the 8 identified cases, there were 5 cases that were considered as CLS cases; an additional case ([redacted]), although not presenting the hallmarks of CLS, is combined with this CLS cases to a conservative approach because of its fatal outcome. Out of the 6 cases mentioned above with the diagnosis of CLS following elasomeran, 2 did not have a history of CLS and 4 had a history of CLS including the case where the first episode occurred after receiving Vaxzevria; for this case, and based on the reported information it seems the denovo CLS episode is mentioned after Vaxzevria and a flare-up after elasomeran, may be indicating this particular patient's susceptibility to develop CLS, although the potential mechanism of action for the two different vaccines is not known. There is no element in these cases explaining denovo CLS vs. flare-up, except that based on the knowledge of this disease, it is more likely to have recurrent episodes after the initial event, even though the frequency is highly variable between individuals. Re-Evaluation Discussion 2022: SCLS is a rare disorder characterized by episodic increases in vascular permeability resulting in acute losses of protein-rich fluid from the intravascular to the interstitial space. A typical presentation begins with a prodrome of fatigue, dizziness, and flulike symptoms followed by the rapid onset of shock, systemic pitting edema, hemoconcentration, and hypoalbuminemia. All of the diseases causing CLS to share the
	same underlying pathophysiologic abnormality—an increase in capillary permeability to proteins. As a result, there is a loss of protein-rich fluid from the intravascular to the interstitial space. In all cases, hypercytokinemia is believed to be the underlying cause of capillary leak. As of to date there is not a biological explanation that would link elasomeran to the development or flare-up of CLS. As of 31 Dec 2021, an estimated 827,274,740 doses of elasomeran had been distributed; 559,872,937 doses are estimated to have been administered. With 8 reported cases of SCLS in the GSDB, that represents a reporting rate of 0.01 cases of CLS per 1 million doses of elasomeran administered. Analysis of the data reported in the MAH GSDB continues to provide support for a lack of a causal association between CLS and elasomeran. Cumulatively, the reporting rate of CLS for elasomeran is substantially lower than one report per million doses.

Conclusion	Overall, the findings reviewed with respect to elasomeran do not show convincing evidence of a link to CLS, based on the analysis of all the data available regarding the topic of CLS as of 31 Oct 2021, the MAH considers that CLS related events are not presently a safety issue of concern that would justify inclusion of any of these terms in the product information and/or the RMP. The MAH will continue to closely evaluate events of "Capillary Leak Syndrome-related events" using routine surveillance. Based on the re-evaluation of the cases reported for CLS in the MAH's GSDB continues to provide support for a lack of a causal association between CLS and elasomeran. Cumulatively, the reporting rate of CLS for elasomeran is substantially lower than one report per million doses. Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers that CLS related events are not presently a safety issue of concern that require any changes to the product information or the RMP, and the MAH will continue to evaluate events of CLS related events using routine surveillance.

Rapporteur assessment comment:

The association between Spikevax and capillary leak syndrome (CLS) was evaluated in a separate signal procedure (EPITT 19743) carried out during previous reporting intervals. As an outcome of the assessment, CLS (flare-up) was added to the SmPC section 4.4 and correspondingly in the PIL.

In the current PSUR, the MAH presented data on CLS received cumulatively through 31-Dec-2021. It is unclear why the MAH decided to present this signal, given that it has been closed in the previous reporting interval, and the MAH did not present any new data on CLS.

In the previous PSUSA, the PRAC Rapporteur commented on the fact that the MAH did not update the signal evaluation report for CLS with the PRAC recommendation for the amendment of the SmPC. Despite that, the MAH has still not updated the signal evaluation.

The MAH is again reminded to present signal status in accordance with PRAC recommendations and not only with MAH initial conclusions.

The MAH concluded that they would continue monitoring CLS via routine pharmacovigilance. This is endorsed. The MAH should not present this signal in the future PSURs, unless new data becomes available that warrants re-opening of the signal.

2.2.2.6. Amenorrhea

[only source-background-conclusions are presented below. For full signal evaluation report, please refer to the PSUR]

Source: The signal evaluation for Amenorrhea was requested by PRAC, EPITT (19781).

Background: Amenorrhea (absence of menstruation) in a female of reproductive age is related to the disturbance of normal hormonal, physiological mechanism, or female anatomic abnormalities. The normal physiological mechanism works by balancing hormones and providing feedback between the hypothalamus, pituitary, ovaries, and uterus. It can be transient, intermittent or a permanent condition. It is can be classified as primary (defined as absense of menarhce by age 15) or sectondary (defined as absent menstruation for more than three monthrs in females who previously had a regular menstrual ccyles or for more than six months among girls or women who previsouly had irregular menstruation). There are many causes of amenorrhea which can be grouped into the following categories: 1) hypothalamus dysfunction (e.g., functional hypothalamic amenorrhea, brain tumors); 2) pitutiary dysfucntion (e.g., hyperprolactinemia, pitutirary tumors); 3) ovarian dysfunction (e.g., premature ovarian

insufficiency); 3) anatomic abnormalities (e..g intrauterine adhestions, congenital abnormality of mullerian development); 4) other (e.g., pregnancy, polycystic ovarian syndrome, thyroid disorder)

Physiologically, menstruation is controlled by the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, and it works on the pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and these two hormones from the pituitary act on ovaries and ovaries finally make estrogen and progesterone to work on the uterus to carry out the follicular and secretory phase of the menstrual cycle. Prolactin also influences the menstrual cycle as it suppresses the release of LH and FSH form the pituitary. Similarly, thyroid hormone also affects the menstrual cycle; low levels of thyroid hormone stimulate the release of TRH from the hypothalamus, which in turn increases both TSH and prolactin release. This increase in prolactin suppresses the release of LH and FSH through a negative feedback mechanism. Amenorrhea can be caused by any mechanism that disrupts this hypothalamic-pituitary-ovarian axis, whether that it by hormonal imbalance or by disruption of feedback mechanisms. It can also be caused by deviation from the normal anatomy of the reproductive organs of a female.

To date, there is no definitive evidence to demonstrate association between amenorrhea and vaccination and there are no vaccine labels that indicate amenorrhea as an adverse event. Furthermore, there is no clear biological plausibility; theoretical hypotheses proposed include that vaccination may hypothetically affect ovarian hormone production and/or the endometrial response at menstruation through the ACE2 receptors have been found on ovarian and endometrial tissue.

Accumulating discussions on social media indicate that women have reported menstrual changes following COVID-19 vaccination. As of 23 November 2022, a total of 51,695 suspected reactions related to a variety of menstrual disorders following COVID-19 vaccination have been reported through the yellow card surveillance in the United Kingdom. (https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adversereactions/coronavirus-vaccine-summary-of-yellow-card-reporting#annex-1-vaccine-analysisprint; https://eudravigilance.ema.europa.eu/Decommissioned/Decommissioned.html). Similar reports have been received by the US vaccine adverse event reporting system (VAERS).

The basic biology of the menstrual cycle is a complex, coordinated sequence of events. Normal variations exist within women over the lifespan. Menstrual cycle features such as volume, pain and PMS symptoms are subjective and data are necessarily collected, in health care as well as research, by self-report. Menstrual disorders are very common and can be perturbed by environmental factors such as stress, extreme exercise, eating disorders, obesity, and infection.

Conclusions:

This validated signal of amenorrhea was re-evaluated in the context of PRAC request received on 13 June 2022. The global safety database was queried including validated, clinical, and spontaneous worldwide cases received from all sources (HCP, regulators, literature, and consumers) reported for SPIKEVAX (Original) and SPIKEVAX bivalent COVID-19 vaccines.

Overall, the observed to expected ratios for amenorrhea using post-marketing data and expected rates from Europe and the United States do not provide evidence of an association of amenorrhea with SPIKEVAX. The reporting rate was 0.01 per 100 person-years. The observed number of cases was lower than the expected number of cases with a rate ratio of below 0.10. Among women of reproductive age, there were no events of amenorrhea reported in the P203 clinical trial and the 4 events of amenorrhea reported in P301 clinical trial were non-serious and 3 had medical history or concomitant medications that provided alternate explanations for amenorrhea. However, information regarding participants baseline menstrual cycle characteristics are not collected in any of the ongoing Moderna sponsored clinical trials and, it is difficult to interpret data regarding amenorrhea in clinical trial participants without knowledge of baseline menstrual characteristics especially given the lack of a placebo group.

There is a geographic disproportion in the origin of reports of amenorrhea with majority of reports originating from European Economic Area (91.2%) and United Kingdom (3.7%) despite more vaccines have been administered in the United States. There doesn't appear to be any biological basis for the observed geographic distribution; it could be due to the different regional surveillance systems as well as coverage of these symptoms in social media and traditional media which might have prompted respondents to notice and report their own symptoms, possibly similar to previous instances of stimulated reporting of symptoms after vaccination. Of the 340 serious cases reporting amenorrhea, none were assessed as "Certain" or "Probable"; majority of the cases had limited data and missing critical information such as gynecologic history including baseline menstrual characteristics, medical history, concomitant medications, diagnostic evaluation performed for amenorrhea and results, treatment, and clinical course, which are needed for an informed case and causality assessment. Consistent with the Netherlands Pharmacovigilance Centre Lareb report (https://www.lareb.nl/media/dxcjbjmv/signals_2022_covid19-vaccines-and-menstrualdisorders_update.pdf) evaluation of recurrence of amenorrhea after subsequent vaccination was challenging, and only a small number of reports had sufficient information to make an assessment. Of the 375 cases reporting at least three doses of COVID-19 vaccine, a very small percentage (0.8%) reported recurrence of amenorrhea. A focused literature search and review did not provide evidence for causal association between COVID-19 vaccines and amenorrhea. The majority of the studies are cross-sectional and collected information on menstrual irregularities, using unvalidated questionnaires. It is difficult to interpret the results from these studies given that amenorrhea is common and may be caused by a multitude of reasons.

Although there have been reports of amenorrhea after COVID-19 vaccination, it is important to note menstrual disturbances are common. There is insufficient information to establish a causal relationship between the administration of SPIKEVAX (Original) and SPIKEVAX bivalent vaccines and the development of amenorrhea. There is also no clear biological plausibility linking SPIKEVAX (Original) and SPIKEVAX bivalent vaccines and amenorrhea; all cases reviewed (clinical trial and post-marketing data) were only temporally associated and a vast majority of them had medical conditions or were on concomitant medications that provided other plausible alternate explanations.

Furthermore, the published data are not able to determine the frequency with which people experience amenorrhea following a Moderna COVID-19 vaccine or determine whether there is a link between a Moderna COVID-19 vaccines and amenorrhea; studies were limited due to lack of unvaccinated control group, recruitment of participants retrospectively, use of unvalidated questionnaires, selection, and recall bias. Despite the limitations, findings from these studies were reassuring, the reported changes were small and quickly reverse. There is also no clear biological plausibility linking SPIKEVAX (Original) and SPIKEVAX bivalent vaccines and amenorrhea; all cases reviewed (clinical trial and post-marketing data) were only temporally associated and a vast majority of them had medical conditions or were on concomitant Medications that provided other plausible alternate explanations. Last, the number of reports of amenorrhea is low in relation the number of people who have received COVID-19 vaccines to date (as of 17 December 2022, an estimated 1,315,589,716 doses of SPIKEVAX (Original) have been delivered to 91 countries and an estimated total of 772,908,958 doses have been administered, 127,413,973 booster doses of SPIKEVAX Bivalent .214 (Original/BA.1) have been delivered to 41 countries and an estimated total of 70,077,685 doses have been administered, 110,745,780 booster doses of Bivalent .222 (Original/BA.4/5) have been delivered to 25 countries and an estimated total of 60,910,179 doses have been administered. Of the estimated total 912,827,813 administered doses, 215,914,901 [23.7 % of all doses] doses were administered in the women of childbearing potential [12-49 years]). Thus, there is insufficient information to establish a causal relationship between the administration of a Moderna COVID-19 vaccine and the development of amenorrhea.

Overall, based on the analysis of all available safety data as of 17 December 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of SPIKEVAX (Original) and SPIKEVAX bivalent vaccines and the development of amenorrhea. No new or emerging safety issue of concern was identified. This health authority validated signal is refuted and no change to the reference safety information, labeling or risk management plan is required. The benefit risk profile of SPIKEVAX continues to be positive and the MAH will continue to monitor events of amenorrhea through routine pharmacovigilance activities.

Rapporteur assessment comment:

Background

The association between amenorrhea and Spikevax was previously evaluated in a stand-alone signal procedure (EPITT no: 19781). The PRAC concluded that the evidence available at that point was insufficient to demonstrate the association. However, the MAH was requested to present an updated cumulative review on the topic in the current PSUR.

In response to the request, the MAH presented the following data:

Clinical data

The MAH searched two MAH-sponsored clinical trials (mRNA-1273-P301 and mRNA-1273-P203) for relevant cases using the PT 'Amenorrhoea'.

Trial mRNA-1273-P203 investigated safety and efficacy of mRNA-1273 in healthy adolescents ages 12 to < 18 years. The MAH did not state how many of these were female. The MAH stated that no events of treatment-emergent amenorrhea were identified from the trial. The MAH did not provide information on the follow up time nor discussed whether the study was designed to identify amenorrhea.

Study mRNA-1273-P301 was a phase-3 RCT enrolling participants ≥18 years old. As per 05-Apr-2022, 7421 women age 18-55 years old received at least one vaccine dose. The duration of the follow-up ranged from 4 to 618 days (mean=355.40 days (Q1-Q3: 281-427 days)). Exposure in this age group was 7220.96 person-years.

The MAH emphasised that the data from clinical trials is difficult to interpret, given that baseline menstrual data were not collected in the MAH's clinical development program.

The MAH identified four cases of amenorrhea reported from the trial mRNA-1273-P301. These cases concerned women age 41-54 years old; cases were confounded by hormonal therapy or age (>45 years) and all were assessed as 'not related' by the investigator.

O/E analysis

The MAH performed an updated O/E analysis, using the background rates of amenorrhea reported in Pettersson et al. (1973) and the risk window of 21 days post-vaccination.

The O/E rate ratios were below 0.01 in the overall and age-stratified analysis.

Disproportionality analyses

The MAH stated that no disproportionality was observed in the VAERS for the PT 'amenorrhea', as per 23/12/2022.

A signal of disproportionality for the PT 'amenorrhea' was observed in the EVDAS, with the ROR of 2.87 (confidence intervals were not stated by the MAH).

The disproportionality analysis performed by the assessor in EVDAS showed ROR=3.00 (95% CI: 2.89-3.12) with N=2,787 cases reported, as per 22/03/2023.

Post-marketing case reports

Cumulatively, 2,945 cases with 2,992 events of amenorrhea were reported for Spikevax. Of the 2,945 cases, 13.9% were serious, 10.6% were medically confirmed and none had a fatal outcome.

The vast majority of cases (90%; 2,650) concerned women of reproductive age (18-49 years old), with the median age 34 years.

When provided, the average TTO was 14.3 days (SD: 221.6). For the reports with known dose number preceding the event, the majority of events were reported after D2 (22.1%), followed by D1 (19.2%) and D3 (7.6%).

Amenorrhea vs delayed menstruation

The MAH was requested to present in detail serious cases of absent menstruation lasting for at least three months and cases where menstruation was delayed for less than three months, but the outcome was 'not resolved' or 'unknown' at the time of the reporting. The MAH summarised 242 serious cases that were evaluated by the MAH using the FIGO-abnormal uterine bleeding case definition and the WHO-UMC causality assessment (please refer to appendix 2 to the signal report presented in the PSUR). It is unclear to the assessor how many of the 242 case reports fulfilled the clinical definition of amenorrhea.

WHO causality assessment

The MAH stated that, of the 242 serious cases, 157 cases (64.9%) had very limited information and a further 80 cases had at least one confounder present. The confounders included age (>45 years or <18 years), infections (e.g. Covid-19), endocrine causes (e.g. thyroid disorder), PCOS, diabetes mellitus, obesity or overweight, use of hormonal therapy including contraception, history of abnormal menses, menopausal symptoms, pregnancy, breastfeeding and structural causes such as presence of a pelvic mass.

Of the 242 serious case reports, the majority (n=218) were classified by the MAH as WHO-unassessable, 20 as WHO-possible and the remaining four reports were classified as WHO-unlikely. The MAH stated that the reports classified as WHO-possible had, in addition to the temporal association, "at least information on medical history and concomitant medication or results of at least one gynecologic diagnostic evaluation for amenorrhea and one or more confounders". The assessor noted that the 20 possible cases contained very limited information and, in most cases, there seems to be temporal association but medical history and details about the patient's menstrual cycle were missing. Only a few of the WHO-possible reports contained information that the concerned female had regular menstruation before having received Spikevax, were not pregnant and had no apparent conditions that could explain lack of menstruation. However, these cases were reported by consumers and lacked detail with regards to patient's diagnostic evaluation, lifestyle factors and medical history. None of these reports were considered as 'index cases' by the assessor.

Reports with positive re-challenge

The MAH identified three cases with positive re-challenge, all reported by consumers, that were presented in appendix 3 to the MAH's signal evaluation report. These cases were as follows:

- [redacted]: 52F experienced two episodes of amenorrhea and night sweats following Covid-19 vaccination. The first episode started on 06-May-2021, the same day when she had received mRNA vaccine D2 (Comirnaty). The second episode started on 26-Nov-2021, the day after she had received mRNA vaccine D3 (Moderna). According to the narrative, periods returned to normal after three months.

The MAH assessed this case WHO-possible. The assessor classified this case as WHO-unassessable, due

to lack of information about the patient's menstruation cycle (e.g. first date of last menstruation and cycle duration), hormonal profiling to exclude menopause and duration of both episodes of amenorrhea. Given that amenorrhea is defined as lack of menstruation for at least 3 months, the TTO of 0-1 days after vaccination is difficult to interpret. It is unclear whether the woman had not been menstruating for nearly three months before she had received the vaccine or whether she was vaccinated on the day when she was supposed to get her menstruation.

- [redacted]: 35F experienced amenorrhea on 26-Jul-2021. She had received mRNA vaccine D3 (Moderna) on 15-Dec-2021. According to the narrative, she had also experienced amenorrhea after D2 (Comirnaty), but it 'levelled off again'. No more details are provided. Medical history is not provided.

The MAH assessed this case as WHO-possible. The assessor classified the case as WHO-unassessable, due to very scarce information, including unclear temporal relationship (D3 given in Dec-2021, amenorrhea started in Jul-2021).

- [redacted]: 42F experienced amenorrhea (lack of menstruation lasting for 3 months) followed by heavy menstrual bleeding (lasting 3 weeks) after vaccination with D2 Spikevax administered on 26-Jul-2021. On 20-Dec-2021, she received Spikevax D3. As of 07/02/2022, she still did not have her menstruation. According to the narrative, tests showed that she was not pregnant or menopausal; however, no details about the tests are provided.

The MAH assessed this case as WHO-possible. The assessor endorsed the MAH's classification, although the level of detail is low. There seems to be a positive re-challenge, but the case lacks information on medical history, including duration and regularity of the patient's menstruation cycles.

Literature

The MAH performed a literature search in PubMed to identify publications related to amenorrhea and COVID-19 vaccines. The search yielded 243 hits, of which the following six publications were presented by the MAH:

- Netherland PV Center Lareb-Update May 2022 (1): An update on the spontaneous reports of menstrual disorders received by The Netherlands Pharmacovigilance Centre Lareb with the focus on amenorrhea and heavy menstrual bleeding. Of the 24,090 case reports of menstrual disorders received, 4065 reports concerned amenorrhea, including 425 cases reported in Spikevax recipients. The majority of women (79%) had not recovered at the time of reporting. The term 'amenorrhea' was used for absence of menstruation regardless of the duration.

- Zhang et al. (2022) (2): Analysis of reports of menstrual disorders following COVID-19 vaccination reported to VAERs. A total of 14,431 reports of menstrual disorders were included in the study, including 13,118 reports that were associated with COVID-19 vaccine. The ROR was 7.83 (95% CI: 7.39-8.28). The most commonly reported event was 'Menstruation irregular' (4998 reports). Amenorrhea was reported in 1655 cases, including 453 cases of amenorrhea reported in the recipients of Moderna vaccine.

- Rodríguez Quejada et al. (2022) (3): A retrospective survey to collect sociodemographic information and characteristics of the menstrual cycle immediately before and immediately after COVID-19 vaccination. In total, 408 women met the inclusion criteria (e.g. history of normal cycles before COVID-19 vaccination) of which 184 reported alterations in the menstrual cycle in relation to vaccine exposure. The average age of women with alterations in the menstrual cycle was 27 years, the majority (74.6%) had BMI within normal range. Amenorrhea was reported among 17 women, including one vaccinated with the Moderna vaccine.

- Amer et al., (2021) (4): A cross-sectional retrospective survey of 1,434 women of childbearing age (15–50 y) conducted in five Arabic countries in October 2021. Mean age of the participants was 30.4 years (SD 3.9), 45.7% had BMI of 18-<25 kg. Of the 1044 vaccinated participants, 418 (38.5%) reported menstruation changes after having received COVID-19 vaccination, including two vaccinated with Moderna vaccine. Amenorrhea, defined as the absence of three consecutive menstrual cycles during the reproductive years (excluding pregnancy), was reported in 98 (27.8%) of the vaccinated participants.

- Muhaidat, et al. (2022) (5): A cross-sectional online survey targeting females of reproductive age living in the Middle East and North Africa who had received Covid-19 vaccine. A total of 2269 females were included; the majority (>97%) received vaccines from Pfizer, Astra Zeneca and Sinopharm. Almost one-third (35.3%) of the participants experienced menstrual abnormalities during the COVID-19 pandemic but before the vaccination. Post-vaccination, 66.3% participants reported any menstrual abnormalities, including 151 participants who reported that 'menstruation has stopped'. The symptoms resolved within two months in the vast majority (93%) of the participants.

- Mínguez-Esteban, et al. (2022) (6): Spanish cross-sectional retrospective survey of 746 women age 18-45 years old vaccinated with at least two doses of mRNA vaccines (Moderna or Pfizer). 65% of the women perceived changes in their menstrual cycle after being administered the vaccines, irrespective of the type of vaccine or number of doses. Absence of menstrual cycle (duration unspecified) was reported in 95 participants.

MAH's conclusions

The MAH considered available information to be insufficient to establish a causal relationship between the administration of SPIKEVAX (Original) and SPIKEVAX bivalent vaccines and the development of amenorrhea. Thus, the MAH did not propose any changes to the SmPC or RMP.

The MAH did not consider additional pharmacovigilance measures to investigate amenorrhea in the current setting to be feasible. The MAH proposed to continue to monitor the literature and other sources of evidence concerning the potential signal of amenorrhoea with vaccines targeting SARS-CoV-2. The MAH referred to ongoing prospective studies to assess potential effects of COVID-19 vaccination on menstruation, which are funded independently from the work of the MAH (e.g., US National Institutes of Health (NIH)) and conducted by Boston University, Harvard Medical School, Johns Hopkins University, Michigan State University, and Oregon Health and Science University.

Rapporteur's assessment and conclusions

Cumulatively, the MAH identified 2,945 cases of amenorrhea in the recipients of Spikevax. It is unclear how many of these fulfilled the definition of amenorrhea, i.e. lack of menstruation for at least 3 months in women with previously regular menstrual cycles, or at least for 6 months in women with a history of irregular cycles.

The MAH provided summaries of serious and non-serious case reports, which included information on the TTO. However, without the information on cycle duration and date of the previous/expected menstruation, the TTO alone is not very informative. The assessor noted that in several cases amenorrhea started on the day of the vaccination (or the day after), which is hard to interpret given that amenorrhea is defined as lack of menstruation for at least three months.

The MAH did provide an overview of causality assessment of all cumulative case reports. The MAH assessed 218/242 serious cases as WHO-unassessable and 20 cases as WHO-possible. The MAH's causality classification appears to be somewhat random, since the assessor could not identify differences between the reports assessed as WHO-possible and WHO-unassessable. Nevertheless, it is noted that the case reports contained in general very limited information thus the high number of reports classified as WHO-unassessable is not surprising.

The MAH presented three cases with possible re-challenge. However, very limited information was provided in these cases and none were considered by the assessor as an 'index case'.

Overall, it seems that there are several case reports with (apparent) temporal association to vaccination with Spikevax. However, no well-described cases were presented by the MAH that could be classified as 'index cases'.

The MAH presented six studies addressing the association between menstrual disorders (including amenorrhea) and Covid-19 vaccines; two analyses of post-marketing cases reported to pharmacovigilance centres (1-2) and four retrospective online surveys (3-6). These studies suffer from obvious methodological limitations, including lack of controls (non-vaccinated group), recall and selection bias (participants experiencing menstrual irregularities likely more willing to participate in online surveys) and lack of information on the duration of amenorrhea (1,2).

No evidence of increased risk of amenorrhea was identified from the MAH's clinical trials. Four cases of amenorrhea (confounded by concomitant hormonal therapy or age >45 years) were observed in the trial mRNA-1273-P301. However, the MAH stated that information on the pre-vaccination menstrual cycle was not collected in the trial, which could explain why no more cases were observed. As per Apr-2022, the trial included 7421 women of reproductive age who were followed for a mean of app. 350 days, which should be sufficient to capture cases of amenorrhea, given its high background incidence and the fact that the post-marketing cases were reported with an average TTO of 14.3 days (SD: 221.6).

Overall, the PRAC Rapporteur considers that available evidence is currently insufficient to establish a causal association between amenorrhea and Spikevax. The MAH is requested to continue monitoring the topic via routine pharmacovigilance and actively report in the literature section when new information from e.g. the NIH funded studies emerges.

1) signals_2022_covid19-vaccines-and-menstrual-disorders_update.pdf (lareb.nl)

2) Zhang B, et al. COVID-19 vaccine and menstrual conditions in female: data analysis of the Vaccine Adverse Event Reporting System (VAERS). BMC Womens Health. 2022;22(1):403.

3) Rodríguez Quejada L, et al. Menstrual cycle disturbances after COVID-19 vaccination. Women's Health (Lond). 2022;18:17455057221109375.

4) Amer AA, et al. Menstrual changes after COVID-19 vaccination and/or SARS-CoV-2 infection and their demographic, mood, and lifestyle determinants in Arab women of childbearing age, 2021. Front Reprod Health. 2022;4: 4:927211.

5) Muhaidat N, et al. Menstrual Symptoms After COVID-19 Vaccine: A Cross-Sectional Investigation in the MENA Region. Int J Womens Health. 2022;14:395-404.

6) Mínguez-Esteban I, et al. Association between RNAm-Based COVID-19 Vaccines and Permanency of Menstrual Cycle Alterations in Spanish Women: A Cross-Sectional Study. Biology (Basel). 2022;11(11):1579

2.3. Evaluation of new information on risks

2.3.1. New Information on Important Identified Risks

2.3.1.1. Anaphylaxis

Source of the New Information

ModernaTx, Inc's. GSDB was queried for valid, clinical, and spontaneous case reports in children <18 years of age, who reported anaphylactic reactions, received from HCP, HA, consumers, and literature, cumulatively (18 Dec 2020 to 17 Dec 2022) and for the PBRER#4 reporting period (19 Jun 2022 to 17 Dec 2022) for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. An additional evaluation was conducted in individuals >18 years of age that received any of the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran as per request from a health authority.

Background Relevant to the Evaluation

Anaphylaxis, a potentially life-threatening hypersensitivity reaction, can occur after any vaccination. Anaphylaxis may be immunologically or non-immunologically mediated. Most persons recover fully with treatment, but serious complications can occur. Reporting from selected healthcare organizations in the US found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses of vaccines other than elasomeran, administered to both children and adults [18]. Available data suggest a particular patient profile for persons who experience anaphylaxis after vaccination: the vast majority have a history of atopy (history of atopic disease, such as asthma, allergic rhinitis, atopic dermatitis, or food or drug allergy); however, anaphylaxis can occur among persons with no known history of hypersensitivity.

During the reporting period, upon PRAC request Anaphylaxis was removed from the EU-RMP as an important identified risk and reclassified as an identified risk (not important) in the RMP v4.0, approved after the end of the PBRER#3 reporting period, on 23 Jun 2022.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTx, Inc. applied the MedDRA SMQ 'anaphylactic reaction' (narrow scope) to retrieve all cases of AEs suggestive of anaphylaxis from the ModernaTx, Inc. GSDB in children <18 years of age who received elasomeran or any of the bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran. Additional, as per a HA request, cases of anaphylaxis after vaccination with any of the Spikevax bivalent vaccines in individuals >18 years of age were also retrieved for evaluation.

To characterize the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration case definition for Anaphylaxis, which includes levels 1-3 of diagnostic certainty, followed by Level 4 (insufficient evidence to meet any level of diagnostic criteria) and level 5 (not a case of anaphylaxis) (Brighton Collaboration, Anaphylaxis 2021).

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran and anaphylaxis to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d [of the PSUR].

A total of 640 literature articles were retrieved using these search criteria for the review period. The literature search results were medically/scientifically reviewed. Most of the articles described the already known association between anaphylaxis and COVID-19 vaccination, and there were also articles that described the importance of having the 3rd and 4th booster vaccination. Overall, detailed review of the articles does not observe any new and significant safety information concerning this previously well-described AE.

ModernaTx, Inc. Vaccine Hypersensitivity/Anaphylaxis Follow-up Questionnaire with the use of Moderna's COVID-19 vaccine (elasomeran)

The targeted follow-up questionnaire (TFQ) is intended to collect structured information on severe cases of anaphylactic reaction including anaphylaxis.

• During the reporting period of this PBRER, a total of 41 TFQs for Vaccine Hypersensitivity/Anaphylaxis were sent by the MAH, of which no responses were received. The response rate to the questionnaire was 0%.

Following approval of EU-RMP version 4.0, dated 23 Jun 2022, Anaphylaxis was recategorized as identified risk (not important) and therefore ModernaTx, Inc. considers, that follow-up questionnaire measures are no longer necessary. Given the extensive use of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and the experience from clinical practice, anaphylaxis is well characterized, where both, healthcare professionals and individuals are recognized to adhere to the anaphylaxis guidance provided in the SmPC and Product Label. Anaphylaxis is considered to have no longer a considerable impact on the benefit/risk balance of COVID-19 vaccines.

Review of the data does not suggest any new identifiable pattern or trend in reports of anaphylaxis that may differ from the already well known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected, Anaphylaxis

See Appendix 11.3 [of the PSUR] for tables showing observed vs. expected analyzes. In interpretation of these analyses, it is helpful to consider that anaphylaxis is already an identified risk of elasomeran and that reporting rates are higher for women, as has previously been noted [19]. In addition, there has been considerable attention regarding anaphylaxis, and monitoring at the place of vaccination following administration may increase the likelihood of reporting. Moreover, reports identified using the narrow SMQ for 'anaphylactic reaction' may sometimes instead involve other conditions.

Overview of Cases in Children

For more details on anaphylaxis cases please refer to Appendix 11.4 [of the PSUR].

The childhood population is categorized in two different age groups:

• Children less than 12-years-old

• Adolescents 12 to 17 years old

Children <12 years of age (Cumulative to 17 Dec 2022)

Cumulatively there is one case reported in this age group in a 9-month-old child, this case was reported during the reporting period of the current PBRER#4. Details of this case are as follows:

[redacted]: This spontaneous case concerns a 9-month-old female patient with no medical history reported, who the same day after receiving the 1st dose of elasomeran, experienced the event of Anaphylactic reaction. On the same day, patient had dinner which consisted of salmon, shrimp, potatoes and dairy and asparagus, and the patient developed angioedema and hives after dinner; it was also reported that patient had eaten these food items before and did not have any allergies. It was not sure if the anaphylaxis was due to the vaccine or the food that the patient had for dinner. Patient did not have any known allergies. The patient was treated for anaphylaxis with steroids. No further details on clinical course, other lab test results were reported. It is unclear whether the reported age is correct.

MAH Comment: It is unclear whether the reported age is correct. The meal reportedly eaten by the child is inconsistent with that expected for a nine-month-old. In addition, the allergic reaction followed dinner which suggests the food rather than the vaccine was the more likely cause of the angioedema and hives. According to the Brighton Collaboration case definition this case is considered Level 4, and according to the WHO causality assessment is unassessable.

Adolescents 12 to 17 years of age (Cumulative to 17 Dec 2022)

Cumulatively, a total of 21 cases (19 serious, 0 fatal) of anaphylaxis-related events in patients 12 to 17-years-old have been received, which included 21 events, (19 serious events). Eighteen (18) cases were medically confirmed. Of the 21 cases, 9 were male (42.9%) and 12 were female (57.1%) and ranged in age from 12 years of age to 17 years of age (mean: 15.2 [SD:1.6], median: 16.0). One case was reported during the PBRER#4 reporting period, and that person recovered.

All 21 reports were received from regulatory authorities. Reports originated most frequently from Asia (9 cases/42.2%), followed by EEA (6 cases /28.6%), and Latin America (3 cases/ 14.3).

Table 16.7 Case Distribution by Gender and Age in Adolescent Subpopulation elasomeran) – cumulative to 17 Dec 2022

Age Group	Prior to Review Period		Review Period		# Cases	% Cases
	# Cases	% Cases	# Cases	% Cases		
12-15Y	9	45.0	0	0	9	42.9
16-17Y	11	55.0	1	100.0	12	57.1
Grand total	**20**	**100.0**	**1**	**100.0**	**21**	**100.0**

Event distribution by dose number and latency are described in Table 16.8. Cumulatively, of the 10 events with known dosing and event onset information, 8 events (38.1%), occurred the day of vaccination (6 events occurred the day of Dose 1 administration and 2 event occurred the day of Dose 2 administration). Dosing and/or event onset information was unknown or not provided for 11 events (52.4%).

Table 16.8 Event Distribution by Dose Number and Time to Onset in Adolescent Subpopulation - Elasomeran) – Cumulative to 17 Dec 2022

Dose Number	TTO (Days)	Prior to Review Period		Review Period		# Events	% Events
		# Events	% Events	# Events	% Events		
Dose 1	Subtotal	7	35.0	0	0	7	33.3
	0 days	6	30.0	0	0	6	28.6
	14-29	1	5.0	0	0	1	4.8
Dose 2	Subtotal	2	10.0	1	100.0	3	14.3
	0 days	1	5.0	1	100.0	2	9.5
	01-02	1	5.0	0	0	1	4.8
Unknown	Subtotal	11	55.0	0	0	11	52.4
	0 days	6	30.0	0	0	6	28.6
	Missing	5	25.0	0	0	5	23.8
Grand total		**20**	**100.0**	**1**	**100.0**	**21**	**100.0**

Most of the events reported cumulatively had an outcome of recovered/ recovering (15; 71.4%). There have been no fatal cases reported in the adolescents age group (Table 16.9). It should be noted that

there are limitations in capturing follow-up information with spontaneous reports, such that the category of "not recovered/not resolved" may represent an overestimate for this category of outcome.

Table 16.9 Event Distribution by Outcome in Adolescent Subpopulation- elasomeran – Cumulative to 17 Dec 2022

Event Outcome	Prior to Review Period		Review Period		Total # of Events	% of Total Events
	# Events	% Events	# Events	% Events		
Not Recovered/Not Resolved	4	20.0	0	0	4	19.0
Recovered/Resolved	9	45.0	1	100.0	10	47.6
Recovering/Resolving	5	25.0	0	0	5	23.8
Unknown	2	10.0	0	0	2	9.5
Grand total	**20**	**100.0**	**1**	**100.0**	**21**	**100.0**

Appendix 11.4 [of the PSUR] contains the salient clinical information concerning the 21 adolescent cases and one child case < 12 years of age. Brighton Collaboration Anaphylaxis case criteria for the diagnosis of anaphylaxis (Brighton-Anaphylaxis 2021) was applied to the 22 cases to evaluate the strength of the evidence to determine if a case fulfils the definition of anaphylaxis. Causality was assessed for each case using the WHO-UMC causality assessment. Four (4) cases reported a medical history of atopy.

Overall, according to the Brighton Collaboration case definition, of the 22 cases (21 adolescent cases and 1 child case), two cases were classified as Level 1 (definitive cases), there were two cases classified as Level 2 (probable cases), seventeen were classified as Level 4 (fails to meet any level of diagnostic certainty), and there was one (1) case that was classified as Level 5 (Not a case of anaphylaxis).

According to the WHO causality assessment, there were 4 reports assessed as probable given not only the temporal relationship between vaccination and the beginning of the events, but also the lack of related medical history that would explain the occurrence of anaphylaxis. There were 17 reports that were considered unassessable due to the lack of information in those reports, including TTO, as well as clinical course. There was 1 report (classified as Brighton Collaboration Level 5) that was not assessed given that it was a not case of anaphylaxis.

Anaphylaxis After Receiving Booster Dose with Elasomeran/imelasomeran

Overview of Cases of Anaphylaxis in Adults > 18 Years of Age Administered elasomeran/imelasomeran

Cumulatively, 11 cases, all serious, (11 serious events) have been reported in adults 18 years of age or older after administration of elasomeran/imelasomeran all these 11 cases were reported during this reporting period.

Of these 11 cases, 6 were medically confirmed, and 1 case had a fatal outcome. The event outcomes were resolved/resolving in the majority of cases. These cases were reported mostly in females (7; 63.6%), three (27.3%) in males, and one case (9.1%) had missing gender information. The median age was 50.0 years (ranging from 23.0 to 80.0 years). Most of the cases were reported via regulatory authority (6; 54.6%), with four cases (36.4%) reported spontaneously and one case (9.1%) from literature. Cases were reported in Japan (4), the UK (4), the Netherlands (2), and Canada (1).

Evaluation of the 11 reports received after administration of elasomeran/imelasomeran according to the Brighton Collaboration case definition showed that there was one (1) report classified as Level 3 (Possible case), there were 5 reports classified as Level 4 (fails to meet any level of diagnostic certainty), and there were 5 cases that were classified as Level 5 (Not a case of anaphylaxis) based on prolonged TTO of the

reported events (more than 24 hours to 6 days), as well as the reported presentation of the events described for these patients.

According to the WHO causality assessment, there were 2 reports assessed as possible given the temporal relationship between vaccination and the beginning of the events. Both reports are confounded by the individual's medical history, including Asthma; Colitis ulcerative; and Food allergy for one, and Emphysema; DM; and Chronic obstructive pulmonary disease (COPD). There were 4 reports that were unassessable due to the lack of information in those reports, including TTO, as well as clinical course. There were 5 reports (those classified as Brighton Collaboration Level 5) that were not assessed given that they were not cases of anaphylaxis.

There was one report that had a fatal outcome during this reporting period after administration of elasomeran/imelasomeran Information is presented below:

[redacted] **(WWID:** [redacted] **):** Fatal report for a female patient of unknown age who was reported to have experienced anaphylactic shock after vaccination with elasomeran/imelasomeran) (unknown dose number). The patient's medical history is significant for emphysema, COPD, and diabetes. There were no known allergic reactions in the past. Ten minutes after vaccination, the patient had trouble breathing and lost consciousness. Two doses of epinephrine injection were administered with no improvement, and the patient died. The reported cause of death was anaphylactic shock; it is unknown if an autopsy was performed. No further information is available.

MAH comment: The patient rapidly developed relevant symptoms of anaphylactic shock shortly after vaccine administration leading to a fatal outcome. Risk factors included relevant medical history of emphysema and COPD, which may be contributory to the fatal outcome. The causality is assessed as possible as these signs & symptoms may also be of solely cardiac origin without allergic component and the case is classified as Brighton Collaboration criteria Level 3, given the limited information.

Anaphylaxis After Receiving Booster Dose with elasomeran/davesomeran

Cumulatively, 2 cases (both serious and reporting 2 serious events) have been reported in adults 18 years of age or older after administration of elasomeran/davesomeran. Both cases were medically confirmed, reported in female patients, and had resolved at the time of report. There were no cases with a reported fatal outcome.

Evaluation of the 2 reports received after administration of elasomeran/davesomeran according to the Brighton Collaboration case definition showed that there was one (1) report classified as Level 1 (Definitive case), and there was 1 report classified as Level 4 (fails to meet any level of diagnostic certainty).

According to the WHO causality assessment, one report was assessed as probable, and the other reports was unassessable due to the lack of information in the reports, including TTO, as well as clinical course.

Discussion

Review of the data received cumulatively and during the reporting period of this PBRER 4 does not suggest any new identifiable pattern or trend in reports of anaphylaxis in children <18 years of age, that may differ from the already known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

In most of the cases where the relevant information was available, these cases were not suggestive of a typical anaphylactic reaction, instead an important confounder of medical histories of atopy including different types of allergies (food, animals, medicines, etc.) were noted in most of the patients reporting anaphylaxis, indicating that the reported events may be an expression of allergic reactions and not true cases of anaphylaxis.

Additionally, analyzes of cases of anaphylaxis in adults 18 years and over, including the events reported after elasomeran/imelasomeran or elasomeran/davesomeranappear to be generally consistent in nature and severity to those reported with elasomeran. For the case that involved a fatal outcome, the alternative aetiology (emphysema, COPD, and diabetes) presented above also provides a plausible explanation for the fatal outcome.

The MAH will continue to monitor the occurrence of anaphylaxis with elasomeran or elasomeran/imelasomeranand elasomeran/davesomeran via routine pharmacovigilance.

Conclusion

Based on the analysis of all the safety data received during the reporting period and cumulatively, ModernaTx, Inc. considers that cases of anaphylaxis reported in children here in temporal association with the administration of elasomeran did not raise any new safety issues of concern for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cases of anaphylaxis reported in adults >18 years of age after booster vaccines elasomeran/imelasomeran and elasomeran/davesomeran appear to be generally consistent in nature and severity to those reported with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and did not raise any new safety issues of concern.

The available safety data are not suggestive of any new or emerging safety trends. ModernaTx, Inc. will continue to monitor events for anaphylaxis using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH presented both cumulative and interval data on anaphylaxis in section 16.3 of the PSUR. The MAH is reminded that only new (i.e. interval) data on the topics classified as safety concerns should be included in section 16.3. Summary of the cumulative data should be presented as part of risk characterization in section 16.4 of the PSUR. There should be a clear distinction between the interval and cumulative data, allowing to follow the MAH's conclusion concerning the impact of interval data on the known risks.

Interval data

Observed/expected analysis

Based on the number of interval case reports of anaphylaxis (n=252) and the interval exposure of 14,371,224 person-years, the MAH calculated the O/E ratio to 0.05 (95% CI: 0.05-0.06). The overall cumulative O/E was 0.15 (95%CI: 0.14-0.16).

During review of the O/E analyses (overall, age- and sex-stratified analysis, and sensitivity analyses) presented by the MAH in the appendix 11.11 to the PSUR, the assessor noted that the O/E ratios are approximately 10-fold lower than those presented in the previous PSUR. For example, the overall cumulative O/E ratios was 0.15 (95%CI: 0.14-0.16) in the current PSUR vs 1.95 (95%CI: 1.82-2.09) in the previous PSUR. The MAH did not comment on that. It is also noted that the source of background incidence rates used in the O/E analyses differ in the current PSUR (Li et al., 2021*) compared to the previous one (ACESSS ES-Fisabio).

In future PSURs, the MAH is reminded to comment on changes in the approach to data analysis and to explain any unexpected results.

Case reports

During the reporting interval, the MAH received two cases of anaphylaxis in children (<18 years old). The cases are presented in the appendix 11.4c and 11.4d to the PSUR.

During the reporting period, the MAH received 13 cases of anaphylaxis in the recipients of the bivalent vaccines; elasomeran/imelasomeran (n=11) and elasomeran/davesomeran (n=2).

One fatal case was received following vaccination with elasomeran/imelasomeran (case no.: [redacted]). The MAH assessed this case as WHO-possible with the justification that the signs and symptoms might be solely of cardiac origin without allergic component. The Rapporteur disagrees with the MAH's causality. Given the short TTO (10 minutes) and lack of alternative aetiology, the case should be classified as WHO-probable, even though the BC criteria for anaphylaxis are not fulfilled.

No new and significant information was identified from the interval cases presented by the MAH.

Literature

The MAH performed a literature search in PubMed for the interval publications relevant for the risk of anaphylaxis. The search yielded 640 articles; the MAH stated that no new and significant safety information was identified in these articles.

The MAH concluded that review of data concerning anaphylaxis did not identify any new patterns or trends in reports of anaphylaxis. The conclusion is endorsed by the PRAC Rapporteur.

During the reporting period, anaphylaxis was removed from the safety concerns in the RMP (RMP v4.0 approved on 23 June 2022). The MAH emphasized that given the extensive exerience with the use of Spikevax, the risk of anaphylaxis is considered to be well characterised. The risk is also well managed via the guidance provided in the product information. In the view of the MAH, anaphylaxis does no longer have considerable impact on the benefit/risk balance of Spikevax.

The MAH did not state clearly whether they propose to remove 'anaphylaxis' from the safety concerns in the PSUR, in line with the changes to the RMP. Within the current PSUSA, the MAH is requested to clarify whether they proposed to remove 'anaphylaxis' from the safety concerns in the PSUR. If yes, the MAH should provide justification for the proposed change applicable in the context of PSUR.

*Li X, Ostropolets A, Makadia R, Shoaibi A, Rao G, Sena AG, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. Bmj. 2021;373:n1435.

2.3.1.2. Myocarditis/Pericarditis

Source of the New Information

New information presented below includes analysis performed on cases received in the GSDB by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022. An additional request from a health authority was received by the MAH on 07 Feb 2023, regarding the review and discussion on the outcome of myocarditis/pericarditis cases following elasomeran exposure. The health authority requested that the review should include not only case reports, but also any data from (observational) studies and published literature. Additional information was included in the background (Section 16.3.1.2.2 [of the PSUR]) relevant to the evaluation to address the request for inclusion of published literature on this subject.

Background Relevant to the Evaluation

An association between myocarditis and/or pericarditis and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events associated with the administration of COVID-19 mRNA vaccines.

The evolution of SARS-CoV-2 has led to the emergence of antigenically divergent and highly transmissible variants with the potential to circumvent infection-induced as well as vaccination induced immunity [20]. Following the emergence of the Delta (B.1.617.2) variant in Summer 2021, the Omicron variant (B.1.1.529) and omicron subvariants (BA.2, BA.2.12.1, BA.4, BA.5), the most antigenically divergent variants known to date, in Fall/Winter 2021-22 caused the highest COVID-19 incidence rates, even in countries with high vaccination coverage [21] [22,23].

Specifically, an evaluation of COVID-19 incidence in the US over time indicates marked increases during the Delta and Omicron variant waves. With the emergence of the Omicron variant, sevenday moving averages for COVID-19 cases were higher compared to all previous waves with peaks observed in excess of 807,000 and peaks in seven-day hospitalization were higher than 159,000. Deaths during the Omicron wave exceeded those observed during Delta with seven-day moving averages peaking above 2,500 [24]. In parallel, real-world data and epidemiological studies indicated a decreased booster vaccine effectiveness during the Omicron [25] [26] [27].

Of major public health concern is whether immunity to early pandemic strains, developed via vaccination (or natural infection), confers protection against newly circulating variants. Administration of a booster dose of 50 µg at least 6 months after administration of the second of 2 doses of the elasomeran primary series greatly enhanced immune responses compared to pre-boost levels. The Omicron variant is partially evasive of previous immunity conferred by COVID-19 vaccines or a previous SARS-CoV-2 infection, which supports additional vaccine booster recommendations [28].

As a result of this new public health concern, the MAH developed two new bivalent vaccines, one containing elasomeran/imelasomeran and elasomeran/davesomeran. Both bivalent vaccines have been authorized as a booster dose in the UK, Canada, Australia, EEA, among other; and the USA respectively as of the DLP of this report. A total of 127,413,973 booster doses of elasomeran/imelasomeran have been delivered to 41 countries and an estimated total of 70,077,685 doses have been administered. Europe, the UK, Asia, and Canada account for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran have been delivered to 25 countries and an estimated total of 60,910,179 doses have been administered. The United States, Canada, Europe, and Asia account for >99% of all doses delivered and administered.

There have been several relevant publications on the risk of myocarditis associated with COVID-19 mRNA vaccines.

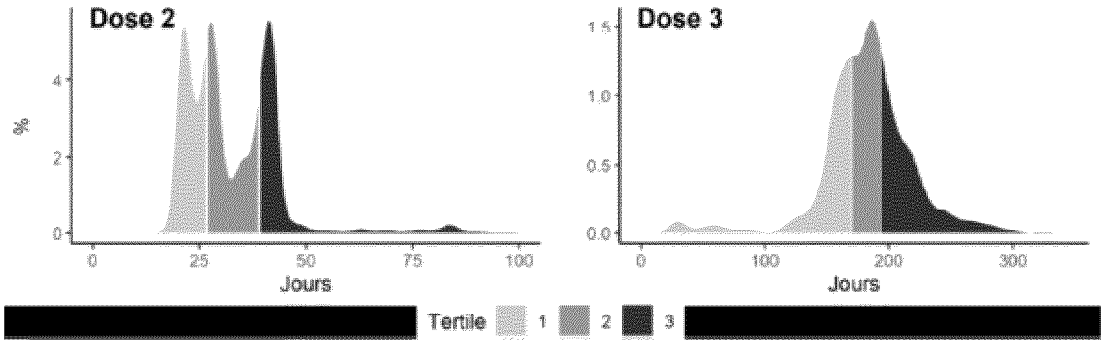
The Epi-Phare group [29] published on 22 Jul 2022, the results of a case-control study using data from the National Health Data System that were linked to national data on COVID-19 vaccination (VAC-SI), as well as screening tests for SARS-CoV-2 (SI-DEP). Cases were defined as all confirmed cases of myocarditis in people aged 12 and over admitted to French hospitals between 27 Dec 2020 and 31 Jan 2022, provided information on the risk for myocarditis associated with a of a third dose of a COVID-19 vaccine, as well as assessing that risk associated with an extended vaccination period (greater than per SmPC) between the 2nd and the 3rd dose (Booster dose) of the vaccine. The authors noted that elasomeran (ModernaTx, Inc.), which had its use suspended on 15 Oct 2021, was made available on 08 Nov 2021, but with use restricted to those aged 30 years and over.

Each case was matched on the date of hospital admission (index date) by age, sex and area of residence to 10 randomly selected controls from the general population (48,900 matched controls). The authors reported 4,890 cases of myocarditis in individuals aged 12 years or older, admitted to French hospitals between 27 Dec 2020 and 31 Jan 2022. The average age of the cases was 39 years old; 72% were male. Individuals aged 50 years and over accounted for 28% of myocarditis cases. The results of the study showed that the risk of myocarditis was increased during the first week following administration of the first, second, and third doses of the BNT162b (Pfizer-BioNTech) and elasomeran (ModernaTx, Inc.)

vaccines. For the BNT162b vaccine, the odds ratios were 1.7 (95% confidence interval [CI], 1.3 to 2.2) for the first dose, 5.9 (95% CI, 5.0 to 7.0) for the second dose, and 3.1 (95% CI, 2.3 to 4.3) for the third dose. For the elasomeran vaccine, the odds ratios were 1.9 (95% CI, 1.1 to 3.5) for the first dose, 19 (95% CI, 14 to 25) for the second dose, and 4.1 (95% CI, 2.5 to 6.6) for the third dose.

To estimate risk associated with the second and third doses, the authors assessed risks according to the time since the previous dose classified into tertiles (<27, 27 to 39, and >39 days for the second dose and <170, 170 to 193, and >193 days for the third dose) (Figure 16-1). For both vaccines, the second and third doses were associated with increased risks of myocarditis regardless of the category of delay since the previous dose. These risks decrease with longer intervals since the previous dose.

Figure 16-1. Distribution of delays between doses of COVID-19 mRNA vaccines



Source: [29].

According to the authors, the excess cases of myocarditis associated with the third dose is globally estimated at 0.25 cases per 100,000 doses of the BNT162b2 vaccine and 0.29 cases per 100,000 doses of the elasomeran vaccine. These rates correspond to one case of myocarditis attributable to vaccination for every 398,000 and 340,000 third doses administered (for BNT162b2 and elasomeran, respectively).

The authors concluded that the risk of myocarditis is increased for the third dose compared with the first dose (first booster dose), although at a lower incidence when compared with the second dose and that myocarditis associated with COVID-19 mRNA vaccines remain infrequent events compared to the number of people exposed. Another conclusion from this study presented by the authors was that the risk of myocarditis decreases with the lengthening of the intervals between each successive dose. "These results help to better characterize the risk of myocarditis associated with mRNA vaccines against COVID-19 and may inform recommendations regarding the administration of booster doses".

During this reporting period, Pasha et al [30] presented information on the evaluation of myocarditis occurring after COVID-19 infection and a subsequent administration of a mRNA COVID-19 vaccine. They concluded that patients with myocarditis secondary to COVID-19 infection may have higher susceptibility to vaccine-related myocarditis, though the mechanism is unclear. The authors hypothesized that the occurrence of myocarditis with COVID-19 infection and recurrence after COVID-19 vaccination could be due to incomplete resolution of primary inflammation. The SARS-CoV-2 virus has a direct effect on the heart by entry into cardiomyocytes through the angiotensin converting enzyme 2 receptors which are upregulated in patients with underlying conditions, including cardiovascular disease and DM. Several studies have reported that viral replication in infected cardiomyocytes leads to cellular edema and necrosis resulting in contractile dysfunction and myocarditis [31]. In patients with prior COVID-19 infection and myocarditis observed following COVID-19 vaccination, it is difficult to establish if the symptoms are a result of a flare-up after vaccine administration due to incomplete infection resolution. The authors recommended increased vigilance and the utility for evaluation with cardiac magnetic

resonance imaging (cMRI) in patients vaccinated with the mRNA COVID-19 vaccine. The cMRI diagnostic criteria for myocarditis are well defined, but the limited availability and increased health-care cost of this diagnostic modality makes this proposal somewhat impractical for general implementation. In most patients, symptoms of myocarditis are mild. Such patients with mild symptoms can be managed with Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and must be instructed to abstain from competitive sports for at least three months, according to the authors.

It is important to note that even though almost all individuals with cases of myocarditis are hospitalized and clinically monitored, most cases follow an uncomplicated clinical course and complete resolution of symptoms is rapidly achieved after receiving only pain management within few days (2 to 4 days). Initial evaluation usually included measurement of troponin level, electrocardiography, echocardiography, and cardiac MRI, which is being recommended as the main modality for confirming the diagnosis of myocarditis since late gadolinium enhancement (LGE) with or without edema in T2-weighted imaging is observed in the majority of patients.

In a recent study [32] conducted at a large pediatric medical center in the US, 16 cases of myopericarditis following COVID-19 mRNA vaccination in patients under 18 years of age, who initially presented from 01 Apr 2021 to 07 Jan 2022, were reviewed with a focus on assessing initial versus follow-up cardiac MRI findings. All cases in the study were associated with receipt of the second dose of the Pfizer COVID-19 mRNA vaccination. All patients included in the study were evaluated by a pediatric cardiologist, underwent ECG, echocardiogram, serial troponin measurements, were admitted for observation with telemetry, underwent cardiac MRI within 1 week of initial presentation and had repeat cardiac MRI at 3-8 months' follow-up The patients' median age was 15 years (range, 12-17 years), were mostly male (n = 15, 94%), White, and non-Hispanic (n = 14, 88%). All patients had chest pain and the most common other presenting symptoms were fever (n = 6, 37.5%) and shortness of breath (n = 6, 37.5%). All patients had elevated serum troponin levels (median 9.15 ng/mL, range 0.65-18.5, normal <0.05 ng/mL), 12 patients had elevated C-reactive protein levels with median value 3.45 mg/dL (range 0-6.5 mg/dL, normal <0.08 mg/dL), 10 (62.5%) patients had an abnormal ECG, with the most common finding being diffuse ST-segment elevation, 2 patients demonstrated mildly reduced Left ventricular (LV) systolic function on echocardiogram (left ventricular ejection fraction [LVEF] of 45% and 53%, normal >55%) with no dilation. No patients had pericardial effusion.

The initial cardiac MRIs were abnormal in all patients; all showed evidence of edema by T2 imaging, and 15 of 16 had LGE in a patchy subepicardial to transmural pattern with predilection for the inferior LV free wall. LV regional wall motion abnormalities were noted in 2 patients. Cardiac MRI LVEF was mildly decreased in 7 patients (median 54%, range 46%-63%). Cardiac MRI global longitudinal strain measurements were abnormal in 12 (75%) patients (median −16.1%, normal <−18%).

On follow-up, abnormal findings persisted on cardiac MRI at follow-up in most patients, albeit with significant improvements (Figure 16-2). Cardiac edema resolved in all but one patient. Eleven patients (68.8%) had persistent LGE, although there was a significant decrease in the quantifiable LGE from the initial study. Cardiac MRI LVEF was significantly improved from initial, with normal LVEF by echocardiogram for all patients, and none of the patients had regional wall motion abnormalities. Global longitudinal strain remained abnormal in most patients (75%) at follow-up. Despite these persistent abnormalities, all patients had rapid clinical improvement and normalization of echocardiographic measures of systolic function. Four patients complained of intermittent chest pain at follow-up with no identifiable abnormality on evaluation; no therapy or intervention was required. No patient received heart failure medication.

Figure 16-2. COVID-19 Vaccine-Associated Myopericarditis Findings in 16 Patients

Diagnostic assessment	Initial, mean ± SD	Follow-up, mean ± SD	*P* value
Echocardiographic LVEF %	59.4 ± 6.0	62.6 ± 2.8	<.05
Electrocardiogram			
Abnormal	10 (62.5%)		
Normal	6 (37.5%)		
Peak serum troponin, ng/mL	9.0 ± 5.2		
Cardiac MRI LVEF %	54.5 ± 5.5	57.7 ± 2.7	<.05
Cardiac MRI LGE % (n = 15[a])	13.5 ± 8.3	7.7 ± 5.7	<.001
Cardiac MRI global longitudinal strain % (n = 15[a])	−16.0 ± 1.7	−16.4 ± 2.1	.5

Additional study observations noted that, of the 3 patients that received IVIg, 1 patient who received IVIg alone and 1 patient who received IVIg plus corticosteroid had resolution of LGE; the other had persistence of LGE. Eight patients (5 of whom had persistent LGE) underwent additional 24-hour cardiac rhythm monitoring and 6 patients with persistent LGE underwent exercise tests, all of which were normal.

In conclusion, the authors suggested that the persistence of LGE and abnormal global longitudinal strain warranted further follow-up assessment and larger multicenter studies to determine the ultimate clinical significance of these abnormalities in patients with post–COVID-19 vaccine myopericarditis. One of the big limitations of this study is the total number of patients reported (16) which is very small and limit the ability to draw conclusions about the effect of treatment modalities or to generalize regarding outcomes of vaccine-associated myopericarditis.

In a systemic review study conducted by Woo et al [33], the authors aimed to study previously published case reports and case series associated with COVID-19 mRNA vaccine-related myocarditis and investigate the risk factors related to clinical outcomes. The authors conducted the search on PubMed/Medline, EPub, Scopus, Embase, and Web of Science databases, that include all articles available on patients with COVID19 mRNA vaccine-associated myocarditis published up to 25 Aug 2021. There were 24 studies identified with myocarditis related to immunization with mRNA (BNT162b2 or mRNA-1273) COVID-19 vaccines. Data was collected based on demographic and clinical characteristics, including information on treatments, outcomes, age, sex, onset of symptoms, pre-existing conditions, laboratory results, immunologic assays, results of electrocardiography and echocardiogram, as well as radiological findings of cMRI, and finally, the length of hospitalization, length of ICU stay, and mortality.

There were 74 patients with myocarditis within the age of 14-40 years old, 49.5% of them were younger than 20 years. Almost all patients (70) were male, and seven patients (9.5%) had underlying medical conditions such as hypertension, diabetes, hyperlipidemia, or endocrinologic disorder. All patients recovered without significant complications, with a third (35.1%) of the patients' symptoms resolving with conservative management. Among the remaining patients, more than half (54.0%) received anti-inflammatory medications such as NSAIDs, colchicine, steroids, or intravenous immunoglobulin. In addition, 16.2% of them were treated with heart failure medications, including beta-blockers, ACE inhibitors/angiotensin-receptor-blocker, diuretics, or inotropic. About 5% of patients (n = 4) experienced complications, including one major (multi-organ failure) and three minor cases (non-sustained ventricular tachycardia).

Twelve patients (16.2%) required ICU care, and about half (43.2%) of the patients were discharged within 4 days. Over two-thirds (78.3%) of patients received the BNT162b2 vaccine, and most (90.5%)

patients presented with myocarditis after the second dose of the vaccine. Patients presented to the hospital from 6 h to 16 days after vaccination, with a median time from vaccination of 3 days.

Most patients presented with chest pain (95.9%), accompanied with fever (33.8%), dyspnea (21.6%), headache (14.9%), fatigue (10.8%), and chills (5.4%). Over two-thirds (87.8%) of patients had abnormal ECG findings: ST-segment (77.0%), T-wave (16.2%), and PR interval (14.9%). Echocardiography revealed that about a third (31.1%) of patients had LF dysfunction (ejection fraction <55%) and 21 patients had regional wall motion abnormality. In regard to laboratory tests, all 74 patients showed elevated levels of cardiac enzymes, 64 (86.4%) patients had high levels of C-reactive protein, and 12 (16.2%) patients had a high level of brain natriuretic peptides (BNP), pro-BNP, or NT-pro-BNP. Most patients (79.7%) underwent cMRI studies in hospitals, and 40 of 59 patients (67.8%) had CMR findings suggesting myocarditis, which met the original or modified Lake Louise criteria.

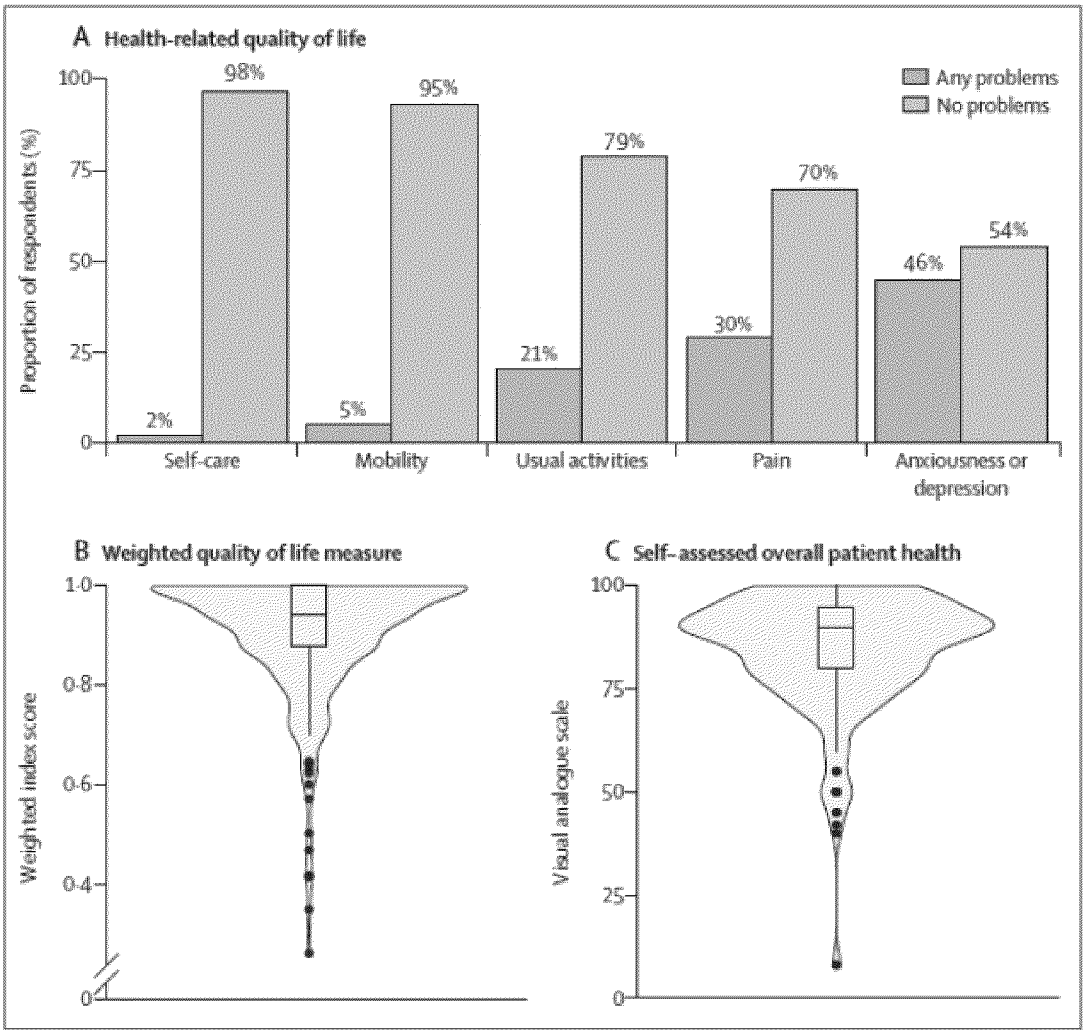
Overall, the study showed that the clinical course of the patients was favorable without mortality, and one-third of patients resolved with conservative care alone, and according to the authors the risk of fatality in myocarditis subjected to mRNA vaccination seems to be low [33].

An ongoing follow-up surveillance study [34], conducted by the Centers for Disease Control and Prevention (CDC) included surveys in US individuals aged 12–29 years with myocarditis after mRNA COVID-19 vaccination, for whom a report had been filed to the VAERS between 12 Jan 2021 and 05 Nov 2021. A two-component survey was administered, one component to patients (or parents or guardians) and one component to health-care providers, to assess patient outcomes at least 90 days since myocarditis onset. Data collected were recovery status, cardiac testing, and functional status, and EuroQol health-related quality-of-life measures (dichotomised as no problems or any problems), and a weighted quality-of-life measure, ranging from 0 to 1 (full health). The EuroQol results were compared with published results in US populations (aged 18–24 years) from before and early on in the COVID-19 pandemic. Between 24 Aug 2021, and 12 Jan 2022, the authors collected information for 519 (62%) of 836 eligible patients who were at least 90 days post-myocarditis onset: 126 patients via patient survey only, 162 patients via healthcare provider survey only, and 231 patients via both surveys. Median patient age was 17 years (Interquartile range [IQR] 15–22); 457 (88%) patients were male and 61 (12%) were female. 320 (81%) of 393 patients with a health-care provider assessment were considered recovered from myocarditis by their health-care provider, although at the last health-care provider follow-up, 104 (26%) of 393 patients were prescribed daily medication related to myocarditis.

Of 249 individuals who completed the quality-of-life portion of the patient survey, four (2%) reported problems with self-care, 13 (5%) with mobility, 49 (20%) with performing usual activities, 74 (30%) with pain, and 114 (46%) with depression. Mean weighted quality-of-life measure (0.91 [SD 0.13]) was similar to a pre-pandemic US population value (0.92 [0.13]) and significantly higher than an early pandemic US population value (0.75 [0.28]; p<0.0001) (Figure 16-3).

Most patients had improvements in cardiac diagnostic marker and testing data at follow-up, including normal or back-to-baseline troponin concentrations (181 [91%] of 200 patients with available data), echocardiograms (262 [94%] of 279 patients), electrocardiograms (240 [77%] of 311 patients), exercise stress testing (94 [90%] of 104 patients), and ambulatory rhythm monitoring (86 [90%] of 96 patients). An abnormality was noted among 81 (54%) of 151 patients with follow-up cardiac MRI; however, evidence of myocarditis suggested by the presence of both LGE and oedema on cardiac MRI was uncommon (20 [13%] of 151 patients). At follow-up, most patients were cleared for all physical activity (268 [68%] of 393 patients).

Figure 16-3. Self-Assessment of Health-Related Quality-of-Life Among Patients with Myocarditis After mRNA COVID-19 Vaccination



Source: [34].
(A) Bar plot of health-related quality-of-life among patients. Patients were administered the EuroQol 5-dimension 5-severity level questionnaire; for analysis, the five health-related dimensions were dichotomised into the frequency of problems (severity levels 2–5) and no problems (level 1). (B) Violin plot of weighted quality-of-life measure converted from each patient health profile from (A) to an index score between 1 (perfect health) and 0 (equivalent to death). (C) Violin plot of patient self-assessed overall health on a scale from 0 to 100 (with 100 representing best possible health and 0 representing the worst possible health). The denominator for the EuroQol questionnaire was 249 respondents. In the violin plots (B, C), the limits of the boxes denote IQR, and the horizontal line denotes median values. Whisker endpoints are equal to the maximum and minimum values below or above the median plus or minus 1·5 times the IQR. The width of the outer shape around the box plots indicates the probability density of values or responses with a given result.

Despite clinical improvements and normalization of most diagnostic test results, as noted by health-care providers, half of patients (178/357) surveyed continued to report at least one symptom potentially associated with myocarditis after COVID-19 vaccination. One possible explanation for the persistence of symptoms is that approximately 50% of patients reported depression or anxiety, conditions that can manifest as symptoms associated with myocarditis, such as chest pain or palpitations [35]. According to the authors, the significance of the cMRI findings among the subset of patients who received cardiac imaging is unclear. Evidence of ongoing myocarditis on followup cMRIs based on modified Lake Louise criteria was uncommon. However, consistent with the few published case series of myocarditis after mRNA COVID-19 vaccination, the authors observed that nearly half of patients (71/151) with follow-up cardiac MRIs had residual late gadolinium enhancement, suggestive of myocardial scarring. In this study

the authors did not note the degree of LGE identified during follow-up, but a recent study that assessed serial cardiac MRIs in patients younger than 19 years with myo-carditis after COVID-19 vaccination and persistent LGE showed improvement over time [36].

In a small subset of patients, initial cardiac imaging at diagnosis was normal but follow-up imaging was abnormal. It is possible that clinical findings in these patients continued to evolve after diagnosis. According to the authors, another possibility is that the initial and follow-up imaging results were evaluated by different health-care providers, who had varying interpretations. In previous studies during the pre-COVID era, cardiac scarring related to myocarditis on follow-up MRI was not uncommon, yet its clinical significance has remained controversial.

This study has several limitations including the fact that for the follow-up evaluation could be conducted by different providers and given the absence of clear clinical practice guidelines for the outpatient follow-up of myocarditis, comparing clinical course among patients could be challenging, especially as the authors mentioned no common standard level of care. The authors recognized substantial heterogeneity in the initial evaluation and follow-up of patients, particularly in the cardiac diagnostic imaging received. Current guidelines recommend restricting patients with myocarditis (eg, athletes) from competitive sports for 3–6 months, although it was noted some variability among health-care providers in clearing patients for a return to all physical activity.

A very important limitation in this study is the passive (or spontaneous) nature of VAERS reporting [37]. Some US cases of myocarditis associated with mRNA COVID-19 vaccination will not have been reported; however, it is unclear how cases reported or not reported initially to VAERS could differ. Selection bias is a possible limitation in any survey activity.

Additionally, the authors relied on health-care provider reports for all diagnostic data results. Unlike prospective studies, they did not have access to central interpretation of tests (eg, electro-cardiograms, echocardiograms, and cardiac MRIs). Although this limitation probably introduces some variability into the findings, it also reflects real-world practice and data appeared not to be missing at random. A fifth limitation is the absence of a control group for the analysis of patient symptoms. Control groups are important for contextualizing symptoms.

Although no pre-myocarditis measures were available for the group of patients with myocarditis, the authors found that quality-of-life measures among those with COVID-19 vaccine-associated myocarditis at follow-up were similar to or better than those of contemporary populations studied before or early in the pandemic.

The authors concluded that after at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination, 81% of patients were considered recovered by their health-care provider. At the time of follow-up, these patients reported quality-of-life measures similar to pre-pandemic reports among individuals of similar ages in the USA. 50% of patients reported at least one symptom at follow-up. Among a subset of 151 patients who had follow-up cardiac MRI results, 54% had an abnormal finding. The CDC is conducting additional follow-up on patients who were not considered recovered at least 12 months since symptom onset, to better understand their longer-term outcomes.

A population-based surveillance study [38] was conducted that included persons aged 18–39 years who were members of integrated health-care organizations within the Vaccine Safety Datalink (VSD) and vaccinated with mRNA vaccines manufactured by either of the MAHs. The study population was limited to 18–39-year-olds because these ages have previously been associated with an increased risk for myocarditis and pericarditis following vaccination and both BNT162b2 and elasomeran vaccines are authorized or approved in this age group. The purpose of the study was to estimate the incidence of myocarditis/pericarditis during days 0 to 7 after mRNA vaccination by age (5-39 years old), sex, dose number, and product. All identified potential cases underwent medical record review which verified the

diagnosis, assessed timing of symptom onset (which resulted in some onsets shifting to day 0, post-vaccination), and collected clinical details about the event. Cases not meeting CDC case definitions for myocarditis or pericarditis were excluded. Results from the study showed the following findings:

• From 14 Dec 2020 through 31 May 2022 (persons 18–39 years) and 20 Aug 2022 (persons 5–17 years), there were 320 potential and 224 verified cases of myocarditis/pericarditis identified 1 to 98 days after 6,992,340 vaccine doses as part of primary series COVID-19 vaccination.

• Of these 224 verified cases, 137 (61%) occurred 0 to 7 days after vaccination; 18 were after the first dose (of 3,562,311 doses administered) and 119 were after the second dose (of 3,430,029 doses administered).

• In these age groups, incidence per million doses 0 to 7 days after vaccination was numerically higher in male than in female persons and after Dose 2, although CIs were wide and overlapped across sex for some age groups. Incidence was highest for male adolescents ages 12 to 15 years and 16 to 17 years following Dose 2.

• From 24 Sep 2021 through 20 Aug 2022, 101 potential cases of myocarditis/pericarditis were identified 1 to 98 days after 1,848,723 first booster doses, with 77 (76%) verified with a median onset of 4.5 days after vaccination; 39 cases (51%) were verified in the first week versus 38 cases during the subsequent 13 weeks.

• In all age groups, incidence 0 to 7 days after first booster was higher for male compared to female persons, with adolescent males having the highest incidence in 16 to 17-year-olds and in 12 to 15-year-olds. In adults for whom both vaccine products were available, postbooster incidence was higher in male than female adults and higher in males aged 18 to 29 years compared to males aged 30 to 39 years.

Important strengths of the study included that information was obtained through active surveillance of a large diverse population and by verification of cases through medical record review and physician adjudication. Important limitations include the lack of a control group and precluding causal inference. Cases were also identified only in emergency or inpatient settings using myocarditis/pericarditis–specific International Classification of Disease-10 codes. Thus, cases were not identified if they were seen only in outpatient settings or if they received lessspecific diagnosis codes such as chest pain (R07.9). Further limitations included the possibility of reporting and ascertainment bias, potential differences between individuals who received ModernaTx, Inc. versus Pfizer vaccines and underreporting of SARS-CoV-2 infection.

Even though myocarditis and pericarditis have been reported more frequently than expected, mainly in male adolescents and young adults, following receipt of the mRNA vaccines [BNT162b2 (Pfizer COVID-19 vaccine) and elasomeran (ModernaTx, Inc. COVID-19 vaccine)], it is important to note that cases have also been reported in NVX-CoV2373 (Novavax COVID-19 vaccine, a protein subunit vaccine) recipients during the phase 3 trials as well as in their postauthorization safety data. These observations strongly suggest that the risk for myocarditis and pericarditis is not specific to the mRNA platform but is related to the spike protein antigens.

A prominent hypothesis for myocarditis after infection and in rare cases after vaccination is that it is mediated by circulating Spike or Spike-S1 protein, and the interaction of that protein with tissues and antigen-experienced immunity. A prospective pilot study of 13 healthcare workers [39] for 18 years and older, with no known history of SARS-CoV-2 infection was conducted from Dec 2020 to Mar 2021, with the objective of providing evidence that circulating SARS-CoV-2 proteins are present in the plasma of participants vaccinated with the elasomeran vaccine. Plasma was collected from 13 participants at 10-13 timepoints between 1 and 29 days after the first injection and 1-28 days after the second injection. Temporal profiling of SARS-CoV-2 antigens and antibodies were acquired using Ultrasensitive single-

molecule array (Simoa) assays providing data on 15 markers to monitor antigen production and immune responses on each participant. Results of the study showed that after the first 100 µg dose, the elasomeran vaccine produced detectable levels of S1 antigen in plasma in 11 participants and spike antigen was detected in three of 13 participants. Nucleocapsid antigen was undetectable or at background levels in all participants after both injections. S1 antigen was detected as early as day one post-vaccination and peak levels were detected on average five days after the first injection. S1 antigen in all participants declined and became undetectable by day 14. After the second vaccine dose, no S1 antigen or spike was detectable, and both antigens remained undetectable through day 56. Out of the 13 healthcare workers, 11 participants had S1 antigen isolated from plasma after the first injection, while nucleocapsid concentrations were insignificant in all participants, confirming that the detected S1 antigen originates from vaccination and not natural infection. The authors concluded that the presence of S1 antigen was likely due to the nature of the encoded mRNA-1273 spike protein, which contains a cleavable S1-S2 site and enables release of S1 protein from the spike trimer. They hypothesize that release of S1 protein could result from cleavage via mammalian cell proteases or circulating proteases. The authors observed an increase in S1 antigen over an initial period of one to five days, suggesting that mRNA translation begins immediately after vaccine inoculation. Interestingly, spike protein appears in three of thirteen participants on average eight days after S1 antigen is produced.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran and myocarditis and pericarditis to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 11.5.

A total of 197 literature articles were retrieved using these search criteria. These literature search results were medically/scientifically reviewed and are discussed above, under section Background Relevant to the Evaluation. There was no additional published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

GSDB

During this PBRER reporting period the ModernaTx, Inc. was queried for valid case reports of myocarditis and pericarditis received from HCP, HA, consumers, and literature for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The MAH used the non-infectious myocarditis/pericarditis MedDRA narrow SMQ that contains the following PTs: Autoimmune myocarditis, Autoimmune pericarditis, Carditis, Chronic myocarditis, Eosinophilic myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis, Myocarditis, Myopericarditis, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, Pleuropericarditis.

To characterize the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration Myocarditis/Pericarditis case definition [40] [41][42].

• Level 1 (Definitive case)

• Level 2 (Probable case)

• Level 3 (Possible case)

• Level 4 is a reported event of myocarditis/pericarditis with insufficient evidence to meet level 1, 2 or 3 of the case definitions

• Level 5 (Not a case of Myocarditis/Pericarditis)

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case (of myocarditis or pericarditis). It is not used to ascertain causality.

The CDC working case definition [43] was used to characterize acute myocarditis and acute pericarditis cases, and was used for medical review of reports identified during this reporting period (19 Jun 2022 to 17 Dec 2022):

• Acute Myocarditis

• Probable

• Confirmed

• Acute Pericarditis

Myopericarditis (This term was used for patients meeting criteria for both Myocarditis and Pericarditis)

Similar to the Brighton definition, the CDC definition identifies the strength of the evidence to support a diagnosis of myocarditis and/or pericarditis. It is not intended to be used for causality assessment. It was established for the purpose of identifying cases observed following receipt of a COVID-19 vaccine.

In contrast, causality assessment (i.e., characterizing the likelihood that a case of myocarditis/pericarditis was attributable to vaccine exposure) was conducted utilizing the WHO-UMC standardized case causality assessment [17].

Further evaluation was conducted in the segment of the reported cases involving patients that were considered (based on epidemiologic characteristics) to be at potentially higher risk for having events of myocarditis and/or pericarditis. This evaluation was conducted in males and females younger than 40 years of age, after the 2nd dose of elasomeran, regardless of the TTO of the events from the administration of the vaccine. An additional, focused evaluation was conducted on all reports involving patients <18 years of age, as well as those who received a 3rd dose or a booster dose.

ModernaTx, Inc. Supplemental Follow-up Questions for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna COVID-19 vaccines (elasomeran, elasomeran/imelasomern, elasomeran/davesomeran)

• During the reporting period of this PBRER a total of 327 TFQs for Myocarditis/Pericarditis were sent by the MAH, of which 9 TFQ responses were received. The response rate to this questionnaire was 3%.

• This very low response rate may be an indicator of the reporter's difficulties to address all the requested follow-up information. It is also important to note that as myocarditis and pericarditis are considered important identified risks for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, respondents may consider that the additional information that is been requested will not provide any new additional information or value to a risk that is already known.

• A low response rate can be due to sampling bias if the nonresponse is unequal among the participants regarding exposure and/or outcome. It also undermines the ability of the collected data and in turn, dilute the reliability of the results, especially when the main purpose of this questionnaire is to collect follow-up information that would allow a better characterization of reports of myocarditis/ pericarditis.

• Given the low response rate, ModernaTx, Inc. concludes that the questionnaire for Potential cases of Myocarditis/ Pericarditis after vaccination with elasomeran is not adequate to collect follow-up information

needed for further characterization of these 2 important identified risks. In order to improve the response rate, the questionnaire may need to be simplified and focused on essential information. ModernaTx, Inc. will evaluate and streamline the information requested within the current questionnaire to try to improve response rate by looking at the type of questions asked, the length of the questionnaire, changing from a written response document to maybe a digital approach, among others.

The MAH would like to note that myocarditis and pericarditis are very complex medical entities, as such, follow-up on cases from spontaneous reporting might not be adequate to characterize these important identified risks. The additional pharmacovigilance activities described in the current approved EU- RMP (v6.3) such as the ongoing clinical studies (mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, and 20-0003) as well as ongoing post-authorization safety studies (mRNA-P903, mRNA-1273-P904), the planned specific study mRNA-1273-P910 (Natural history and clinical outcomes of vaccine-associated myocarditis) and an ongoing study mRNA-1273-P911 (Long-term outcomes of myocarditis following administration of Spikevax) would probably bring more relevant information.

Based on the analysis of all the safety data available as of 17 Dec 2022, the MAH considers cases included under the AESI of myocarditis and pericarditis to be consistent with the well-known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for elasomeran far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected

See Appendix 11.3.

Overview of Cases

Myocarditis and Pericarditis (Cumulative to 17 Dec 2022)

Cumulatively, through 17 Dec 2022, a total of 6,702 cases (7,102 events) of myocarditis and pericarditis have been received for all the elasomeran vaccines, including the bivalents. Out of those, 6,677 cases (7,076 events; 6,843 serious events) of myocarditis and/or pericarditis have been reported for elasomeran only, with 4,704 (70.5%) cases medically confirmed. There were 82 cases (85 events) with fatal outcomes.

Table 16.10 Number and Percentage of Reported Cases of Myocarditis and Pericarditis for Elasomeran, Elasomeran/Imelasomeran and Elasomeran/Davesomeran – Cumulative as of 17 Dec 2022

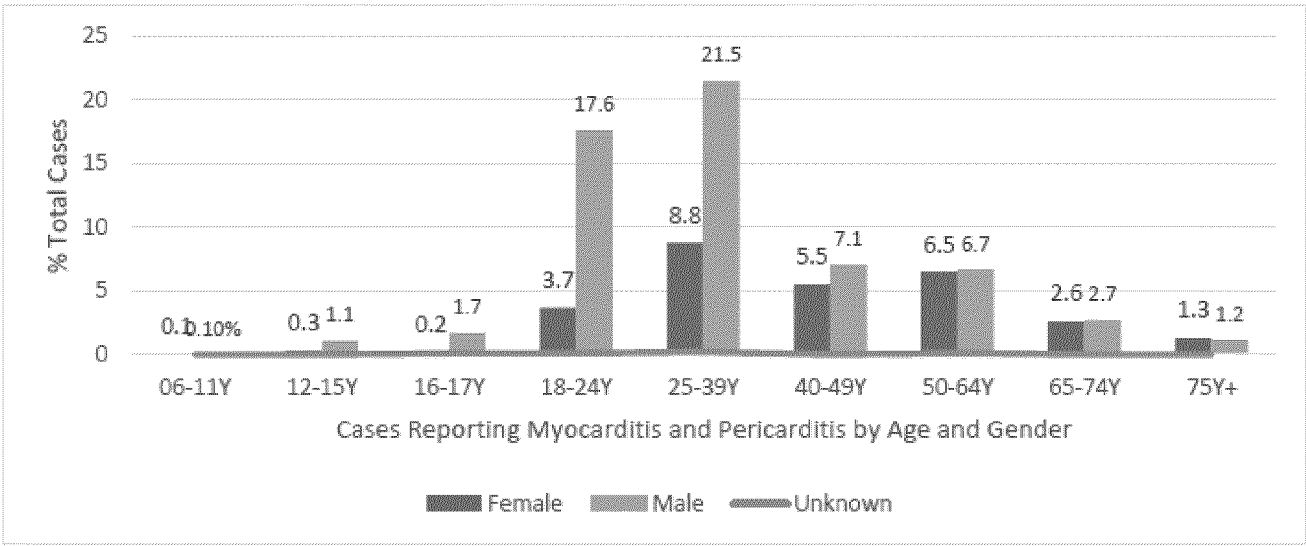
Product Name	PBRER # 3		PBRER # 4		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases		
Elasomeran	5,521	82.4	1159	17.3	6,677	99.6
Elasomeran/imelasomeran	0	0	20	0.3	20	0.3
Elaosmeran/davesomeran	0	0	5	0.1	5	0.1
Grand total	**5,521**	82.4	**1,184**	17.7	**6,702**	100.0

Cumulatively, there were no significant changes observed regarding demographics in the reported cases of myocarditis and pericarditis when compared to this PBRER reporting period, with the majority of cases reporting myocarditis and/or pericarditis continue to involve male. The proportion of events reported in males (4,420; 66.2%) remains higher when compared to females (2,114; 31.7%) while 143 reports

(2.1%) did not report gender information. The mean age of the patients was 37.4 years (SD 16.7), with a median age of 33 years (min 6/max 94); 707 cases were missing age information.

The majority of cases reporting myocarditis and pericarditis events continued to involve males between the ages of 18 to 39-years-old (2,615; 39.2%). Regardless of gender, more than half (52%) of cases were reported in patients in the 18 to 39-year-old age group (Figure 16-4).

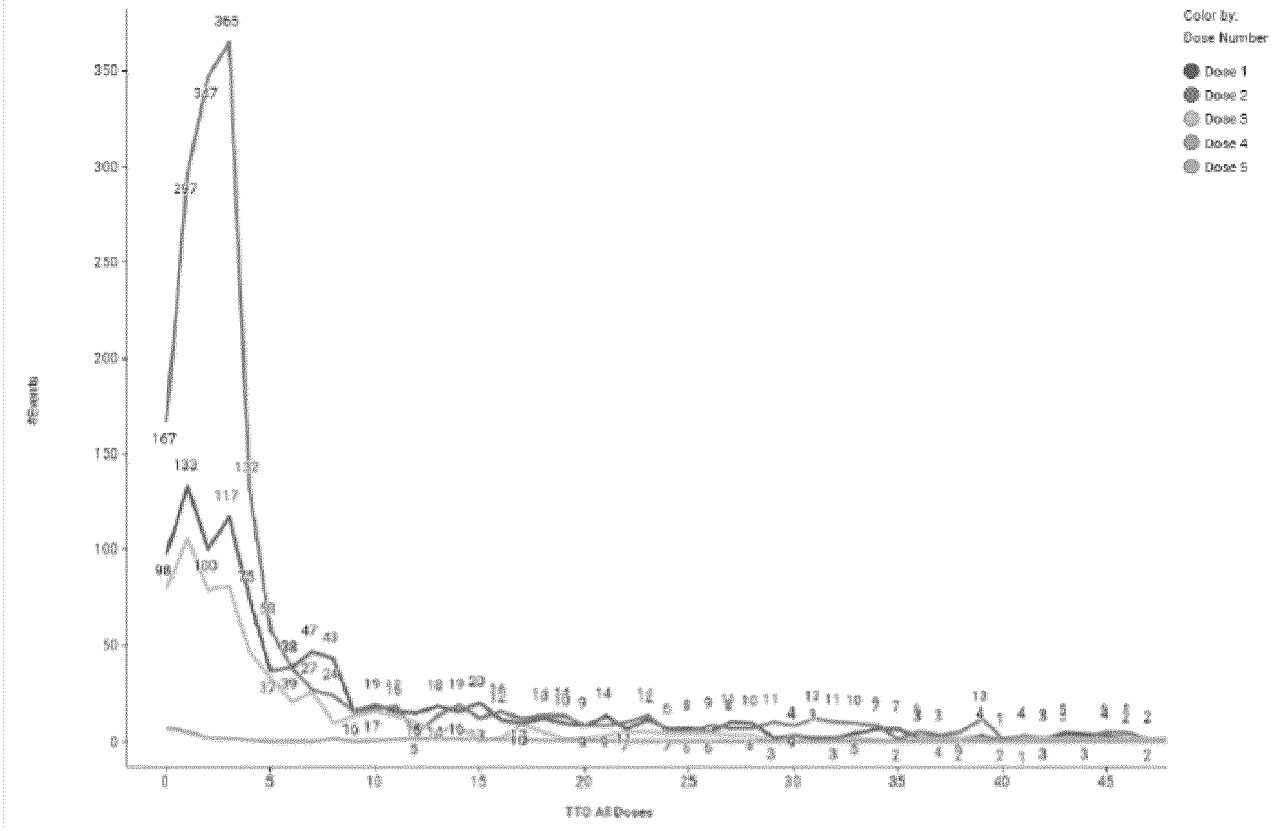
Figure 16-4. Percentage of Cases Reporting Myocarditis and Pericarditis by Age and Gender-Cumulative to 17 Dec 2022- elasomeran



Source: ModernaTx, Inc. GSDB - Monthly Spotfire dashboard

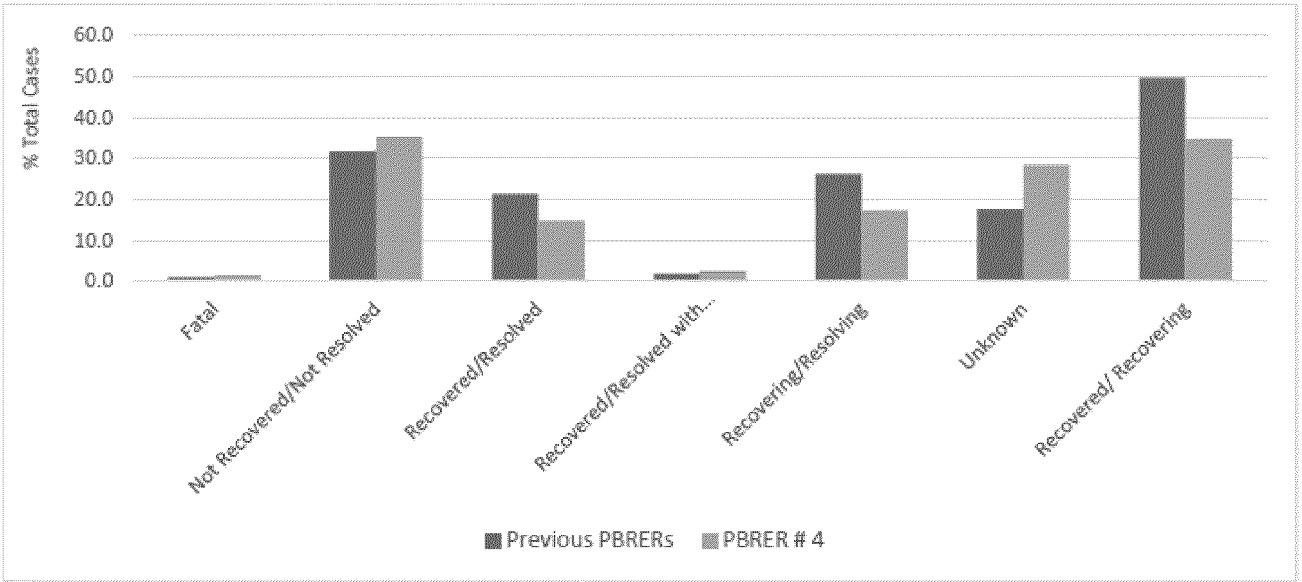
Trending of reported events of myocarditis and pericarditis continued to show that events of myocarditis and pericarditis most frequently occur after the 2nd dose (2,010; 28.4%). In events with known dose number, over half of the events had an onset less than 7 days from vaccination (2,462; 65.5%), inclusive of 457 events following 3rd and 4th doses (Figure 16-5). There were 3,317 events (46.9%) reported unknown dose number.

Figure 16-5 Distribution of Events by Time to Onset Stratified by Dose Number for elasomeran and Spikevax bivalent vaccines – Cumulative to 17 Dec 2022



Cumulative as of 17 Dec 2022, there have been 3,330 events (46.9%) that have reported a recovered/ recovering outcome. In some instances, additional short-term follow-up information has been provided demonstrating a recovery of symptoms within 3 to 6 months after experiencing the event of myocarditis or pericarditis. There is an important number of events (1,384; 19.5%) that did not provide outcome information. There were 2,302 events (32.4%) that had a reported outcome of not resolved. Unfortunately, most of these reports do not have additional follow-up information, and the reported outcome of not resolved may be associated with the outcome at the time of the reporting date of the event, instead of information received after a short-term follow-up (Figure 16-6).

Figure 16-6. Percentage of Cases Reporting Myocarditis and Pericarditis by Reported Outcome-Cumulative to 17 Dec 2022–elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran



* Recovered/Recovering constitute the sum of events reported as recovered/resolved plus Recovered/ Resolved with sequelae and Recovering/Resolving

Cumulative, there are 144 cases that reported an outcome of recovered with sequelae (Appendix 11.5), Out of those 115 (79.9%) did not provided information or description of what the referred sequelae was. The rest of the reports (28; 19.4%) provided limited information like "hoarseness and tightness of chest"; "paralysis of the elbow joint and hand due to right upper arm compartment syndrome, which was caused by the patient removing an arterial sheath"; "brain death", etc. None of these reports provided any detail information that would allow a more detail evaluation of these reports. Additional information is included in Appendix 11.5.

There have been 83 cases (1.6%) (86 events) of myocarditis/ pericarditis reporting a fatal outcome cumulative for individuals vaccinated with elasomeran (82 cases), and elasomeran/imelasomeran (1 case); there has not been any fatal reports after elasomeran/davesomeran vaccination. There were 63 cases (66 events) during the previous reporting periods, and 20 cases (20 events) during the reporting period of this PBRER (Appendix 11.5).

Out of those 83 fatal reports:

- 5 cases included both myocarditis and pericarditis, or myopericarditis, events
- 7 cases involved only pericarditis
- 66 cases involved only myocarditis
- 1 case of Giant cell myocarditis
- 4 cases of carditis
- Gender: 55 Males (66.3%), 26 Females (31.3%), 2 Unknown (2.4%)
- Age: 16 to 94 (Median: 58 year/ Mean: 56 years)
- Median TTO is 5 days (min:0/max:377)

• No important differences on the number of reports after any dose, with 16 (18.8%) after dose 1; 23 (27.1%) after dose 2; 14 (16.5%) after dose 3; and 4 (4.7%) after dose 4. There are 28 (32.9%) cases that dose number was not reported.

Out of those 83 fatal reports:

• There were 7 reports (8.4%) that reported not having an autopsy performed

• There were 37 reports (44.6%) that reported having an autopsy performed

• There were 39 reports (47.0%) that it is unknown if an autopsy was performed

Out of the 37 reports that reported having an autopsy performed:

• There were 28 reports (75.7%) where results were not provided

• There were 9 reports (24.3%) where relevant results were provided. Information on these reports is included in Appendix 11.5.

Additional information on the evaluation of outcomes in individuals with reported events of myocarditis/ pericarditis based on the Interim Report of study mRNA-1273-P903 is included in Appendix 11.5.

Myocarditis and Pericarditis (Reporting Period–19 Jun 2022 to 17 Dec 2022)-elasomeran

During the reporting period of this PBRER, a decreasing trend in the number of reported cases of myocarditis and pericarditis was observed. Noting that relatively more vaccine doses are increasingly being administered as booster doses, this reduction in the number of reported cases may be possibly associated with the observed lower risk for myocarditis/ pericarditis after a 3rd or more doses of elasomeran. As new safety data from the Spikevax bivalent vaccines becomes available, a lower risk of myocarditis and pericarditis is observed in those exposed to the Spikevax bivalent vaccines, compared to after Dose 2 with elasomeran.

During the reporting period of this PBRER, a total of 1,159 cases (1,236 events) were reported. There were 901 (77.7%) cases medically confirmed. There were 19 cases (20 events) with a fatal outcome.

There were 667 (58.4%) cases of myocarditis and pericarditis reported for males, and 431 (37.2%) reported in females; 51 cases (4.4%) did not include gender information. The mean of the patients' ages was 37.3 years (SD 16.9), with a median age of 34.0 years (min 6/max 91); 217 cases were missing age data.

During the reporting period, myocarditis and pericarditis cases reported continued to involve males aged 18 to 39-years-old at a greater frequency than any other demographic (346, 29.9%) Table 16.11.

Table 16.11 Number and Percentage of Myocarditis and Pericarditis Cases by Age and Gender-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
06-11Y	4	0.3	7	0.6	0	0.0	11	1.0
12-15Y	9	0.8	27	2.3	0	0.0	36	3.1
16-17Y	6	0.5	22	1.9	2	0.2	30	2.6
18-24Y	36	3.1	132	11.4	4	0.3	172	14.8
25-39Y	106	9.1	214	18.5	1	0.1	321	27.7
40-49Y	75	6.5	70	6.0	1	0.1	146	12.6
50-64Y	87	7.5	68	5.9	2	0.2	157	13.6
65-74Y	19	1.6	16	1.4	0	0.0	35	3.0
75Y+	21	1.8	13	1.1	0	0.0	34	2.9
Missing	68	5.9	108	9.3	41	3.5	217	18.7
Grand total	**431**	**37.2**	**677**	**58.4**	**51**	**4.4**	**1,159**	**100**

Of the 1,236 events reported during this reporting period 538 (43.5%) were myocarditis related events, and there were 543 events of (43.9%) pericarditis. Table 16.12.

Table 16.12 Number and Percentage of Myocarditis and Pericarditis Events by PT-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

PT	# Events	% Total Events
Myocarditis	538	43.5
Pericarditis	543	43.9
Myopericarditis	138	11.2
Carditis	8	0.6
Pleuropericarditis	6	0.5
Eosinophilic myocarditis	2	0.2
Pericarditis adhesive	1	0.1
Grand total	**1,236**	**100**

In events with a known dose number, most of the events of myocarditis and pericarditis during this reporting period continued to occur after the 2nd dose (153; 12.4%) and the 3rd dose (126; 10.2%); 858 (69.4%) events did not provide dose information. In the events where TTO was provided, events continue to occur less than 7 days after vaccination regardless of the dose number (244; 64.6%) (Table 16.13). The median TTO was 3 days (min: 0/max: 502).

Table 16.13 Distribution of Reported Events of Myocarditis and Pericarditis by Dose Number and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO All Doses (Days)	# Events	% Total Events
Dose 1	*Subtotal*	*77*	*6.2*
	0 days	20	1.6
	01-02	18	1.5
	03-04	12	1.0
	05-06	1	0.1
	07-13	12	1.0
	14-29	6	0.5
	30+	8	0.6
Dose 2	*Subtotal*	*153*	*12.4*
	0 days	31	2.5
	01-02	46	3.7
	03-04	26	2.1
	05-06	4	0.3
	07-13	6	0.5
	14-29	13	1.1
	30+	27	2.2
Dose 3	*Subtotal*	*126*	*10.2*

Dose Number	TTO All Doses (Days)	# Events	% Total Events
	0 days	10	0.8
	01-02	30	2.4
	03-04	24	1.9
	05-06	10	0.8
	07-13	12	1.0
	14-29	13	1.1
	30+	27	2.2
Dose 4	*Subtotal*	*20*	*1.6*
	0 days	5	0.4
	01-02	5	0.4
	03-04	1	0.1
	05-06	1	0.1
	07-13	6	0.5
	14-29	1	0.1
	30+	1	0.1
Dose 5	*Subtotal*	*2*	*0.2*
	30+	2	0.2
Unknown	*Subtotal*	*858*	*69.4*
	0 days	34	2.8
	01-02	70	5.7
	03-04	37	3.0
	05-06	14	1.1
	07-13	22	1.8
	14-29	28	2.3
	30+	35	2.8
	Event onset prior to first dose reported	0	0
	Missing	618	50
Grand total		**1,236**	**100**

Myocarditis (Reporting Period – 19 Jun 2022 to 17 Dec 2022)-(elasomeran)

During this review period, there were 539 cases (540 events) of myocarditis related events, with or without pericarditis, received; of which all 539 cases were serious. There were 412 cases that were medically confirmed.

There were 18 cases with fatal outcomes. There were 336 (62.3%) cases of myocarditis reported in males and 169 (31.4%) in females, with 34 cases (6.3%) missing gender information. The mean age of the patients was 36.4 years (SD: 18.2) with a median age of 33 years (min: 7/max: 91); age data was missing in 108 cases. During the review period, events of myocarditis continued to be reported in males between the ages of 18 to 39 years of age at a greater frequency than any other demographic (163; 30.2%) (Table 16.14).

Table 16.14 Number and Percentage of Myocarditis Cases by Age and Gender - Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
06-11Y	3	0.6	7	1.3	0	0.0	10	1.9
12-15Y	3	0.6	22	4.1	0	0.0	25	4.6
16-17Y	1	0.2	13	2.4	2	0.4	16	3.0
18-24Y	13	2.4	73	13.5	3	0.6	89	16.5
25-39Y	33	6.1	90	16.7	1	0.2	124	23.0
40-49Y	31	5.8	33	6.1	0	0.0	64	11.9
50-64Y	37	6.9	28	5.2	2	0.4	67	12.4
65-74Y	10	1.9	7	1.3	0	0.0	17	3.2
75Y+	13	2.4	6	1.1	0	0.0	19	3.5
Missing	25	4.6	57	10.6	26	4.8	108	20.0
Grand total	**169**	**31.4**	**336**	**62.3**	**34**	**6.3**	**539**	**100**

During the reporting period, when dose number and TTO were reported, events of myocarditis most frequently occurred after the 2nd (85; 15.7%) and the 3rd (67; 12.4%) doses of elasomeran. The majority (133; 70.4%) of events most often occurred within 7 days from vaccination (Table 16.15).

Table 16.15 Distribution of Reported Events of Myocarditis by Associated Dose Number and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	*Subtotal*	*21*	*3.9*
	0 days	5	0.9
	01-02	4	0.7
	03-04	5	0.9
	07-13	3	0.6
	14-29	2	0.4
	30+	2	0.4
Dose 2	*Subtotal*	*85*	*15.7%*
	0 days	14	2.6%

Dose Number	TTO (Days)	# Events	% Total Events
	01-02	33	6.1%
	03-04	18	3.3%
	05-06	2	0.4
	07-13	2	0.4
	14-29	5	0.9
	30+	11	2.0
Dose 3	*Subtotal*	*67*	*12.4*
	0 days	5	0.9
	01-02	18	3.3
	03-04	15	2.8
	05-06	5	0.9
	07-13	5	0.9
	14-29	8	1.5
	30+	11	2.0
Dose 4	*Subtotal*	*15*	*2.8*
	0 days	5	0.9
	01-02	4	0.7
	07-13	5	0.9
	14-29	1	0.2
Dose 5	*Subtotal*	*1*	*0.2*
	30+	1	0.2
Unknown	*Subtotal*	*351*	*65.0*
	0 days	11	2.0
	01-02	16	3.0
	03-04	14	2.6
	05-06	3	0.6
	07-13	7	1.3
	14-29	11	2.0
	30+	13	2.4
	Missing	276	51.1
Grand total		**540**	**100**

Pericarditis (Reporting Period 19 Jun 2022 to 17 Dec 2022)- elasomeran

During this reporting period, there were 541 cases (550 events) received that reported pericarditis related events, of which, 426 cases were medically confirmed. There were no cases with fatal outcomes.

There were 308 cases (56.9%) reported in males and 228 cases (42.1%) reported in females; 5 cases (0.9%) did not report gender. The mean age of the patients was 39 years (SD: 15.7), with a median age of 36 years (min: 6/max: 82). Age information was missing in 85 cases. Cases with pericarditis events were reported most frequently in patients between 25-39 years of age (182; 33.6%) (Table 16.16).

Table 16.16 Number and Percentage of Pericarditis Cases by Age and Gender - Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
06-11Y	1	0.2	0	0.0	0	0.0	1	0.2
12-15Y	4	0.7	4	0.7	0	0.0	8	1.5
16-17Y	4	0.7	9	1.7	0	0.0	13	2.4
18-24Y	16	3.0	44	8.1	0	0.0	60	11.1
25-39Y	64	11.8	118	21.8	0	0.0	182	33.6
40-49Y	41	7.6	34	6.3	1	0.2	76	14.0
50-64Y	44	8.1	42	7.8	0	0.0	86	15.9
65-74Y	9	1.7	7	1.3	0	0.0	16	3.0
75Y+	7	1.3	7	1.3	0	00.	14	2.6
Missing	38	7.0	43	7.9	4	0.7	85	15.7
Grand total	**228**	**42.1**	**308**	**56.9**	**5**	**0.9**	**541**	**100**

Pericarditis related events reported during the reporting period occurred at a similar rate. There were 56 events (10.2%) after the 2nd dose, 53 events (9.6%) after the 1st dose, and 50 events (9.1%) after the 3rd dose. The majority of the events occurred within 7 days in events with known dose number (98; 60.1%) (Table 16.17).

Table 16.17 Number and Percentage of Pericarditis Events by Dose and TTO - Reporting Period 19 Jun 2022 to 17 Dec 2022- Elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	*Subtotal*	*53*	*9.6*
	0 days	15	2.7
	01-02	13	2.4
	03-04	6	1.1
	05-06	1	0.2
	07-13	9	1.6
	14-29	4	0.7
	30+	5	0.9
Dose 2	*Subtotal*	*56*	*10.2*
	0 days	17	3.1
	01-02	13	2.4
	03-04	5	0.9
	05-06	2	0.4
	07-13	4	0.7
	14-29	7	1.3
	30+	8	1.5
Dose 3	*Subtotal*	*50*	*9.1*
	0 days	3	0.5
	01-02	12	2.2
	03-04	5	0.9
	05-06	4	0.7
	07-13	6	1.1
	14-29	5	0.9
	30+	15	2.7
Dose 4	*Subtotal*	*4*	*0.7*
	01-02	1	0.2
	03-04	1	0.2
	05-06	1	0.2
	30+	1	0.2
Unknown	*Subtotal*	*387*	*70.4*
	0 days	21	3.8
	01-02	52	9.5
	03-04	16	2.9
	05-06	11	2.0
	07-13	15	2.7
	14-29	15	2.7
	30+	18	3.3
	Missing	239	43.5
Grand total		**550**	**100**

Fatal Case Summaries- elasomeran)

During this review period there were 19 cases reporting fatal outcomes for events of myocarditis and pericarditis. Please note: Two additional fatal cases were found upon medical review. Overall, during this reporting period, 21 cases reported a fatal outcome.

Brighton Collaboration Case Classification, CDC Working Case Definition, and WHO-UMC Causality Assessment – Report Period 19 Jun 2022 to 17 Dec 2022-elasomeran

Further evaluation was conducted in the segment of the reported cases involving patients that were considered (based on epidemiologic characteristics) to be at potentially higher risk for having events of myocarditis and/or pericarditis. This evaluation was conducted in males and females younger 40 years of age or younger, after the 2nd dose of elasomeran, regardless of the TTO of the events from the administration of the vaccine. An additional, focused evaluation was conducted on all reports involving patients <18 years of age, as well as those who received a 3rd dose or a booster dose

Following that strategy, the MAH conducted an evaluation of all the cases identified as cases of Myocarditis and Pericarditis utilizing the Brighton Collaboration Case Definition for Myocarditis/Pericarditis [40] which allows classification of the cases on whether they are true cases of myocarditis or pericarditis.

Cases were also evaluated using the CDC working case definition [43] for Acute myocarditis and Acute pericarditis which allows for classification of the cases on whether or not they are probable or confirmed cases of myocarditis and/or pericarditis based on: 1) characteristic symptoms associated with these events; 2) diagnostic test results (e.g. an elevated troponin level or abnormal findings on ECG, echocardiogram, or CMR imaging) that are associated with these syndromes; and 3) absence of other identifiable cause.

Those cases that were classified as Level 1 to Level 3, and probable or confirmed cases of acute myocarditis or pericarditis were assessed using the WHO-UMC causality assessment (which allow the clinician(s) to perform a combined assessment of the reported cases taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation [17].

Using the CDC working case definition for myocarditis and/or pericarditis, reported cases of possible acute myocarditis or pericarditis with insufficient evidence or information to meet the case definition were classified as "Unassessable." Reported cases of possible acute myocarditis or pericarditis with evidence of NOT meeting any of the parameters for the case definition were classified as "Not a case."

Following the search strategy mentioned above, there were a total of 200 cases reported in patients 40 years of age and younger, identified as occurring in males (145; 72.5%) and females (51; 25.5%), and 4 (2.0%) that did not provide gender information. There were 117 (58.5%) reports after the 2nd dose, 81 (40.5%) reports after a 3rd dose, and 2 reports (1%) after a 4th dose or booster dose.

According to the Brighton Collaboration case definition for myocarditis and pericarditis from those 200 cases, 39 cases met Level 1 definition, 42 cases met Level 2 definition, and 19 cases met Level 3 definition. The rest of the reports were considered Level 4 (92 cases) based on the lack of information required to make a diagnostic case classification or Level 5 (8 cases) based on other diagnosis that may explain the occurrence of the events.

According to the CDC working definition (used to define myocarditis and pericarditis) [43] there were 75 "Probable" cases of myocarditis, 20 'Confirmed" cases, 96 "Unassessable" cases, and 1 "Acute Pericarditis" case.

According to the WHO causality assessment (used to characterize strength of association between event and vaccine exposure) there were 2 "Probable" cases, and 82 "Possible" cases, with most of the reports considered "possible" based on information provided, including elevated troponin levels, abnormal ECG, Echocardiogram, and CMR Imaging (MRI) results compatible with myocarditis or pericarditis. The rest of

the reports were considered conditional, unlikely or unassessable due to the lack of required information (including symptoms, TTO, dose information or both, myocardial biomarkers, and imaging studies information).

Subpopulation Analyzes

Myocarditis and Pericarditis in Adolescents (12 to 17 years old)–Cumulative to 17 Dec 2022-elasomeran

Cumulatively, there were 224 cases (238 events) of myocarditis and pericarditis in adolescents 12 to 17 years of age, with 195 cases medically confirmed. There were 187 (83.5%) cases reported in males, 35 cases (15.6%) in females; and 2 cases (0.9%) did not include gender information. The mean age of the adolescents was 15.4 years (SD: 1.6) and the median age was 16 years (min: 12/max: 17). The majority of the cases reported in adolescents were in males aged 16 to 17 years (111; 49.6%) (Table 16.18).

Table 16.18 Number and Percentage of Myocarditis and Pericarditis Cases in Adolescents (12 to 17 years old) by Age and Gender-Cumulative to 17 Dec 2022

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	19	8.5	76	33.9	0	0	95	42.4%
16-17Y	16	7.1	111	49.6	2	0.9	129	57.6
Grand total	**35**	**15.6**	**187**	**83.5**	**2**	**0.9**	**224**	**100**

Cumulatively, there were 139 events of myocarditis (with or without pericarditis) reported in adolescents who received elasomeran. When dose number and TTO were reported, the greatest proportion of events (59; 42.4%) occurred after dose 2 with the majority (64; 81.0%) of events occurring at a TTO of less than 7 days.

Cumulatively, there were 52 events of pericarditis reported in adolescents who received elasomeran. When dose number and TTO were reported the greatest proportion of events (14; 26.9%) occurred after Dose 2 with the majority (6; 80%) of events occurring at a *TTO of less than 7 days*.

Myocarditis and Pericarditis in Adolescents (12 to 17 years old)–Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

During the reporting period, there were 66 cases (71 events) of myocarditis and pericarditis reported in adolescents 12 to 17 years of age, with 63 cases medically confirmed. There were 49 cases reported in males (74.2%), 15 in females (22.7%); and 2 cases (3%) with missing gender information. The mean age of the adolescents was 14.8 years (SD: 1.7 years) and the median age was 15 years (min: 12/max: 17). Myocarditis and pericarditis cases in adolescents were most often reported in males aged 12-15 years (27; 40.9%) (Table 16.19).

Table 16.19 Number and Percentage of Myocarditis and Pericarditis Cases by Age and Gender in Adolescents (12 to 17 years old) – Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	9	13.6	27	40.9	0	0.0	36	54.5
16-17Y	6	9.1	22	33.3	2	3.0	30	45.5
Grand total	**15**	**22.7**	**49**	**74.2**	**2**	**3.0**	**66**	**100**

Myocarditis (with or without Pericarditis) in Adolescents (12 to 17 years old) – Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

During the reporting period, there were 41 events of myocarditis reported in adolescents 12 to 17 years old who received elasomeran. When dose and time to onset were reported, events were most frequently reported after Dose 2 (21; 51.2%) with the majority (18; 81.8%) of events occurring at a TTO of less than 7 days.

Table 16.20 Number and Percentage of Events Reporting Myocarditis in Adolescents (12 to 17 years old) by Dose and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO All Doses (Days)	# Events	% Total Events
Dose 1	*Subtotal*	*0*	*0*
Dose 2	*Subtotal*	*21*	*51.2*
	0 days	3	7.3
	01-02	10	24.4
	03-04	4	9.8
	05-06	1	2.4
	14-29	2	4.9
	30+	1	2.4
Dose 3	*Subtotal*	*1*	*2.4*
	01-02	1	2.4
Unknown	*Subtotal*	*19*	*46.3*
	0 days	3	7.3
	01-02	4	9.8
	03-04	2	4.9
	Missing	10	24.4

Dose Number	TTO All Doses (Days)	# Events	% Total Events
Grand total		**41**	**100**

Pericarditis in Adolescents (12 to 17 years old) – Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

During the reporting period, 22 events of pericarditis were reported in adolescents 12 to 17 years of age who received elasomeran. When dose number and TTO were reported, events most frequently were reported after Dose 2 (4; 18.2%) with all events occurring at a TTO of less than 7 days.

Table 16.21 Number and Percentage of Events Reporting Pericarditis in Adolescents (12 to 17 years old) by Dose and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	*Subtotal*	*3*	*13.6*
	0 days	2	9.1
	07-13	1	4.5
Dose 2	*Subtotal*	*4*	*18.2*
	0 days	2	9.1
	01-02	1	4.5
	05-06	1	4.5
Unknown	*Subtotal*	*15*	*68.2*
	0 days	1	4.5
	01-02	3	13.6
	03-04	1	4.5
	05-06	1	4.5
	14-29	0	0
	Missing	9	40.9
Grand total		**22**	**100**

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – Adolescents (12 to 17 years old)- elasomeran

According to the Brighton Collaboration case definition for myocarditis and pericarditis from those 66 cases, 3 cases met Level 1 definition, 13 cases met Level 2 definition, and 13 cases met Level 3 definition. The rest of the reports were considered Level 4 (37 cases) based on the lack of information required to make a diagnostic case classification.

According to the CDC working definition (used to define myocarditis and pericarditis) [43] there were 19 "Probable" cases of myocarditis, 2 "Confirmed" cases, 1 "Acute pericarditis" case and 44 "Unassessable" cases based on the lack of information required to make a diagnostic case classification.

According to the WHO causality assessment (used to characterize strength of association between event and vaccine exposure) there was 1 "Probable" case, 9 "Possible" cases with most of the reports considered possible based on information provided, including elevated troponin levels, abnormal electrocardiogram (ECG), Echocardiogram, and cardiac MRI results compatible with myocarditis or pericarditis. The rest of the reports were considered "Conditional" cases (18), "Unlikely" cases (3) and "Unassessable" cases (35) due to the lack of required information (including symptoms, TTO, dose information or both, myocardial biomarkers, and imaging studies information).

Myocarditis and Pericarditis in Children (<12 years old)- elasomeran

Cumulatively, through 17 Dec 2022, a total of 11 cases (11 events) reporting myocarditis and pericarditis have been received. All cases were medically confirmed. All cases were received during this reporting period. Ten cases (90.9%) were received from Taiwan and one case (9.1%) was received from Australia.

Given this reported cluster of cases of myocarditis from only one country (Taiwan), additional information on all these reported cases is being requested from the reporting health authority.

Cumulatively, there were no fatal outcomes. There were 7 cases (63.6%) in males and 4 cases (36.4%) in females. The mean age of the patients was 9.3 years (SD: 1.5) with a median age of 10 years (min 6 /max 11). When dose number and TTO were reported, all doses occurred after Dose 2 and all events occurred at a TTO of less than 4 days. (Table 16.22).

Table 16.22 Number and Percentage of Events Reporting Myocarditis in Children (<12 years old) by Dose and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022-elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 2	*Subtotal*	*10*	*90.9*
	01-02	8	72.7
	03-04	2	18.2
Unknown	*Subtotal*	*1*	*9.1*
	07-13	1	9.1

Dose Number	TTO (Days)	# Events	% Total Events
Grand total		11	100.0

Myocarditis in Children <12 years old (Cumulative to 17 Dec 2022) – elasomeran

Cumulatively, through 17 Dec 2022, a total of 10 cases (10 events) reporting events of myocarditis have been received in children <12 years old, with all 10 cases medically confirmed. There have been more cases reported in males (7; 70%) than females (3; 30%). The mean age of the patients was 9.6 years (SD 1.1), with a median age of 10 years (min: 7 /max: 11). All 10 cases were received during the reporting period.

All 10 events occurred after Dose 2 with a TTO of less than 7 days from vaccination (Table 16.23).

Table 16.23 Number and Percentage of Events Reporting Myocarditis in Children (6-11 Years Old) by Dose and Time to Onset (TTO) –Cumulative to 17 Dec 2022-elasomeran

Dose Number	TTO (Days)	Total # Events	% Total Events
Dose 2	*Subtotal*	*10*	*100*
	01-02	8	80
	03-04	2	20
Grand total		10	100

Pericarditis in Children <12 years old (Cumulative to 17 Dec 2022) - elasomeran

Cumulatively, through 17 Dec 2022, one medically confirmed case with 1 event of Pericarditis has been received in a child under the age of 12 years of age who received elasomeran. The case was reported during the reporting period and concerned a 6-year-old female who experienced the event of "Pericarditis" approximately 9 days after receiving an unspecified dose number of elasomeran. At the time of this report the event outcome was reported as "Recovered".

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – Children (<12 years old)- elasomeran

Assessment of the children case reports per the Brighton Collaboration Case Definition Myocarditis – Levels of Diagnostic Certainty [40] determined there were 2 cases met Level 1 definition, 6 cases met Level 2 definition, and 3 cases met Level 4 definition.

According to the CDC working definition [43] there was 1 "Acute Pericarditis" case, 7 "Probable" cases, and 3 "Unassessable" cases given that important information was missing including symptoms, myocardial biomarkers, or imaging studies information.

According to the WHO causality assessment there were 8 "Possible" cases based on information provided including elevated troponin levels, abnormal ECG, and Echocardiogram result compatible with myocarditis. Three reports were considered "Unassessable" due to important missing information including laboratory values, dose information, TTO, medical history, clinical course of current conditions.

Myocarditis and Pericarditis in Patients Receiving a 3rd or Booster dose of Elasomeran

Cumulatively, through 17 Dec 2022, a total of 660 cases (689 events) reporting events of myocarditis and pericarditis have been received following a 3rd or booster dose of elasomeran, of which 612 cases were considered serious and 394 were medically confirmed. There were 17 cases with fatal outcomes. The cases involved more males (426; 64.5%) than females (231; 35.0%), with a mean age of 42.3 (SD: 17.4) and a median age of 40 years (min: 13.0/ max: 86.0). When dose number and TTO was reported, the majority (126; 85.1%) of events were reported after Dose 3, with 663 events (96.2%). The greatest proportion (457; 66.3%) of events occurred with a TTO of less than 7 days.

During this reporting period, there were 141 cases (148 events) of myocarditis and pericarditis following a 3rd or booster dose of elasomeran, of which 141 were considered serious and 90 were medically confirmed. There were 11 cases with fatal outcomes. The cases involved 80 males (56.7%) and 59 females (41.8%), with a mean age of 43.5 years (SD: 19.1) and a median age of 40 years (min: 16/max: 86). When dose number and TTO was reported, the majority (126; 85.1%) of events were reported after Dose 3, with 20 events (13.5%) reported after Dose 4, and just 2 events (1.4%) reported after Dose 5. The greatest proportion (86; 51.8%) of events occurred with a TTO of less than 7 days. Please note: 40 additional booster cases were found upon medical review. Overall, during this reporting period, 180 cases of myocarditis and pericarditis were reported following a 3rd or booster dose of elasomeran.

Information for those reports that fulfil the Brighton Collaboration case definition Level 1 to 3, as well as the CDC working case definition probable and confirmed and were classified as possible or probable as per the WHO causality assessment.

Myocarditis and Pericarditis in Pregnancy- elasomeran

During the reporting period, 3 reports of myocarditis among pregnancy cases were received. However, two of the case reports ([redacted] and [redacted]) appear to be misclassified as a pregnancy case given the lack of information in the reports regarding pregnancy, as well as their advanced age.

Myocarditis and Pericarditis After Receiving Booster Dose with elasomeran/imelasomeran

Cumulatively, and during this review period, there were 20 cases (20 events) received with events of myocarditis and pericarditis reported after receiving a 3rd or booster dose of elasomeran/imelasomeran. More cases were reported in males (13; 65%) than females (5; 25%); 2 cases (10%) did not report gender information. The mean age was 45 years and a median age of 41 years (min: 22/max: 90). When dose number and TTO were reported, the greatest proportion of events occurred after Dose 4 (5; 25%) and the majority (7; 87.5%) of events occurred at a TTO of less than 4 days.

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – 3rd dose or Booster Dose with elasomeran/imelasomeran

Assessment of the individuals receiving a 3rd dose or booster doses with elasomeran/imelasomeran case report per the Brighton Collaboration Case Definition Myocarditis – Levels of Diagnostic Certainty [40] determined one case met Level 1 definition, five cases met Level 2 definition, two cases met Level 3 definition, and 12 cases met Level 4 definition as important information was missing including clinical course, investigations supporting the diagnosis and treatment received, as well as age and TTO in many reports.

According to the CDC working definition [43] there was one "Confirmed" case, one "Acute Pericarditis" case, five "Probable" cases, and 13 "Unassessable" cases given that important information was missing including symptoms, myocardial biomarkers, or imaging studies information.

According to the WHO causality assessment there were five "Possible" cases, one "Probable" case, one "Conditional" case, one "Unlikely" case, and 12 "Unassessable" cases due to important missing information including laboratory values, dose information, TTO, medical history, clinical course of current conditions, etc.

Myocarditis and Pericarditis After Receiving Booster Dose with elasomeran/davesomeran

Cumulatively and during this review period, there were 5 cases (6 events) received of myocarditis and pericarditis after receiving a 3rd or booster dose of elasomeran/davesomeran. There were 4 cases (80%) reported in males, no cases reported in females, and 1 case (20%) was missing gender information. The mean age was 40.3 years (SD: 16.6) with a median age of 41.5 years (min: 19/max: 59). Of the 6 events reported, 4 events (66.7%) did not report a dose number or time to onset.

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – 3rd dose or Booster Dose with elasomeran/davesomeran

Assessment of the individuals receiving a 3rd dose or booster doses with elasomeran/davesomeran case report per the Brighton Collaboration Case Definition Myocarditis–Levels of Diagnostic Certainty [40] determined one case met Level 1 definition, one cases met Level 2 definition, one case met Level 3 definition, and two cases met Level 4 definition as important information was missing including clinical course, investigations supporting the diagnosis and treatment received, as well as age and TTO in many reports.

According to the CDC working definition [43] there was one "Confirmed" case, two "Probable" cases and two "Unassessable" cases given that important information was missing including symptoms, myocardial biomarkers, or imaging studies information.

According to the WHO causality assessment there was two "Possible" cases, one "Unlikely" case, and two "Unassessable" cases due to important missing information including laboratory values, dose information, TTO, medical history, clinical course of current conditions, etc.

Discussion

A review of the data received during the reporting period of this PBRER, showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. The same pattern was observed for cases reported after receiving a 3rd or more doses of elasomeran. There were twenty-five reports of myocarditis or pericarditis following exposure to any of the Spikevax bivalent elasomeran/imelasomeran or elasomeran/davesomeran in this reporting period. To date, the safety profile of those reports of myocarditis after any of the Spikevax bivalent vaccines (elasomeran/imelasomeran or elasomeran/davesomeran) does not differ from the elasomeran safety profile, with cases presenting as

mild cases, and recovering within a short time following standard treatment and rest. For elasomeran/imelasomeran there were 13 cases reported for males, 5 cases reported for females, and 2 reports that did not identify gender. Elasomeran/davesomeran reported 4 cases for males and 1 report did not identify gender.

Cumulatively, 10 of the 11 cases reporting events of myocarditis in children <12 years of age have been reported from Taiwan even though elasomeran vaccines (Original and both Bivalents) are authorized for children <12 years old throughout the world in more than 70 countries. Given this reported cluster of cases of myocarditis from only one country (Taiwan), additional information on all these reported cases is being requested from the reporting health authority.

Overall, evaluation of data received during this reporting period of those patients receiving a 3rd dose or a booster dose shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series, as it had been described in the literatures [29,44].

The observed clinical profile of patients experiencing myocarditis/ pericarditis following exposure to a COVID-19 mRNA vaccine continue to present as events that result with a relatively short period of hospitalization, most cases follow an uncomplicated clinical course and complete resolution of symptoms is rapidly achieved and can be effectively treated with a standard medication treatment with ibuprofen and colchicine, without any CMR-detectable consequence [45].

Analysis of safety data housed in the MAH's GSDB, as well as review of the literature, showed that most of the individuals who experienced an event of myocarditis/ pericarditis after vaccination with elasomeran were considered recovered by health-care providers after at least 90 days following the onset of myocarditis/pericarditis. In addition, their quality-of-life measures were comparable to those in pre-pandemic and early pandemic populations of a similar age [34].

Cumulative and periodic data analyzed in this PBRER, support an update of the product information, particularly the sentence related to the severity of myocarditis after vaccination with elasomeran compared to myocarditis in general. An updated version of the SmPC will be proposed by the MAH along with this PBRER procedure.

Based on the analysis of all the safety data available as of 17 Dec 2022, the MAH considers cases included under the AESI of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for elasomeran far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.

Conclusion

A review of the data received cumulatively and during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine elasomeran with a TTO of less than 7 days. myocarditis and pericarditis are generally mild and uncomplicated with rapid resolution.

Review of the data also show no difference in the observed safety profile of elasomeran for children (6 months to 12 years of age), the adolescent population (12 years to 17 years of age), or in those individuals receiving a 3rd dose of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when compared to >18 years old. Reporting rates are lower for children than for adolescents and young adults.

During the reporting period of this PBRER, a decreasing trend in the number of reported cases of myocarditis and pericarditis was observed, which can be possibly associated with the observed lower risk for myocarditis/ pericarditis after a 3rd or more doses of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. As new safety data from the elasomeran/imelasomeran and

elasomeran/davesomeran becomes available, a lower risk of myocarditis and pericarditis is observed in those exposed to the bivalent vaccines, compared to elasomeran after dose 2.

Based on the information provided by both literature and surveillance sources consistently describing an increase in the incidence of myocarditis, predominantly within the first 7 days following receipt of a second dose of vaccine, that appears largely isolated to younger men (<40 years of age).

Based on the analysis of all the safety data received during the reporting period of this PBRER, ModernaTx, Inc. considers that cases of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulative and periodic data analyzed in this PBRER, support an update of the product information, particularly the sentence related to the severity of myocarditis after vaccination with elasomeran compared to myocarditis in general. An updated version of the SmPC will be proposed by the MAH along with this PBRER procedure. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including 2 ongoing and 2 planned post-authorization safety studies to further characterize them. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has upon request provided a cumulative review for myocarditis and pericarditis for the 2-year-period from 18 Dec 2020 to 17 Dec 2022 and a literature-based presentation of health-related outcomes.

Source of information

Selected literature about the outcome of myocarditis/pericarditis following elasomeran exposure is presented, and according to request, data from observational studies and published literature were included. However, the MAH could have provided information from more studies to further qualify the proposed update of the SmPC. Please see additional studies referenced in the conclusion below.

The Global Safety Database (GSDB) was searched for all cases of myocarditis and/or pericarditis following vaccination against COVID-19 with elasomeran-containing vaccines including the bivalents elasomeran/imelasomeran and elasomeran/davesomeran. Data from the entire period (18 Dec 2020 to 17 Dec 2022) are presented. Cases were retrieved from the GSDB using the PTs: "autoimmune myocarditis, autoimmune pericarditis, carditis, chronic myocarditis, eosinophilic myocarditis, giant cell myocarditis, hypersensitivity myocarditis, immune-mediated myocarditis, myocarditis, myopericarditis, pericarditis, pericarditis adhesive, pericarditis constrictive, pleuropericarditis".

The MAH identified all cases according to the CDC working definition for acute myocarditis and acute pericarditis cases as well as the Brighton Collaboration case definition for myocarditis/pericarditis, and has furthermore performed causality assessment utilizing the WHO-UMC standardized case causality assessment.

Review of the Global Safety Database

Cumulatively, a total of 6,702 cases (7,102 events) of myocarditis and/or pericarditis were identified. Of these, 6,677 cases (7,076 events) were for elasomeran only, while there for elasomeran/imelasomeran were 20 cases (0.3%), and five cases (0.07%) for elasomeran/davesomeran. There were 83 cases with fatal outcomes, of which 21 cases were within the interval review period.

Of the 7,076 events following the elasomeran only vaccines the 6,843 events (96.4%) were considered serious, and 4,704 (70.5%) cases were medically confirmed.

Age and gender distribution

In 89.5% of the cases the age was known; the age range was 6-94 years with a median age of 33 years. It is important to notice, that although 52% of cases were reported in 18 to 39-year-old patients there is

a skewed gender ratio confirming that myocarditis and/or pericarditis predominantly involve males aged 18-39 years, as this group itself makes up as many as 2,615; 39.2% of cases.

The gender distribution of all cases was 66.2% males, 31.7% females, and 2.1% of unreported gender. The pronounced gender difference is seen regardless of dose number, also for boosters, 3rd and 4th and for elasomeran only as well as for the bivalent vaccines.

Myocarditis and pericarditis in adolescents (12-17 years old)

Cumulatively for the entire 2-year-period, there were 224 cases (238 events) of myocarditis and pericarditis in adolescents 12 to 17 years of age, 195 cases (87%) were medically confirmed. The gender distribution of the cases was 83.5% males, 15.6% in females, 0.9% without gender information.

In the subpopulation analysis of children < 18 years, the MAH presented a 14-year-old male considered with BC level 2 myocarditis ([redacted]). This case was neither included in the present PSUR section of new information on myocarditis nor in the PSUR appendix 11.5 myocarditis/pericarditis. **The MAH is requested to clarify this discrepancy in the current procedure and once more the MAH is requested to be thorough and precise in the presentation of data.**

Myocarditis and pericarditis in children (<12 Years of Age)

Cumulatively, through 17 December 2022, there were 11 cases (11 events) of myocarditis and/or pericarditis, all medically confirmed. All cases were received during the reporting period 19 June 2022 to 17 December 2022. Remarkably, 10 of the 11 cases (90.9%) occurred in Taiwan and one case (9.1%) in Australia. The MAH has informed that additional information on these cases will be requested from the reporting health authority.

Of the 11 cases 10 were myocarditis, one was pericarditis. The gender distribution was 7 (63.6%) males and 4 (36.4%) females; the age span was 6-11 years with a median age of 10 years. All 10 myocarditis cases occurred after 2nd dose, and all had a TTO of less than 7 days. The case of pericarditis occurred approximately 9 days following vaccination of unknown dose number.

Dose number and time to onset

Close to the half (46.9%) of all events are of unknown dose number. However, in events with known dose number, these are continuously reported more frequently following the 2nd dose (28.4%) and second most have been reported following 1st dose.

In the events where TTO is known, events continue to occur within 7 days after vaccination regardless of the dose number.

Outcome

Health-related outcome following myocarditis and/or pericarditis is done data-based from GDSB and literature-based.

Events by outcome based on cumulative data from the GSDB until 17 Dec 2022.

Recovered

In total 3,330 events (46.9%) were "recovered/resolved", "recovering/resolving" or "recovered/resolved with sequelae"; of these the latter group was definitely the smallest group with cumulatively 144 cases (2.1%). Cases reported to be recovered/resolved with sequelae has for each reporting period throughout the two years been approximately 1%-2%. Information describing the sequelae was only provided for 28 cases; the information varies by case and by detail degree, and the number of cases accounts for as few as 0.4% of all reported cases, no specific conclusion is drawn from these data.

Not recovered

For 2,302 events (32.4%) the outcome was reported as "not recovered/not resolved". This is, of course, associated with the outcome status at the time of the reporting date of the event, and as most of these reports do not have additional follow-up information they will continue to be registered as not resolved.

Fatal outcome

Cumulatively, 83 cases (86 events) of myocarditis and/or pericarditis had fatal outcome.

Fatal outcome by vaccine was clearly associated to elasomeran with 82 cases; 1 case was in relation to elasomeran/imelasomeran, none after elasomeran/davesomeran.

The age span for patients with fatal outcome was 16 to 94 years with a median age of 58 years. The gender distribution was 55 males (66.3%), 26 Females (31.3%), 2 of unknown gender (2.4%)

Myocarditis and/or pericarditis with fatal outcome listed by dose reflects the same trend as is seen for all 6,702 cumulative cases of myocarditis and/or pericarditis with most cases after 2nd dose (23 cases, 27.1%), second most after 1st dose (16 cases, 18.8%), fewer after 3rd (14 cases, 16.5%) and 4th (4 cases, 4.7%), and approximately a third (28, 32.9%) was of unknown dose number.

TTO for reported fatal cases showed a median of 5 days, however, the range for TTO was 0-377 days, where some due to late onset would not be assessed as causally associated to the vaccine.

Cases only involving myocarditis were overrepresented among cases with fatal outcome as 66 cases (79.5%) involved only myocarditis in contrast to 7 cases (8.4%) involving only pericarditis. The rest of the cases included 5 cases (6.0%) with both myocarditis and pericarditis or myopericarditis, 4 cases (4.8%) with carditis, and 1 case (1.2%) with giant cell myocarditis.

Unknown outcome

For 1,384 events (19.5%) outcome information has never been provided.

Literature-based information about outcomes

The MAH has provided a review of selected literature for further information about myocarditis and/or pericarditis after vaccination with elasomeran and health outcomes after myocarditis and/or pericarditis. Some points and trends of quite varying focus are worth highlighting:

According to a case-control study there is an excess of myocarditis cases associated with the 3rd dose globally, and the study points towards that the risk of myocarditis is increased for the 3rd dose compared with the 1st dose, but with a lower incidence than for 2nd dose. The same study found that the risk of myocarditis decreases with the lengthening of the intervals between each successive dose. So, both the 2nd and 3rd doses were associated with increased risks of myocarditis regardless of the delay since the previous dose, however, the risk decreased with longer intervals since the previous dose. Please see comment and request below about the availability of these presented data.

Another study looked into myocarditis after COVID-19 infection and subsequently after receiving an mRNA COVID-19 vaccine. It seems that patients with myocarditis secondary to COVID-19 infection may have higher susceptibility also to develop vaccine-related myocarditis. And in these patients with prior COVID-19 infection and myocarditis observed following COVID-19 vaccination, it is difficult to establish whether the symptoms are a result of a flare-up after vaccine administration due to incomplete infection resolution.

It is mentioned how SARS-CoV2 can play a role for cardiac involvement, and that viral replication in infected cardiomyocytes leads to cellular oedema and necrosis resulting in contractile dysfunction and myocarditis, however, whether this is a plausible consequence from COVID-19 vaccines is not discussed.

It is described that even though almost all individuals with myocarditis are hospitalized and clinically monitored, most cases follow an uncomplicated clinical course and that complete resolution of symptoms is achieved after receiving only pain management for 2 to 4 days. However, although most patients have only mild symptoms of myocarditis that can be managed with NSAIDs, patients must also be instructed to abstain from competitive sports for at least three months. Current guidelines recommend restricting patients with myocarditis from competitive sports for 3–6 months.

Measurement of troponin level, electrocardiography, echocardiography, and cardiac MRI, are recommended examinations for the initial evaluation.

An ongoing follow-up surveillance study among individuals aged 12–29 years with myocarditis after mRNA COVID-19 vaccination has data from questionnaire items about quality-of-life, and overall the mean weighted quality-of-life measure was similar to a pre-pandemic US population value. Nevertheless, secondary consequences were common: At least 90 days after onset of myocarditis as many as 21% had problems performing their usual activities, 30% had pain, and almost half (46%) reported anxiousness or depression.

Another population-based surveillance study that was limited to 18–39-year-olds found that 61% of cases occurred 0-7 days after vaccination; some after 1st dose but more after 2nd dose. The incidence per million doses 0-7 days after vaccination was numerically higher in males than in females. The incidence was highest for male adolescents aged 12-17 years following 2nd dose.

It should be emphasized, that the presented studies do not raise concern about mortality, and the MAH refers to a study which reports that the risk of fatality in myocarditis subjected to mRNA vaccination seems to be low.

Conclusion

Myocarditis and/or pericarditis are acknowledged as an infrequent adverse drug reaction to mRNA vaccines, in this case to elasomeran-containing vaccines (elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran). Cumulatively, a total of 6,702 cases (7,102 events) of myocarditis and/or pericarditis were reported. Of these cases 99.6% were seen after elasomeran only, 0.3% after a dose of elasomeran/imelasomeran, and 0.07% after elasomeran/davesomeran.

It is noted, that 96.4% of all cases were considered serious, and 70.5% were medically confirmed. There were 83 cases with fatal outcomes, this corresponds to 1.2% of all reported cases.

Myocarditis and/or pericarditis predominantly involve males aged 18-39 years, this group constitutes as many as 39.2% of all cases.

Myocarditis and/or pericarditis affect all age groups, the age range being 6-94 years, but mainly younger adults, the median age being 33 years; 52% of all cases were reported in 18 to 39-year-old patients. There is a pronounced gender difference with 66.2% males, 31.7% females, 2.1% of unreported gender. The pronounced gender difference is seen across age groups, and regardless of dose number including boosters, 3rd and 4th dose, for elasomeran only as well as for the bivalent vaccines, and for fatal cases (66.3% males, 31.3% females, 2.4% unknown).

Of the 224 cases in 12 to 17-year-olds 83.5% were males, 15.6% females, 0.9% without gender information. Of the 11 cases in children aged 6-11 years was 63.6% males, 36.4% females. No cases have been reported in children younger than 6 years.

TTO is reported with a wide range, but most events continue to occur within 7 days after vaccination regardless of the dose number.

Close to the half (46.9%) of all events are of unknown dose number. However, in events with known dose

number, these are continuously reported most frequently following the 2nd dose (28.4%) and second most following 1st dose.

The MAH presented results from a case-control study which points towards an increased risk of myocarditis for the 3rd dose compared with the 1st dose, but with a lower incidence than for 2nd dose. However, the PRAC rapporteur could not identify these results online (Ref 29. Epi-Phare. Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France Study based on data from the National Health Data System (SNDS).). **The MAH is requested in the current procedure to point directly to where these study results can be found. The provided information will be taken into consideration for the update of the SmPC/PIL text when the PRAC rapporteur has been presented to the results in details.**

The same study pointed to that the risk of myocarditis decreases with the lengthening of the intervals between each successive dose. So, both the 2nd and 3rd doses were associated with increased risks of myocarditis regardless of the delay since the previous dose, however, the risk decreased with longer intervals since the previous dose. Another study found that myocarditis secondary to COVID-19 infection may lead to higher susceptibility to vaccine-related myocarditis.

The MAH referenced a systematic review (Woo et al.) of previously published case reports and case series associated with mRNA vaccine-related myocarditis (n=74). Most cases were mild and followed an uncomplicated clinical course after receiving pain management for a few days. Even for patients with mild symptoms of myocarditis patients should be instructed to abstain from competitive sports for at least three months. Current guidelines recommend restricting patients with myocarditis from competitive sports for 3–6 months. Measurement of troponin level, electrocardiography, echocardiography, and cardiac MRI, are recommended examinations for the initial evaluation.

Almost half of cases in the GSDB (46.9%) were reported as recovering, recovered, or recovered with sequelae; almost a third (32.4%) were reported as not recovered at the reporting date of the event and most of these reports do not have additional information.

The group reported to have recovered with sequelae is 2.1% of cases in the GSDB. For most of these cases the information on sequelae is poor. However, according to some published studies, secondary sequelae to myocarditis and/or pericarditis following mRNA COVID-19 vaccination may need further studies. A study conducted by the Center for Disease Control and Prevention in the US (CDC) (Kracalik et al) among 12 to 29-year-olds found that secondary consequences were present at least 90 days after onset of myocarditis: 21% had problems performing their usual activities, 30% had pain, and 46% reported anxiousness or depression. Mean weighted quality-of-life measure was similar to a pre-pandemic population value. The study had several limitations including the likelihood of systematic bias and the results should be read with caution.

Fatal outcomes were seen in 2.1% of all cases, the age span was 16-94 years with a median age of 58 years. Gender distribution, dose number and TTO corresponds to what is found in general; 66.3% were males, 31.3% females, 2.4% of unknown gender, most cases after 2nd dose (27.1%), second most after 1st dose (18.8%), also after 3rd (16.5%), few after 4th (4.7%), and approximately a third (32.9%) of unknown dose number. TTO for reported fatal cases had a median of 5 days. Cases only involving myocarditis were overrepresented among cases with fatal outcome; 66 cases (79.5%) involved only myocarditis, 5 cases (6.0%) included both myocarditis and pericarditis or myopericarditis.

The MAH did not include results from a recent register-based study on Nordic data (Husby et al.). The study identified that myocarditis after SARS-CoV-2 mRNA vaccination, including elasomeran, was associated with a lower risk of heart failure and death within 90 days of admission to hospital compared with myocarditis associated with conventional myocarditis.

The MAH did not include results from a recent case-control study of patients in France (Le Vu et al.). The median length of hospital stay did not differ between vaccine-associated myocarditis/pericarditis and "classical" myocarditis/pericarditis (n=4/2), however, the mean was lower for the vaccine-associated. A lower incidence of admission to intensive care unit, and death was also observed.

It should be emphasized, that the studies presented in the literature review do not raise concern about mortality. Furthermore, the MAH refers to a study which reports that the risk of fatality in myocarditis subjected to mRNA vaccination seems to be low. Consequently, cumulative data indicate that that the short term (≤3 months) course and outcome of myocarditis and pericarditis following vaccination is milder and less severe than myocarditis or pericarditis in general.

The MAH suggests changes to the SmPC section 4.4:

> Myocarditis and pericarditis
>
> There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax. The majority of these cases have been reported in young males, 18 through 24 years of age.
>
> These conditions ~~can develop within just a few days after vaccination, and~~ have primarily occurred within 7 to 14 days after vaccination. They have been observed more often after the second dose compared to the first dose~~, and more often in younger males~~ and less often after booster doses compared with the second dose (see section 4.8). ~~The risk profile appears to be similar for the second and the third dose.~~
>
> Although some cases required intensive care support, these are typically mild cases and individuals tend to recover within a short time following standard treatment and rest.
>
> ~~Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.~~
>
> Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.
>
> ~~Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.~~

The MAH also suggests corresponding changes to the PIL section 2:

2. What you need to know before you are given Spikevax

The vaccine must not be given if you are **allergic** to the active substance or any of the other ingredients of this vaccine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Spikevax if:

- you have previously had a severe, life-threatening **allergic** reaction after any other vaccine injection or after you were given Spikevax in the past.
- you have a very weak or compromised immune system
- you have ever fainted following any needle injection.
- you have a bleeding disorder
- you have a high fever or severe infection; however, you can have your vaccination if you have a mild fever or upper airway infection like a cold
- you have any serious illness
- if you have anxiety related to injections

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Spikevax (see section 4). The majority of these cases have been reported in young males, 18 through 24 years of age.

These conditions ~~can develop within just a few days after vaccination and~~ have primarily occurred within 7 to 14 days after vaccination. They have been observed more often after the second dose compared to the first dose, and ~~more~~ less often ~~in younger males~~after booster doses compared with the second dose (see section 4.8).

Although some cases required intensive care support, these are typically mild cases and individuals tend to recover within a short time following standard treatment and rest.

Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before you are given Spikevax.

Please see in section 3 Recommendations, the PRAC rapporteur's suggestion of changes to the SmPC and PIL text based on the above assessment taking the MAH's suggestion into consideration. **The MAH is requested within the procedure to comment on this updated suggestion of PI changes.**

References

Epi-Phare. Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France Study based on data from the National Health Data System (SNDS).

Woo W, Kim AY, Yon DK, Lee SW, Hwang J, Jacob L, et al. Clinical characteristics and prognostic factors of myocarditis associated with the mRNA COVID - 19 vaccine. Journal of medical virology 2022;94(4):1566-80.

Kracalik I, Oster ME, Broder KR, Cortese MM, Glover M, Shields K, et al. Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: a follow-up surveillance study. The Lancet Child & Adolescent Health 2022;6(11):788-98.

Husby A, et al. BMJMED 2023;2:e000373. doi:10.1136/bmjmed-2022-000373

Le Vu S, Bertrand M, Jabagi MJ, Botton J, Drouin J, Baricault B, Weill A, Dray-Spira R, Zureik M. Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines. Nat Commun. 2022 Jun 25;13(1):3633. doi: 10.1038/s41467-022-31401-5. PMID: 35752614; PMCID: PMC9233673.

2.3.2. New Information on Important Potential Risks

2.3.2.1. Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

Source of the New Information

The ModernaTx, Inc.'s GSDB was queried for valid, clinical and spontaneous case reports received from HCPs, HAs, consumers and literature, cumulative from 18 Dec 2020 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

Vaccine-associated enhanced diseases are modified presentations of clinical infections affecting individuals exposed to a wild type pathogen after previously having received a vaccination for the same pathogen. Vaccine-associated enhanced respiratory disease refers to disease with predominant involvement of the lower respiratory tract [46]. Given that these enhanced responses are triggered by failed attempts to control the infecting virus, VAED typically presents with symptoms related to the target organ of the infecting pathogen.

Research points to disease enhancement being triggered by one of two major mechanisms although other mechanisms may also contribute. The first and least well characterized is when priming by the initial infection results in a Th2 biased immune response mediated more by myeloid lineage cells, including neutrophils and eosinophils with immune complex formation and complement activation. While this inflammatory phenotype may be preferred for parasitic infections it is not ideal for viruses, for which an adaptive T-cell and antibody mediated Th1 type response is preferable.

This "Th2 biased" phenotype is most associated with enhanced disease as resulting from the formalin-inactivated measles and respiratory syncytial virus (RSV) vaccines. In these cases, postvaccination exposure of previously naïve vaccines resulted in an immune response characterized by high interleukin (IL) 4, 5 & 13 levels and localized tissue inflammation associated with neutrophil and eosinophil infiltration, immune complex deposition and pulmonary inflammation and obstruction [47].

The second and far better characterized mechanism related to vaccines is antibody dependent enhancement (ADE). This results from the generation of binding but poorly neutralizing antibodies induced by heterologous antigens generated either by heterologous viral strains (e.g., dengue), by chemically disrupted antigens (e.g., formalin-inactivated RSV and measles) or by epitope altering mutations such as feline infectious peritonitis. These antibodies bind to but do not neutralize the virus and facilitate Fc receptor mediated entry of viable virus into macrophages. This can result in an accelerated and more marked viremia and more severe disease. This scenario is the one associated with dengue vaccine virus, its virus and vaccine-associated ADE. Antibody dependent enhancement for dengue can also result from sub-neutralizing concentrations of neutralizing antibodies, such as that seen in infants as maternal antibodies wane [47].

The potential for any SARS-CoV-2 vaccine to potentiate subsequent SARS-CoV-2 viral infection has been hypothesized. This hypothesis is based upon the observation that antibody responses may paradoxically be misdirected to facilitate viral cell entry, thereby resulting in a more severe infection than would have occurred in the absence of vaccine priming. In the case of coronaviruses, it has been observed that in laboratory studies in which cats were exposed to large inocula of wild type feline coronavirus, the experimental animals were at elevated risk for feline when subsequently exposed to wild type virus. A commercial feline coronavirus vaccine has been available for some years, with no reported increase in the incidence of feline peritonitis [48] to the knowledge of the MAH, there have been no cases of VAED in

humans who have been repeatedly exposed to any of the 4 common human coronaviruses, or to the viruses causing SARS, Middle East respiratory syndrome (MERS), or SARS-CoV-2.

There is currently no widely accepted case definition for VAED; however, a recent publication by the Brighton Collaboration provides some guidance for assessment of potential VAED in COVID-19 [46]. In this guidance, it is suggested that VAED may be identified first as a vaccine failure (i.e., VAED requires exposure to and infection by SARS-CoV-2 in a person who has been fully immunized). The authors acknowledge that there is presently no pathognomonic set of clinical findings to characterize VAED. Furthermore, case classifications that can be readily applied to individual level data from spontaneous reporting are not defined. The Brighton Collaboration working group states that a definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. Probable cases must show an increase in severity or rates of atypical findings when compared to a non-vaccinated control group, however this criterion must be considered at a population or group level rather than an individual level. Given that there have been numerous epidemiologic studies evaluating effectiveness of mRNA vaccines in millions of vaccinees and given that there have not been findings showing an increased risk of COVID-19 disease in vaccinees (or a subgroup of vaccinees) compared to those not vaccinated, real-world evidence for occurrence of VAED is lacking. Moreover, there is an absence of medical literature supporting the existence of VAED due to elasomeran or mRNA vaccines against COVID-19.

The authors further suggest that the clinical presentation must then be recognized as atypical or severe. It is further suggested that assessment of the type and frequency of clinical presentations is recommended. Clinical parameters of interest include respiratory, cardiovascular, hematological, inflammatory, renal, gastrointestinal, and central nervous system conditions. Both vaccine efficacy and safety have been studied in animal models with many vaccines including SARS-CoV-1 candidate vaccines [49]. Whole-inactivated viral vaccines developed in the 1960s against both respiratory syncytial virus (RSV) and measles elicited VAED when vaccinated children were subsequently naturally infected. These adverse outcomes were associated with T-helper (Th) 2-skewed CD4+ T-cells and the induction of poor-quality antibodies with little to no neutralizing activity. Animal models, where this immune profile is elicited after vaccination, recapitulate RSV and measles VAED with hallmarks of increased inflammation and pulmonary eosinophilia after challenge that exceeds that in unvaccinated control animals [50].

Elasomeran was evaluated to determine whether it might elicit potentially adverse immune responses that could be associated with VAERD [51]. This was performed by comparing antibody and T-cell responses generated from subprotective and protective doses of elasomeran (0.1 and 1 mg, respectively) to those elicited by regimens previously associated with disease enhancement following infection. The immunological and safety signature of elasomeran in challenge studies using the mouse-adapted SARS-CoV-2, passage 10, lethal challenge virus (MA10) [52,53]. BALB/c mice were immunized twice with whole-inactivated SARS-CoV-1 or SARS-CoV-2virus, heat-denatured spike protein (S-2P), or elasomeran. Whole-inactivated virus and denatured Sprotein were formulated with alum to recapitulate conditions that resulted in VAED in a prior preclinical coronavirus vaccine study [54]. These regimens consistently induced low to moderate concentrations of S-binding and neutralizing antibody and Th2-skewedS-reactive CD4+ T-cells. After viral challenge, these mice were partially protected from weight loss and viral replication yet displayed enhanced pulmonary inflammation and eosinophil infiltration. In contrast, elasomeran elicited potently neutralizing antibodies and a balanced or type-1-skewed response, particularly at the 1 mg dose, and mice were protected from viral replication and lung inflammation after viral challenge. Importantly, a subprotective mRNA dose of 0.1 mg was associated with reduced immunopathology after challenge compared to the control and Th2-skewing groups. These results demonstrate that elasomeran elicits potent antiviral immunity and a favorable immune profile not associated with VAERD, even at sub-protective doses.

As of the DLP of this PBRER, SARS-CoV-2 vaccines have not been associated with VAED in preclinical studies or in any ongoing or completed clinical studies for elasomeran, nor in any post-marketing reports received in the GSDB. Even with the potential for new variants/serotypes of SARS-CoV-2, to provoke sub-neutralizing antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as it was the case for SARS-CoV-2 variant Omicron, which demonstrates a drop in neutralizing antibody titres in patients who have received two doses of a mRNA COVID-19 vaccine [55]. Despite this drop in neutralization, enhancement of disease has not been reported. Infection with other variants of SARS-CoV-2 have also been shown to impact antibody binding to SARS-CoV-2 and its variants post-vaccination through imprinting, but no disease enhancement has been reported in these cases either [56]. Seasonal coronaviruses also appear to provide a level of back-boosting or cross-protection in some individuals [57,58]. Cross-reactivity has been observed between SARS-CoV-1 and SARS-CoV-2, which results in improved vaccine-induced immune responses by provoking the generation of broadly- neutralizing antibodies against a wide variety of coronaviruses [59]. Waning antibody levels, which are a cause of ADE in dengue virus infection, have been observed 6 months following vaccination with a dengue vaccine [60,61]. However, regarding vaccination with COVID-19 vaccines, a level of protection is still being observed to date in vaccinated people and there have been no documented cases of VAED owing to this or any other cause in SARS-CoV-2. Memory T-cells induced in response to vaccination have been shown to have highly heterogenous antigen-specific responses, which are thought to contribute to long-term protection against severe disease [62]. Even with robust antibody escape as seen in Omicron, T-cell responses are likely to be sustained [63].

Gartlan et al., [47] reviewed the literature surrounding the phenomenon of VAED in pathogenic human coronaviruses, including MERS-CoV, SARS-CoV-1 and SARS-CoV-2. According to the author, histopathological data of poor quality and a lack of consistency in defining severe pathology and VAED in preclinical studies of MERS-CoV and SARS-CoV-1 vaccines in particular make it difficult to interrogate potential cases of VAED, but overall, the authors concluded that genetic vaccine platforms (mRNA and viral vectors) are in theory less likely to induce associated enhanced disease than inactivated vaccines or natural infection. This is because genetic platforms ensure that responses are generated against unmodified neutralizing epitopes, encoded by the platform, while inactivated whole-virus vaccines have a wider variety of epitopes for the immune system to generate responses against.

Based on all the information provided the MAH is proposing the removal of VAED including VAERD as an Important Potential Risk from the Spikevax EU-RMP, and to continue monitoring VAED including VAERD through routine surveillance.

Regarding the ModernaTx, Inc. Supplemental Follow-up Questions for Reports of Suspected/Confirmed COVID-19 Events with the use of Moderna COVID-19 vaccine (elasomeran)-COVID-19/Vaccine Failure Questionnaire:

• During the reporting period of this PBRER, a total of 1,706 TFQs for Suspected/Confirmed COVID-19 events were sent by the MAH, of which 45 TFQ responses were received. The response rate to this questionnaire was 3%.

This very low response rate indicates that the current requested follow-up information does not substantiate and contribute to additional risk characterization. ModernaTx, Inc. intends and applies within this PBRER procedure to remove VAED as an important potential risk and upon approval no follow-up measures and questionnaires deemed to be necessary.

Discussion

Although VAED was raised as a safety concern for COVID-19 vaccines early in the pandemic, current evidence does not suggest that this hypothetical construct presents a confirmed risk. More than 772 million elasomeran doses are estimated to have been administered since the first EUA, and it is likely that

VAED would have been observed and reported if it were both confirmed and more than a very rare event. Motivation to monitor COVID-19 vaccine recipients for possible VAED arose from sources such as animal models in which pathogenesis suggested a common potential mechanism producing VAED related to RSV vaccines in MERS and SARS-CoV-1 [49]. To date, no pathognomonic presentation of VAED has been recognized following immunization of >902 million individuals with elasomeran vaccines. Further, analysis of the immune profile of elasomeran in a mouse model shows elicitation of a protective immune profile that is not associated with vaccine-enhanced disease upon SARS-CoV-2 challenge [51]. Given the diverse clinical manifestations and sequelae of wild type COVID-19 disease, however, it is nearly impossible to assert that a given clinical course of disease represents enhancement of what would have been observed in the absence of vaccination. As such, identification of VAED at the individual case level continues to be infeasible at this time [46]. At a population level, VAED can only occur as a result of infection with wild type virus following vaccination, and its incidence (if identifiable) would be challenging to ascertain based both upon challenges in diagnosis and in ascertainment through post-authorization data sources (e.g., limitations in the thoroughness of spontaneous reports). Use of historical incidence data would be unlikely to provide useful context given inextricable linkage to factors such as local incidence of COVID-19 in the source population [64]. Further, severity associated with prevailing variants may change over time, making it difficult to claim that a change in severity is attributable to VAED.

Interpretation of analyzes considering the possibility of VAED has not changed based on data accrued during this review period. Although surveillance for signs of VAED has been conducted by ModernaTx, Inc. and HAs since the EUA, currently available post-authorization data do not provide evidence to support the hypothesis that this phenomenon exists. In the absence of a pathognomonic presentation, ModernaTx, Inc. will continue to review cases of vaccine failure to determine whether discernable changes in population level characteristics of disease presentation vary for vaccine failure events.

The large scale use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered. Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 408,226,293 individuals received a first dose, 275,197,667 received a second dose, 166,419,347 received a third dose, and 62,984,506 received a fourth dose, with third and fourth doses including both original elasomeran and Spikevax bivalent booster dose formulations.

Additionally, the SPEAC working group, recommend the following guidance for duration of surveillance activities related to VAED:

• The Working Group recommended a minimum period of 1 year surveillance for VAED in vaccine CTs where it is potential AESI.

• For any pathogens with a seasonal distribution, it is recommended to continue follow-up through at least two years in case there is variation in strains from year to year which could impact on natural disease severity.

With this large number of doses of elasomeran that has been administered worldwide, no cases of VAED have been reported to the MAH's GSDB. The MAH has a comprehensive and systematic approach to evaluating all available safety information, including that pertaining to VAED. As of the DLP for this PBRER (17 Dec 2022), there is no evidence to support the hypothesis that this phenomenon exists. The MAH is proposing the removal of VAED as an Important Potential Risk from the Spikevax EU-RMP, and to continue monitoring VAED through routine surveillance.

• The MAH has monitored VAED in each PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and given the amount of safety data accumulated given the unprecedent use of these vaccines, the MAH has found no evidence to support the hypothesis that this phenomenon exists or that there is a causal relationship to the vaccine.

• Despite the large number of doses of elasomeran that has been administered worldwide, no cases of VAED have been reported to the MAH's GSDB.

• As of the DLP of this PBRER, SARS-CoV-2 vaccines have not been associated with VAED in preclinical studies or clinical use. Even with the emergence of multiple new variants/serotypes of SARS-CoV-2, with their potential to provoke sub-neutralizing antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as was the case for SARS-CoV-2 variant Omicron, no enhancement of disease has been reported.

• Despite widespread use of the elasomeran vaccines (>800 million individuals vaccinated with at least one dose) there is no convincing evidence to support the hypothesis that VAED exists or that it has a causal relationship to the vaccine.

• There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to VAED.

Based on all the information provided the MAH is proposing the removal of VAED including VAERD as an Important Potential Risk from the EU-RMP, and to continue monitoring VAED including VAERD through routine surveillance.

Conclusion

After careful review of all new safety data received cumulative and during the reporting period for the safety topic of VAED, the benefit-risk profile for elasomeran, elasomeran/imelsomeran and elasomeran/davesomeran remains favorable.

The MAH has monitored VAED in each MSSR as well as PSUR since EUA (18 Dec 2020) at the request of the EMA. Over the years of analysis and the large scale use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found no evidence to support the hypothesis that this phenomenon exists. The MAH is proposing the removal of VAED including VAERD as an Important Potential risk from the EU-RMP, and to continue monitoring VAED including VAERD through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Rapporteur assessment comment:

The MAH proposed removal of VAED including VAERD as an Important Potential Risk from the EU-RMP, which is endorsed (see section 3.1.4.1.1. . Furthermore, the MAH proposed to continue monitoring VAED including VAERD through routine surveillance. The PRAC Rapporteur wants to specify that, based on the cumulative evidence, this risk is refuted and no longer considered important in the context of the RMP **and** the PSUR. I.e. it should be removed from the PSUR list of safety concerns and an evaluation of new information on this topic in future PSURs is not expected.

2.3.2.2. IgA Nephropathy (safety concern in PSUR only)

Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTx, Inc. for the Cumulative period for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed cover the period from 18 Dec 2020 to 17 Dec 2022.

Background Relevant to the Evaluation

IgA nephropathy is considered the most common type of primary glomerulonephritis and is diagnosed only by kidney biopsy, with a global incidence of 2.5/100,000 adults per year. This condition occurs more commonly in Asian populations, followed by Europeans, and less commonly in African populations. The most frequent sign or symptom of IgA nephropathy is blood in the urine (hematuria) followed by albuminuria; however, the frequent lack of signs or symptoms in the early stages of IgA nephropathy makes it difficult to determine how many people are affected. This glomerular disease results from deposits of immunoglobulin A (IgA) in the glomerulus and mesangium. IgA nephropathy can progress for years with no noticeable clinical symptoms or findings on routine tests. For example, a study in Japan found IgA deposition in 14.5% of donated kidneys from unrelated donors, and nearly 2% exhibited mesangio-proliferative changes with C3 deposits characteristic of IgA nephropathy. Also, IgA nephropathy accounts for up to 40% of native kidney biopsies from eastern Asia. In some cases, IgA nephropathy runs in families and scientific studies have recently found several genetic markers that may be associated with its development. In addition, development of IgA nephropathy may be related to respiratory or intestinal infections and the associated immune activity. Studies have found that patients with IgA nephropathy have serum IgA that contains less galactose than normal; such galactose-deficient IgA may become immunogenic and lead to development of IgA and/or IgG antibodies against the galactose-deficient IgA, with the subsequent development of immune complexes. The only definitive diagnosis of IgA nephropathy is by renal biopsy with findings of IgA complexes deposited in the glomeruli and mesangium. IgA nephropathy is generally more common in men than women and can be diagnosed at all ages. Diagnosis is most common in the second and third decades of life, with approximately 80% of patients between the ages 16-35 years at time of diagnosis. The exact etiology and pathophysiology of IgA nephropathy are presently not known.

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

Clinical Trial Data

The topic of IgA nephropathy was cumulatively reviewed in the clinical trial datasets (no new data is available for this reporting period, hence no change in the available information from the previous PBRER#3), within the following studies of:

• P301 study (ages ≥18 years; DLP: 04 May 2021), There were approximately 30,000 participants randomized in 1:1 ratio to dose groups placebo (n = 15,000) and mRNA-1273 100 µg (n = 15,000) with vaccine schedule of 2 IM doses, 28 days apart.

• P203 study (ages 12-17 Years; DLP: 27 Jan 2022) There were approximately 3,000 participants randomized in 2:1 ratio with a vaccine schedule of 100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart.

• P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022). There were approximately 4500 participants in different age groups randomized in 3:1 ratio with a vaccine schedule of 25, 50, 100 µg mRNA-1273 (25 µg only for 6 months to < 2 years age group) or placebo (3:1) 2 IM doses, 28 days apart.

Review of these studies found zero cases.

List of PTs in MedDRA HLT of Glomerulonephritis and Nephrotic Syndrome:

Alagille syndrome, Alport's syndrome, Anti-LRP2 nephropathy, Anti-glomerular basement membrane disease, Benign familial haematuria, C1q nephropathy, C3 glomerulopathy, Chronic autoimmune glomerulonephritis, Congenital nephrotic syndrome, Denys-Drash syndrome, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Frasier syndrome, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis chronic, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Goodpasture's syndrome, Granulomatosis with polyangiitis, HIV associated nephropathy, Henoch-Schonlein purpura nephritis, Hepatitis virus-associated nephropathy, IgA nephropathy, IgM nephropathy, Immunotactoid glomerulonephritis, Membranous-like glomerulopathy with masked IgG-kappa deposits, Mesangiolipidosis, Mesangioproliferative glomerulonephritis, Microscopic polyangiitis, Nephritic syndrome, Nephritis allergic, Nephrotic syndrome, Paraneoplastic glomerulonephritis, Paraneoplastic nephrotic syndrome, Post infection glomerulonephritis, Post streptococcal glomerulonephritis, Primary coenzyme Q10 deficiency and Pulmonary renal syndrome.

Review of the Pharmacovigilance Database

The MAH queried the GSDB, cumulative to 17 Dec 2022 for valid case reports of Glomerulonephritis and Nephrotic Syndrome received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the MedDRA HLT glomerulonephritis and nephrotic syndrome. All case reports identified from the above search (whether or not the PT IgA Nephropathy was coded) were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected

See Appendix 11.3. in the PSUR.

Overview of Cases:

Cumulative data Review (cumulative to 17 Dec 2022)

Cumulatively as of the DLP (17 Dec 2022), a total of 237 cases (272 events) were retrieved using the broad search criteria specified above. These 237 cases (whether or not the PT IgA Nephropathy was coded) were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy. See the following (Appendix 11.17 in the PSUR) for line listings and MAH review assessments of these 237 cases, with a focus on IgA nephropathy.

Medical review identified 68 cases involving IgA nephropathy; 43 cases were new onset (DeNovo) IgA nephropathy, and 25 cases were considered IgA nephropathy flares because they were reported to have exacerbation of IgA nephropathy that had been diagnosed prior to elasomeran vaccination. The largest numbers of cases were reported from the United States (18; 33.3%), Japan (16; 23.5%), Germany (6; 8.8%), Switzerland (5; 7.4%) and Taiwan, Province of China (5; 7.4%) Table 16.101.

Table 16.101 Summary of Cases Reported, by Country, stratified by IgA DeNovo and IgA Flare

Region	IgA Nephropathy				Total # Of Cases	Total % Of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
United States	10	14.7	8	11.8	18	26.5
Japan	13	19.1	3	4.4	16	23.5
Germany	5	7.4	1	1.5	6	8.8
Switzerland	3	4.4	2	2.9	5	7.4
Taiwan	2	2.9	3	4.4	5	7.4
France	1	1.5	2	2.9	3	7.4
Spain	1	1.5	1	1.5	2	4.4
Norway	2	2.9	0	0	2	2.9
United Kingdom	0	0	2	2.9	2	2.9
Ireland	1	1.5	0	0	1	1.5
Italy	0	0	1	1.5	1	1.5
Sweden	1	1.5	0	0	1	1.5
Poland	0	1.5	1	1.5	1	1.5
Finland	1	1.5	0	0	1	1.5
Qatar	1	1.5	0	0	1	1.5
Korea, Republic Of	1	1.5	0	0	1	1.5
Denmark	0	0	1	1.5	1	1.5
Netherlands	1	1.5	0	0	1	1.5
Grand Total	**43**	**63.2**	**25**	**36.8**	**68**	**100.0**

There were no reports of fatalities in the medically confirmed IgA nephropathy cases. IgA nephropathy was reported more often in Females (38; 55.9%) compared to Males (30; 44.1%), which is different from general data showing that IgA nephropathy is more common in men than women. UpToDate states: "Patients with IgA nephropathy cases may present at any age, but there is a peak incidence in the second and third decades of life. There is approximately a 2:1 male-tofemale predominance in North American and Western European populations in both adults and children, although the sexes are equally affected among populations in East Asia." An Overview of 68 Cases is presented in Table 16.102.

Table 16.102 Summary of Cases Reported for IgA Nephropathy by Age and Gender

Age Group	Female		Male		Total # of Cases	Total % of Cases
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
12-17	2	2.9	1	1.5	3	4.4
18-29	8	11.8	7	10.3	15	22.1
30-39	8	11.8	5	7.4	13	19.1
40-49	9	13.2	7	10.3	16	23.5
50-64	6	8.8	6	8.8	12	17.6
65-74	3	4.4	4	5.9	7	10.3
Missing	2	2.9	0	0	2	2.9
Grand Total	**38**	**55.9**	**30**	**44.1**	**68**	**100.0**

Figure 16-14 and Figure 16-15 indicate the time from vaccination with elasomeran to onset of IgA nephropathy, where this information was available, and are based on medical review of the cases. Onset of IgA nephropathy occurs mostly in the two days following vaccination with more events after the second vaccination. This coincides with the known enhanced immune response seen with boosted vaccinations. This pattern is generally similar to that of all AEs reported following elasomeran immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. At this time, with the limited number of reports, this finding is an observation, as there is no clear biological explanation.

Figure 16-14. Reported IgA Nephropathy DeNovo Events by Dose & Time to Onset Cumulative thru 17 Dec 2022

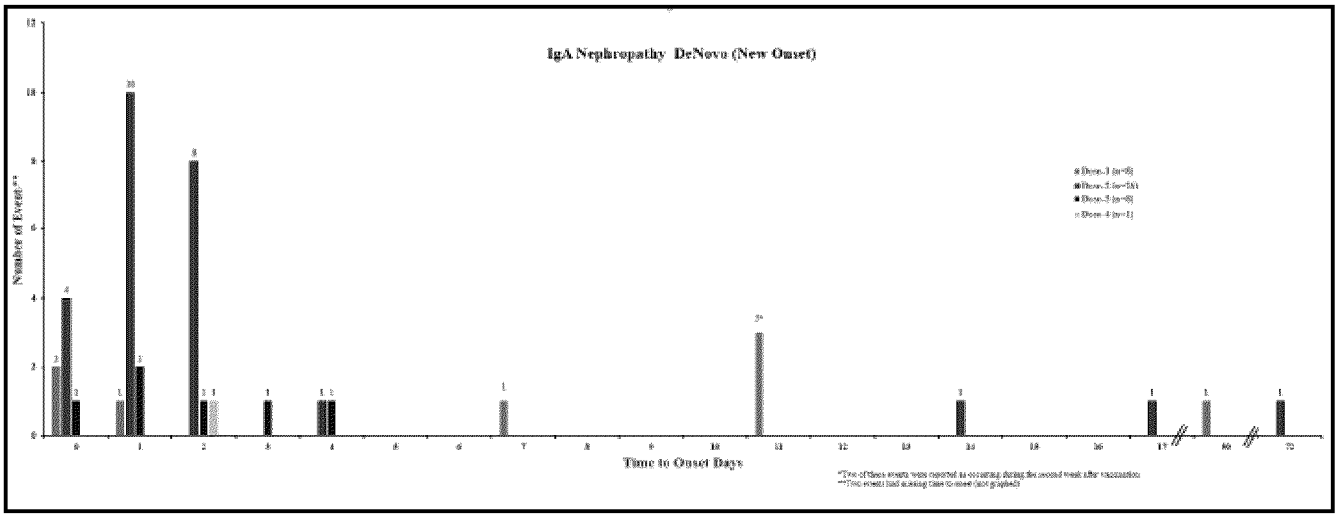
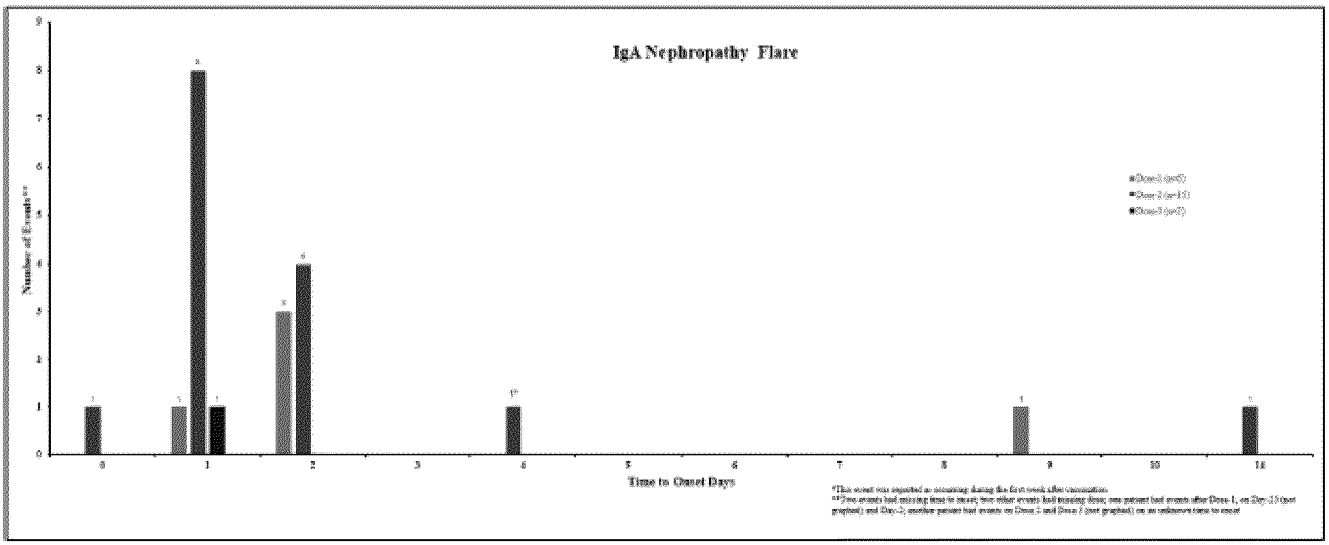


Figure 16-15 Reported IgA Nephropathy Flare Events by Dose & Time to Onset Cumulative thru 17 Dec 2022



The MAH has evaluated cumulatively all cases with IgA nephropathy, DeNovo and flare, temporally associated with elasomeran according to the WHO-UMC causality classification. Most of the cases (37; 54.4%) were considered possible due to temporal association and lack of adequate information for complete clinical evaluation. A summary of WHO causality assessments is presented below in Table 16.103.

Table 16.103 WHO-UMC Causality Classification for IgA Nephropathy Cases As of 17 Dec 2022

WHO Causality	IgA Nephropathy				Total # Of Cases	Total % Of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
Conditional	10	14.7	4	5.9	14	20.6
Possible	24	35.3	13	19.1	37	54.4
Probable	0	0	5	7.4	5	7.4
Unassessable	8	11.8	3	4.4	11	16.2
Unlikely	1	1.5	0	0	1	1.5
Grand Total	**43**	**63.2**	**25**	**36.8**	**68**	**100.0**

Review of counts of IgA nephropathy cases by initial receipt date and PBRER reporting period shows that in the current PBRER#4 reporting period there has been a decrease in number of cases reported (14 cases), compared to the prior two periods which both had 23 cases (Table 16.104). The cumulative reporting rate remains < 1 case per 10 million doses.

Table 16.104 Distribution of IgA Nephropathy Cases by PBRER Period and Reporting Rate

PBRER Period/# (Doses Administered)	IgA Nephropathy				Total Cases	Total % Cases	Cumulative Reporting rate per 10 million Doses
	DeNovo		Flare				
	# Cases	%	# Cases	%			
PBRER-1 (182,716,703)	6	8.8	2	2.9	8	11.8	0.44
PBRER-2 (466,804,529)	12	17.6	11	16.2	23	33.8	0.66
PBRER-3 (662,871,167)	16	23.5	7	10.3	23	33.8	0.81
PBRER-4 (903,896,822)*	9	13.2	5	7.4	14	20.6	0.75
Grand Total	**43**	**63.2**	**25**	**36.8**	**68**	**100.0**	-

*Doses administered include Bivalent elasomeran/imelasomeran and elasomeran/davesomeran

Reporting Period Data Review (19 Jun 2022 through 17 Dec 2022)

During the reporting period, a total of 52 cases (59 events) were identified using the broad search criteria specified above (using the HLT glomerulonephritis and nephrotic syndrome). These reports were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy; see PSUR Appendix 11.17 for line listings and MAH review assessments of these 52 cases.

Medical review identified 14 cases of IgA nephropathy; 5 cases were IgA flares, having already been diagnosed with IgA nephropathy prior to elasomeran, and 9 cases were newly diagnosed (DeNovo) IgA nephropathy. Most of the cases were reported from Japan (10; 71.4%), with four other countries reporting one case each Table 16.105).

Table 16.105 Summary of Cases Reported for Region stratified by IgA DeNovo and IgA Flare (19 Jun 2022 to 17 Dec 2022)

Region	IgA Nephropathy				Total # of Cases	Total % of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
Japan	7	50	3	21.4	10	71.4
Denmark	0	0	1	7.1	1	7.1
Ireland	1	7.1	0	0	1	7.1
Spain	0	0	1	7.1	1	7.1
Taiwan	1	7.1	0	0	1	7.1
Total Cases	**9**	**64.3**	**5**	**35.7**	**14**	**100**

There were no reports of fatal cases. IgA Nephropathy was reported in 9 females (64.3%) and 5 males (35.7%) In Asia, where background incidence of IgA nephropathy is highest, approximately equal proportions of men and women are affected. Patients with IgA nephropathy cases may present at any age, but there is a peak incidence in the second and third decades of life. There is approximately a 2:1 male-to-female predominance in North American and Western European populations in both adults and children (UpToDate). Demographic information on the 14 cases is presented in Table 16.106.

Table 16.106 Summary of Cases Reported for IgA Nephropathy by Age and Gender (19 Jun 2022 to 17 Dec 2022)

Age Group	Female		Male		Total # of Cases	Total % of Cases
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
18 -29	2	14.3	0	0.0	2	14.3
30 - 39	2	14.3	0	0.0	2	14.3
40 -49	2	14.3	3	21.4	5	35.7
50 -64	2	14.3	1	7.1	3	21.4
65 - 74	1	7.1	1	7.1	2	14.3
Grand Total	**9**	**64.3**	**5**	**35.7**	**14**	**100**

Figure 16-16 and Figure 16-17 indicate dose and time from vaccination with elasomeran to onset of IgA nephropathy, where this information was available, and are based on medical review of the cases. IgA nephropathy symptoms, whether from flare or DeNovo illness, were reported with onset in the two days following vaccination. This coincides with the known reactogenicity seen with vaccinations. This pattern is also generally similar to that of all AEs reported following elasomeran immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. At this time, with the limited number of reports, this TTO pattern remains an observation, not materially different from the pattern of previous reporting periods, and there is no clear biological explanation.

Figure 16-16. Reported IgA Nephropathy DeNovo Events by Dose & Time to Onset (19 Jun 2022 through 17 Dec 2022)

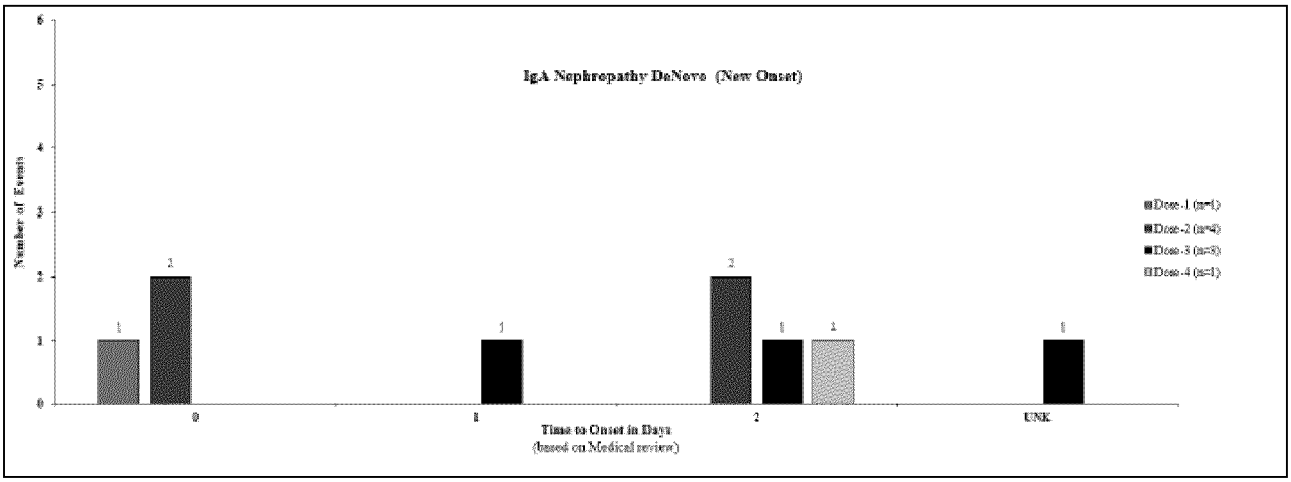
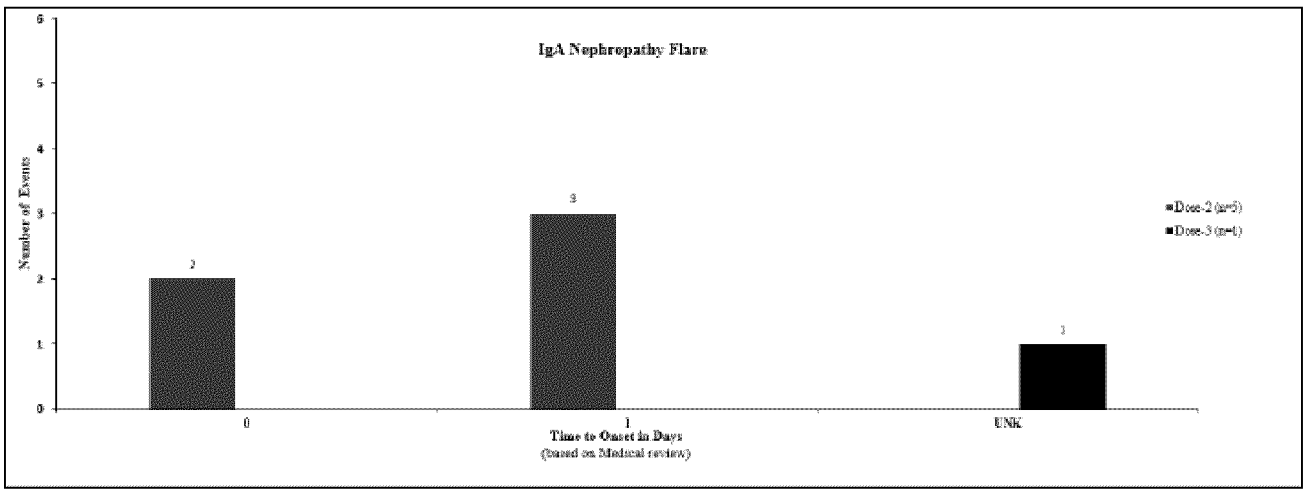


Figure 16-17. IgA Flare Events (*6 events in 5 cases*) by Dose and Time to Onset (19 Jun 2022 through 17 Dec 2022)



Brighton Collaboration/ CDC Working Case Definition/ WHO Causality Assessment

Neither the Brighton Collaboration nor CDC has established a case definition for IgA nephropathy. We have considered a case as IgA nephropathy if there was reported renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy. WHO Causality Assessment. The MAH has evaluated cumulatively all cases with DeNovo or flare IgA nephropathy reported following elasomeran according to the WHO-UMC causality classification. Most of the cases (8; 57.1%) were considered possible due to temporal association and lack of adequate information for complete clinical evaluation, with the presence of confounding factors also in some cases. A summary of WHO causality assessments is presented in Table 16.107. Additional information on individual case assessments, with justification of the causality determinations, appears in the Appendix 11.17 to the PSUR.

Table 16.107 WHO-UMC Causality Classification for IgA Nephropathy Cases (as of 19 Jun 2022 through 17 Dec 2022)

WHO Causality	IgA Nephropathy				Total # of Cases	Total % of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
Conditional	5	35.7	1	7.1	6	42.9
Possible	4	28.6	4	28.6	8	57.1
Grand Total	**9**	**64.3**	**5**	**35.7**	**14**	**100.0**

IgA Nephropathy in Persons with Age < 18 years

There were no reports of IgA in the pediatric population.

IgA Nephropathy After Receiving Booster Dose with elasomeran/imelasomeran

There were no reports of IgA nephropathy associated with elasomeran/imelasomeran.

IgA Nephropathy After Receiving Booster Dose with elasomeran/davesomeran

There were no reports of IgA nephropathy associated with elasomeran/davesomeran.

Literature Review:

The MAH performed a focused search of PubMed for elasomeran and IgA Nephropathy to retrieve relevant literature during this reporting period. The exact search criteria are specified in Appendix 12.1d. A total of 177 literature articles was retrieved. Medical/scientific review of these articles identified one article that provided new and significant safety findings. This article's key information is summarized below.

Title: Incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination is not increased [161].

Authors: Matthias Diebold, Eleonore Locher, Philipp Boide, Annette Enzler-Tschudy, Anna Faivre, Ingeborg Fischer, Birgit Helmchen, Helmut Hopfer, Min Jeong Kim, Solange Moll,Giliane Nanchen, Samuel Rotman, Charalampos Saganas, Harald Seeger and Andreas D. Kistler

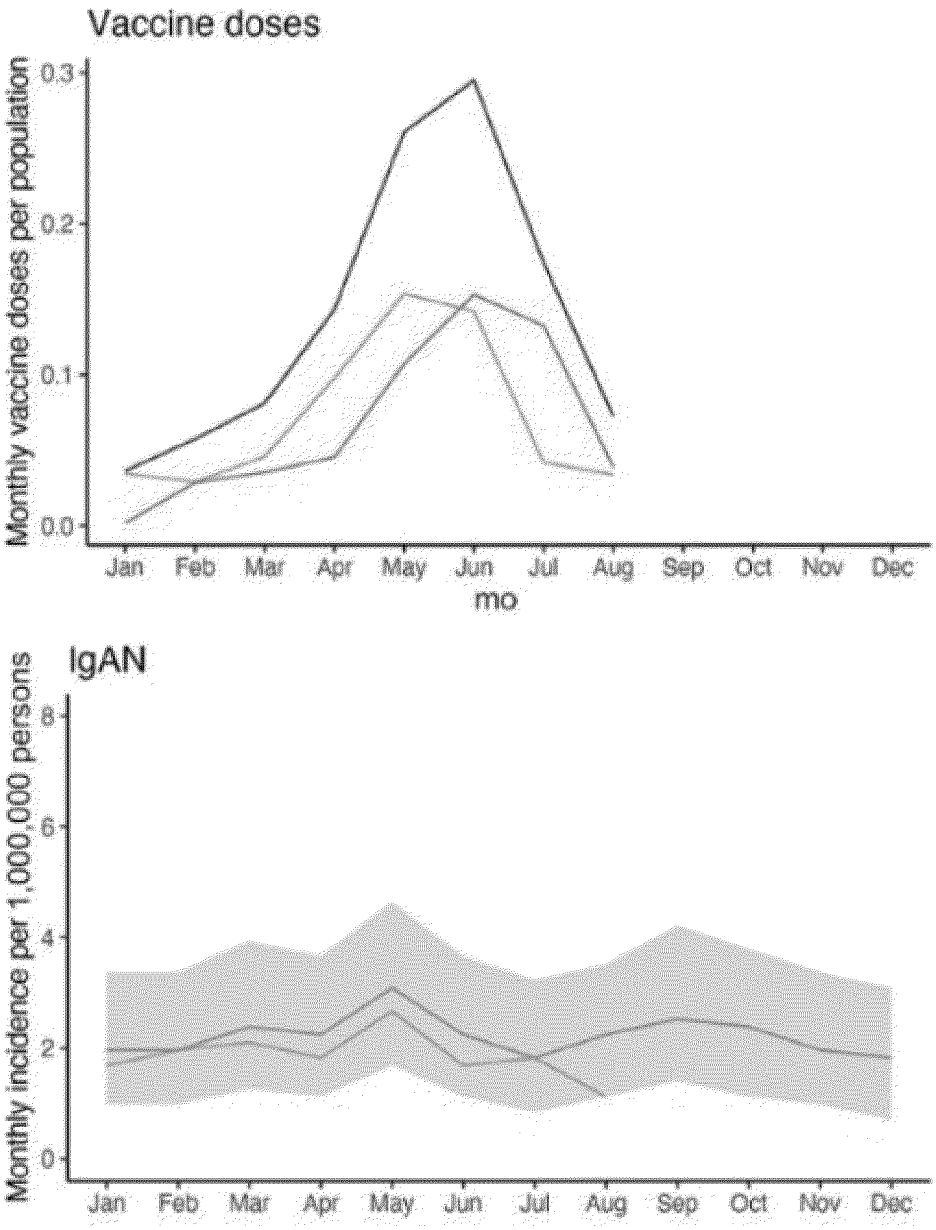
Citation: Kidney International 2022; 102:1409-1419. doi: 10.1016/j.kint.2022.08.021

Abstract: [161] studied the incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination in a nationwide retrospective cohort and case-cohort design study in Switzerland during the vaccination campaign in Jan 2021 to Aug 2021. Data from all Swiss pathology institutes processing native kidney biopsies were used to calculate incidence of IgA nephropathy and other nephropathies in the adult Swiss population. Using a Bayesian model based on the years 2015 to 2019 as the comparator, the observed incidence during the vaccination campaign was not significantly different from the expected incidence (incidence rate ratio 0.86, 95% credible interval 0.73–1.02) and did not cross the upper boundary of the 95% credible interval for any month. Among 111 patients 18 years and older with newly diagnosed glomerulonephritis between Jan 2021 and Aug 2021, 38.7% had received at least one vaccine dose before biopsy, compared to 39.5% of the general Swiss population matched for age and calendar time. The calculated risk ratio for the development of new onset biopsy-proven glomerulonephritis was not elevated at 0.97 (95% confidence interval 0.66–1.42) in vaccinated vs. unvaccinated individuals. Patients with glomerulonephritis manifesting within four weeks after vaccination were similar clinically to those with illness temporally unrelated to vaccination. To summarize this article's main findings, mRNA vaccination against SARS-CoV-2 was not associated with new onset glomerulonephritis in these two

complementary studies, and most temporal associations between SARS-CoV-2 vaccination and glomerulonephritis were likely coincidental and consistent with background events in the years prior to the pandemic.

With specific reference to IgA nephropathy, of the 111 new onset glomerulonephritis patients in the study the majority (58, 52.3%) were histologically diagnosed with IgA nephropathy. The figures below, from the article by Diebold et al, clearly and graphically demonstrate the lack of temporal association between the Swiss mRNA vaccination campaign and the incidence of IgA nephropathy in this nationwide study. In addition, in the case-cohort analysis, the risk ratio for development of biopsy-proven IgA nephropathy compared to matched comparator individuals was 1.14 (95% CI 0.67-1.97, p=0.73).

Figure 16-18 Expected and observed incidence of glomerulonephritis during the vaccination campaign



Reference: [161].

Figure 16-18 shows Expected and observed incidence of glomerulonephritis during the vaccination campaign. Shown is the number of first (orange), second (blue), and total (gray) doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines as a fraction of all patients aged ≥20 years (upper-left panel) and the observed incidence of glomerulonephritis in patients aged ≥18 years from Jan 2021 to Aug 2021 (red line) compared with the expected incidence based on the years 2015–2019 (blue line) with 95% credible intervals (green shading) for IgA nephropathy.

Company Comment: Taken together the findings of the article by Diebold et al provide rigorous population-based evidence against a causal association between mRNA vaccines and incidence of IgA nephropathy. The study included all renal biopsy centers in Switzerland, so that case ascertainment was complete, or nearly so. In addition, the study period was at the peak of mRNA vaccine administration; therefore, if an effect of vaccination on incident IgA nephropathy were to be observed, the dates of the study were optimal to detect such an effect; however, no effect was observed.

Discussion

IgA nephropathy is the most common form of primary glomerulopathy. The prevalence of IgA nephropathy is unknown because of the often-latent nature of the disease. It may remain silent for years without clinical signs or symptoms. IgA nephropathy has been found in families and recent data have demonstrated various genetic markers. Potential triggers include respiratory and gastrointestinal illnesses as well as other immune activation events. The exact etiology and pathophysiology of IgA nephropathy remain unknown.

There have been no high-quality studies finding a causal link between IgA nephropathy and elasomeran or the ModernaTx, Inc. bivalent vaccines. Moreover, the study by Diebold et al, summarized above, provided rigorous and reassuring findings from a nationwide study in Switzerland showing a lack of association between mRNA vaccines and DeNovo IgA nephropathy. Further, in the MAH's CTs noted above, there have been zero cases of IgA nephropathy. No pathophysiologic process has been shown to explain a causal association between elasomeran or the ModernaTx, Inc. bivalent vaccines and IgA nephropathy, and there is also no identified pathognomonic sign of such an association.

Cumulatively in the MAH's GSDB, there have been 68 reports of IgA nephropathy following elasomeran vaccination among an estimated 772.9 million vaccinees. This represents a reporting rate of < 1 case of IgA nephropathy per 10 million elasomeran vaccinees, constituting an extremely rare occurrence. For elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran 903,896,822 doses have been administered. For the elasomeran/imelasomeran an estimated total of 70,077,685 doses have been administered, with zero cases of IgA nephropathy reported. For the elasomeran/davesomeran an estimated 60,910,179 doses have been administered, also with zero cases of IgA nephropathy reported.

Of the 68 reports of IgA nephropathy following elasomeran vaccination, 43 cases were DeNovo and 25 cases were flares. The number of vaccinees with IgA nephropathy is unknown. Persons with IgA nephropathy are already likely to seek medical attention when they have gross hematuria or other signs and symptoms of renal dysfunction. No data have indicated the value of active screening or additional education of IgA nephropathy patients' post-vaccination. Renal patients are at increased risk of serious illness and death due to COVID-19 disease; thus, vaccination is of great benefit to them.

Conclusion

Overall, similar to PBRER#3, based on the analysis of all available safety data as of 17 Dec 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the development of IgA nephropathy. No new or emerging safety issues of concern were identified in the

current reporting period. The MAH will continue to carefully monitor IgA Nephropathy events using routine pharmacovigilance surveillance.

Rapporteur assessment comment:

The signal of IgA Nephropathy (IgAN) was reviewed, refuted and closed in the previous PSUR/PSUSA#3. In the current reporting period (DLP 17 Dec 2022), the following data on this important potential risk was reported by the MAH.

No new data from clinical trials were available (previous trials found no cases of IgAN).

O/E analysis update

Using Wyatt et al (2013) as reference, no overall statistically significant overreporting of IgAN was found in the reporting period nor cumulatively. The gender and age stratification, even considering 25% reporting, showed no deviation from the expected.

A cumulative sensitivity analysis for medically reviewed DeNovo cases alone (n=39) and including flares (n=23), totalling 62 cases with known TTO <22 days for the three risk-windows of 21, 7 and 3 days, respectively, showed no significant overreporting "as observed". However, assuming 50% reporting, significant overreporting was noted in the 3-day window including all 62 cases (1.81 (1.31, 2.51)) and assuming 25% reporting also for DeNovo-cases alone (2.21 (1.61, 3.02)). Further, including all 62 cases, the 7-day risk window and assuming 25% reporting, a small, but significant overreporting was noted (1.68 (1.35, 2.08)).

The rapporteur notes that in the O/E analysis potential overreporting of medically reviewed IgAN cases was most likely within the first week after vaccination.

Overview of Cases

By MAH definition, a case was considered as IgA nephropathy if there was reported renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy.

Cumulatively, medical review identified 68 cases involving IgA nephropathy. 43 cases were new onset (DeNovo) IgA nephropathy, and 25 cases were considered IgA nephropathy flares. Half of the cases were reported from US or Japan. An overall female preponderance (56%) was noted, while an overall male preponderance would be expected. The age distribution of cases was about equal among subjects in the 18-64 years age range. There were no fatalities reported.

In accordance with the O/E analysis, it was observed that the onset of IgA nephropathy occurs mostly in the two days following vaccination with more events after the second vaccination. As noted by the MAH, "this coincides with the known enhanced immune response seen with boosted vaccinations" and thus compatible with the expected biology of IgAN as an ADR, "but could also represent reporting bias for events proximal to vaccination or could be related to immune stimulation from vaccination that occurs within the first days after vaccination." This is endorsed.

During the review period medical review identified 14 cases of IgA nephropathy of which 5 cases were flares. Most of the cases were reported from Japan (10; 71.4%), and of note, none were reported from the US (cumulatively contributing with most cases, table 16.101).

Most of the 14 cases (8; 57.1%) were considered WHO-UMC Possible "due to temporal association and lack of adequate information for complete clinical evaluation, with the presence of confounding factors also in some cases." The remainder of cases were considered Conditional, i.e. with insufficient data to support assessment. Based on key data, the rapporteur assumes that the first 14 cases in PSUR Appendix 11.17d represent the 14 cases presented from the current review period. Nine of the cases originated from the literature, however some of the references provided in PSUR Appendix 11.17e did not return

relevant publications using PubMed. Based on the provided information and justification in Appendix 11.17d, the causality classification is not disputed.

However, the MAH is requested to supply literature references that are not readily accessible to the rapporteur in full-text format in English. The request concerns the following two publications:

- **Fukuda Y, Namiki M, Taniguchi M, Takata F, Osaki K, Taro Y et al. A case of recurrence of IgA nephropathy induced by vaccination with the COVID- 19 vaccine. The Japanese Journal of Nephrology. 2022;64 (6-W):173**
- **Higashi T, Ko T, Nakamura K, Adachi M, Mukoyama M. A case of IgA nephropathy diagnosed after gross hematuria after SARS-CoV-2 vaccination. The Japanese Journal of Nephrology. 2022;64 (6-W):P-174.**

In addition, the MAH is requested to provide English translation of the abstracts that were used as a source for cases number [redacted], [redacted] and [redacted], and that were published in:

- **The 65th Annual Meeting of the Japanese Society of Nephrology published in The Japanese Journal of Nephrology, 2022; 64(3)**

There were no reports of IgAN in the pediatric population and no reports associated with booster doses with elasomeran/imelasomeran nor with elasomeran/davesomeran.

Literature review

Case reports are considered above. The MAH identified 1 new article of interest from the reporting period:

Diebold M et al. Incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination is not increased. Kidney International 2022; 102:1409-1419. doi: 10.1016/j.kint.2022.08.021.

The authors studied the incidence of *new onset glomerulonephritis* after SARS-CoV-2 mRNA vaccination in a nationwide retrospective cohort and case-cohort design study in Switzerland during the vaccination campaign in Jan 2021 to Aug 2021. The authors conclude that "To summarize this article's main findings, mRNA vaccination against SARS-CoV-2 was not associated with new onset glomerulonephritis in these two complementary studies, and most temporal associations between SARS-CoV-2 vaccination and glomerulonephritis were likely coincidental and consistent with background events in the years prior to the pandemic."

Using the study data showing no difference between observed and expected rated of IgAN during the vaccination campaign, the MAH comments that "Taken together the findings of the article by Diebold et al provide rigorous population-based evidence against a causal association between mRNA vaccines and incidence of IgA nephropathy."

However, several limitations of the study are highlighted by the authors (limited national population, care not standardized, retrospective design, risk of selection bias, and others), also noting that "our results are limited to new-onset glomerulonephritis and cannot answer the question, whether SARS-CoV-2 vaccination could trigger relapses in patients with previously diagnosed glomerulonephritis, because relapses are usually diagnosed clinically without repeat biopsy."

Also, of note is the Journal Editor's boxed front-page comment: "This excellent study discusses new-onset glomerular disease in the face of coronavirus disease 2019 (COVID-19) mRNA vaccination. The readership is reminded that there has been an abundance of reports suggesting activation or worsening of pre-existing glomerular diseases after receiving the vaccines, especially IgA nephropathy and minimal change disease. Although these reports do not provide mechanistic proof of causation, timing of disease

exacerbation is consistent, and the association is plausible".

Overall conclusion

The rapporteur concludes that reporting of IgAN is rare and that the evidence is currently inconclusive regarding a possible causal role of vaccination with elasomeran. Thus, the MAH should **maintain IgAN as an important potential risk in the future PSURs**. **In the next PSUR, it is therefore expected that the MAH will present new information on IgA nephropathy and risk characterization in PSUR section 16.3 and 16.4, respectively. The MAH is also requested to include the following publication in the risk characterization in the next PSUR:**

- **Ma Y, Xu G. New-onset IgA nephropathy following COVID-19 vaccination. QJM. 2023 Feb 14;116(1):26-39. doi: 10.1093/qjmed/hcac185.**

2.3.3. Update on missing information

2.3.3.1. Use in Pregnancy

Source of the New Information

Information presented below includes analyzes performed on pregnancy cases received by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for the elasomeran and bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran). Cumulative data covers the period from 18 Dec 2020 to 17 Dec 2022.

The Company clinical and GSDB was queried for valid case reports of individuals who received elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran before or during pregnancy and reports concerning fetuses/neonates/infants whose mothers were vaccinated during gestation, received from HCP, HA, consumers and literature sources, cumulatively and for the reporting period, worldwide, for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

Use of ModernaTx, Inc. COVID-19 vaccines during pregnancy is an area of missing information in the RMP; no CTs were conducted among pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications in this [65] [66]. However, there is recognition that in absence of CTs, vigilant post-EUA passive report monitoring, real-world evidence, and pregnancy registries was needed to continue monitoring the safety of COVID vaccination in pregnant women.

There have been no specific safety concerns identified for COVID maternal immunization. Epidemiological studies have not indicated any increased risk of adverse perinatal outcomes including spontaneous abortion, preterm birth, small for gestational age birth, stillbirth, or neonatal intensive care admission after COVID-19 vaccination during pregnancy [67,68] [69,70] [71,72] [73] [74]. More specifically, a case-control study case-control study from Norwegian registries of 13,956 women with ongoing pregnancies (958 vaccinated) found adjusted odds ratios of 0.91 (0.75 to 1.10) for COVID-19 vaccination in the previous three weeks following a spontaneous abortion and 0.81 (0.69 to 0.95) for vaccination in the previous five weeks, showing no risk of early pregnancy loss after COVID-19 vaccination [71]. Another study used the VSD to analyze the odds of receiving a COVID-19 vaccine in the 28 days before a spontaneous abortion [69]. It found that pregnancies ending in a spontaneous abortion did not have an

increased odds of exposure to a COVID-19 vaccination in the previous 28 days compared with ongoing pregnancies.

A large registry-based study of births in Sweden and Norway (28,506 vaccinated; 129,015 unvaccinated) found no significant increased risk of adverse pregnancy outcomes including preterm birth, stillbirth, small for gestational age, or Neonatal intensive care unit (NICU) admission among people vaccinated against SARS-CoV-2 during pregnancy [71]. The results were similar for vaccinations during the second or third trimester, with one or two doses of vaccine, and with different mRNA vaccine types. A large (>10 000 people vaccinated during pregnancy) US based multisite retrospective cohort using VSD, with a diverse population and comprehensive data on vaccination did not find an increase in preterm birth or small for gestational age birth overall, stratified by trimester of vaccination, or the number of vaccine doses received during pregnancy, compared with unvaccinated pregnant women [70].

Another important perinatal outcome of interest after maternal vaccination is risk of fetal anomalies. Given the importance of timing in pregnancy and risk of fetal anomalies, a large cohort study evaluated the association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies and found no difference in incidence of congenital anomalies among people who received at least one dose of COVID-19 vaccine versus unvaccinated people [73]. Importantly, after control for potential confounders such as hemoglobin A1c level in the first trimester and age at delivery, vaccination within the highest risk period for teratogenicity was not associated with presence of congenital anomalies identified by ultrasonography (adjusted odds ratio 1.05, CI: 0.72 to 1.54). Additional studies have not found an increased risk of congenital anomalies among pregnant people received COVID-19 vaccines including elasomeran during pregnancy [72].

Additionally, emerging evidence provide support that infants receive protective benefits from maternal vaccination against COVID-19 [75,76]. One study evaluated the effectiveness of maternal vaccination during pregnancy against COVID-19 related hospital admission among infants during the first six months of life. Of 176 infants admitted with COVID-19, 16% of their mothers had been vaccinated compared with 32% of 203 infants admitted without COVID-19 [75]. Effectiveness of maternal vaccination during pregnancy against COVID-19 related hospital admission in infants aged <6 months was found to be 61% (31% to 78%). Effectiveness of a two dose covid-19 vaccination series was 32% (−43% to 68%) in the first 20 weeks of pregnancy and 80% (55% to 91%) after 21 weeks through 14 days before delivery. The gestational age breakdown has wide confidence intervals and should be interpreted with caution. Overall, completion of a 2-dose mRNA COVID-19 vaccination series during pregnancy seems to reduce COVID-19 related hospital admissions among infants aged <6 months, but the duration of clinical protection remains uncertain.

Although, there are still limited published data regarding elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy, the available data show no increased risk of adverse pregnancy outcomes among people vaccinated against SARS-CoV-2 during pregnancy, supporting recommendations for vaccination of pregnant people against SARS-CoV-2. Post-marketing safety data with elasomeran are relevant to the Spikevax bivalent vaccines because these vaccines are manufactured using the same process. Clinical trials and PMS including postauthorization safety studies thus far demonstrate that the reactogenicity and safety profile of the bivalents are similar and to date, no new safety concerns for the bivalents elasomeran/imelasomeran and elasomeran/davesomeran have been identified.

The MAH is closely monitoring the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in this population through routine pharmacovigilance [77].

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals during pregnancy and while breastfeeding in each PSUR, and rather only include new

information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of "Use in pregnancy and while breastfeeding" as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals during pregnancy and while breastfeeding through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports in ModernaTx, Inc. GSDB:

The MAH queried the GSDB for valid case reports of individuals who received elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran before or during pregnancy and reports concerning fetuses/neonates/infants whose mothers were vaccinated during pregnancy (referred to as "pregnancy cases"), received from healthcare providers, HAs, consumers, and the literature, cumulatively (18 Dec 2020 –17 Dec 2022) and for the reporting period (19 Jun 2022 – 17 Dec 2022).

The search strategy used to identify "pregnancy cases" (Pregnancy [MI-PREG&Pts Preg] was comprised of multiple components:

• Argus field "Patient Pregnant" = Yes OR

• MI-Preg (See Product Signaling Strategy Form [PSSF] 9.0) = Yes and Patient Preg = No AND gender=female and Age Group= (12-54) OR

• MI-Preg =Yes AND Patient Preg = No AND Age group <2 y/o OR "missing" AND PREGFetal Outcome <> (Empty) OR

• MI-Preg = Yes and Patient preg =No AND Argus field "Child Case Only" = Yes

The MAH reviewed and performed descriptive analysis of all events reported cumulatively and during the reporting period by type of vaccine (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). These analyses were also performed for pregnancy cases who received three or more doses of elasomeran, pregnancy cases among 12-17 years old (adolescents) and 6-11 years old, as well as children aged 0-5 years old born to mothers who received elasomeran and bivalents during pregnancy. Pregnancy cases are pulled by case identification numbers and contain "All PTs" The PTs that are captured in the Pregnancy and Neonatal Topics MedDRA SMQ are referred to as pregnancy-specific events, and those that are not, are referred to as non-pregnancy-specific events. The cases and events were classified by the SOC, HLT and PT stratified by event seriousness and review period. For the calculation of TTO and the attribution of Dose Number to individual events an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a dose was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number.

Pregnancy outcomes were examined by timing of vaccination/gestational period stratified by prospective/retrospective classification. The "prospective" classification, (if MAH initially received information about the exposure and associated event before the pregnancy completion) should be interpreted with caution because there is a high likelihood of coding errors; there was no evidence in the report to support a "prospective" classification for many of the pregnancy reports. Outcomes were identified using the variable "Pregnancy Outcome". This variable was derived using the strategy below:

• STILLBIRTH, or MI-FULLTERM = YES then the PT term is entered as outcome OR

• Use the response to the "PREG-Fetal Outcome" variable if populated

• Otherwise, classified as "undetermined"

Gestational period was identified using the variable "Gestational Period Group," and categorized into four groups shown below in accordance with the Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/313666/2005)".

• First Trimester

• After first trimester

• Before conception (0-2 weeks)

• Unknown

All fatal cases were medically reviewed and summarized; the fatal section focuses on maternal deaths defined as the death of an individual during pregnancy or within one year of the end of pregnancy from a pregnancy complication, a chain of events initiated by pregnancy, or the aggravation of an unrelated condition by the physiologic effects of pregnancy [78] and deaths of neonates/infants born to mothers who received elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran prenatally. However, the MAH receives reports in which fetal deaths are coded as fatal cases originating from regulatory reports or due to coding discrepancies. Upon medical review, reports coded as "foetal death" and "stillbirth" are classified as spontaneous abortion if they occur before 20 weeks gestational age (GA) and as stillbirth if they occur at ≥20 weeks gestational age. The threshold of 20 weeks is in accordance with the definitions applied in the United States [79]. Stillbirths are summarized in the Spontaneous abortions, Stillbirths, and Fetal Deaths section below.

All pregnancy cases reporting a PT from the SOC: Congenital, familial and genetic disorder underwent medical review; two groups of cases were identified: 1) fetuses and neonates with prenatal exposure to a Moderna COVID-19 vaccine with a reported congenital anomaly and 2) non-pregnancy cases with a represented medical history miscoded as an AE, or a pre-existing congenital anomaly detected (such as an arteriovenous malformation or atrial septal defect identified at the time of an AE such as cerebrovascular accident). All reported pregnancy cases reporting congenital malformations with prenatal exposure to a Moderna COVID-19 vaccine were reviewed, adjudicated and classified by MAH physicians using the Metropolitan Atlanta Congenital Defects Program (MACDP) [80] which is a population-based tracking system for birth defects. All major congenital malformations in accordance with MACDP were included in the cumulative observed number of cases.

Appendices for the pregnancy subpopulation analysis are in Appendix 11.6 [of the PSUR]:

• Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event seriousness for Interval and Cumulative (elasomeran)

• Summary of pregnancy outcomes by trimester of exposure, and retrospective/prospective case classification, Reporting Period (elasomeran)

• Summary of pregnancy outcomes by trimester of exposure, and retrospective/prospective case classification, Cumulative (elasomeran)

• Summary of reported congenital anomalies by HLT and PT that occurred in fetuses and neonates, Reporting period

• Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event Seriousness for Adolescents, Review Period and Cumulative (elasomeran)

• Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event Seriousness for elasomeran/imelasomeran and Cumulative

• Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event Seriousness for elasomeran/davesomeran, Reporting period and Cumulative

Literature Search Methodology:

A targeted literature search for relevant publications on pregnancy and lactation and elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran was conducted on a weekly basis during the PBRER#4 reporting period (19 Jun 2022 – 17 Dec 2022) using PubMed of the National Library of Medicine; search strategy is documented in Appendix 12.1d [of the PSUR]. Review of the abstracts and titles was performed to identify articles relevant to the safety and benefit/risk profile of vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during pregnancy and lactation. Articles that were excluded were those regarding COVID-19 during pregnancy or lactation, COVID-19 infection of fetuses/neonates, COVID-19 vaccination coverage during pregnancy or lactation, outcomes including safety after COVID-19 vaccination during pregnancy or lactation that did not include a Moderna COVID-19 vaccine, acceptance of COVID-19 vaccination among pregnant or lactating persons, safety of non-COVID-19 vaccinations during pregnancy or lactation, and case reports or case series regarding the use of a Moderna COVID-19 vaccine during pregnancy or lactation. Only articles with information regarding the safety and benefit/risk profile of vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy and lactation were reviewed and only those with new information or substantiative findings that affect the benefit/risk profile of the use of a Moderna COVID-19 vaccine during pregnancy are discussed in this PBRER.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Pregnancy Cases Who Received Elasomeran

Cumulatively, ModernaTx, Inc. has received 5,131 pregnancy cases with 16,817 events (pregnancy and non-pregnancy-specific), of which 5,467 events were serious, after receipt of elasomeran. Of the 5,131 pregnancy cases, 2,463 cases were medically confirmed, 1,817 (35.4%) cases were serious, and 32 had fatal outcomes.

During the reporting period, 388 pregnancy cases were identified with 1,298 events (pregnancy and non-pregnancy-specific), of which 403 events were serious, after receipt of elasomeran. Of the 388 pregnancy cases, 181 were medically confirmed and 188 (48.5%) cases were serious. A higher proportion (48.5%) of the cases during the review period were reported as "serious" compared to cumulative period (35.4%). The difference observed in this reporting period might be due to the small numbers of pregnancy cases reported and/or reflects the changing geographic patterns of reporting given it relates to varying country coding practices. Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" with no reported clinical events and are reported as "serious" cases; See Serious and Fatal Cases and Serious Pregnancy-related Events section. Serious cases should be interpreted with caution as many do not meet the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in a given serious case.

Of the 388 pregnancy cases during the reporting period, three were coded as fatal and are discussed in the *"Serious and fatal cases"* section. Of the three fatal cases, there was one maternal death ([redacted]) reported due to postpartum hemorrhage and causality was deemed unlikely due to a prolonged TTO (293 days) after vaccination; the remaining two cases were fetal deaths of pregnancies with prenatal exposure to elasomeran (one spontaneous abortion with congenital anomaly [[redacted]] and causality was deemed unlikely, and one stillbirth with multiple congenital anomalies ([redacted]) and causality was deemed unassessable given the limited available information provided.

The majority of pregnancy-specific cases occurred in the 18 to 39-year age group (Table 16.24), consistent with typical childbearing age. The age distribution for this review period continues to be similar to what was seen previously. Cases in the age group < 6 years of age represent fetuses or children with prenatal exposure to elasomeran. Cases in the age group < 6 years and 12-17 years old are further discussed in the *Children < 6 years of Age with A Medical History of Maternal Exposure to elasomeran During Pregnancy and the Adolescent* subsections, respectively, below.

Table 16.24 Age Distribution of Pregnancy Cases by Review Period and Cumulative – elasomeran*

Age Group All (11)	Prior to Review Period		Review Period		# of Total Cases*	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
0-5 months**	38	0.8	8	2.1	46	0.9
6 months - <2 years**	10	0.2	4	1.0	14	0.3
12-15 years***	4	0.1	0	0	4	0.1
16-17 years***	15	0.3	1	0.3	16	0.3
18-24 years	161	3.4	19	4.9	179	3.5
25-39 years	3,550	74.1	257	66.2	3,772	73.4
40-49 years	349	7.3	31	8.0	377	7.3
50-64 years****	57	1.2	3	0.8	60	1.2
65-74 years****	8	0.2	0	0	8	0.2
75 years+****	5	0.1	0	0	5	0.1
Missing	591	12.3	65	16.8	655	12.8
Grand total	**4,783**	**100.0**	**388**	**100.0**	**5,131**	**100.0**

* The addition of the cases from the prior review period and cases from the review period do not always add up to the number of total cases because a case that was reported prior to review period can also be included in this review period if a new event was reported during the review period.

** The cases under 6 years of age represent fetal cases or newborns/children with prenatal exposure to elasomeran and are discussed in the *Children < 6 years of Age with A Medical History of Maternal Exposure to elasomeran During Pregnancy* section.

*** These cases are discussed in the *Adolescent* section below.

**** Cases 50-years or older also include Regulatory Authority cases (that cannot be queried) that report pregnancy in older females, are non-pregnancy cases, and/or are cases with coding errors that will be corrected.

The most frequently reported PTs during the reporting period were reactogenicity events, consistent with the product safety profile and is similar between the reporting period and the cumulative period.

Cumulatively, there have been 20 pregnancy reports with the PT "Myocarditis" and/or "Pericarditis" after receipt of elasomeran resulting in 19 cases. Based on medical review, it was determined that two reports ([redacted] and [redacted]) pertained to the same individual.

During the reporting period, 3 reports of "Myocarditis" among pregnancy cases were received. However, two of the case reports ([redacted] and ([redacted]) appear to be misclassified as a pregnancy case given the lack of information in the reports regarding pregnancy or lactation as well as their advanced age (52 years and 49 years, respectively). See Section 16.3.1.2 [of the PSUR] for more information.

Pregnancy-specific events – elasomeran)

Cumulatively, there have been 4,659 pregnancy cases with 6,095 pregnancy-specific events of which 2,287 events were serious. Of the 4,659 pregnancy cases with a pregnancy-specific event, 2,325 were medically confirmed, 1,708 were serious cases, and 30 had a fatal outcome.

During the reporting period, 322 pregnancy cases were identified, with 385 pregnancy-specific events of which 194 events were serious. Of the 322 pregnancy cases with a pregnancy-specific event, 163 were medically confirmed, 162 cases were serious, and three had a fatal outcome. (*Note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ*).

After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome, the most frequently reported PTs for this reporting period is similar to the cumulative period. "Abortion spontaneous" is the most frequently reported adverse pregnancy event/outcome for both the reporting and cumulative period. (*Refer to Spontaneous abortions, Stillbirths, and Fetal Deaths evaluations added below*).

A summary table of all pregnancy outcomes, stratified by timing of exposure as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/313666/2005)" is presented in Appendix 11.6 [of the PSUR].

Serious Pregnancy-specific Events and Fatal Cases– elasomeran

During the reporting period, of the 188 serious pregnancy cases, 150 cases reported 194 serious pregnancy-specific events; 77 cases were medically confirmed. Three cases had a fatal outcome.

After excluding the pregnancy cases reporting only PTs that do not indicate an adverse pregnancy-specific event/outcome, (e.g., "Biochemical pregnancy", "Delivery", "Exposure during pregnancy", "False negative pregnancy test", "First trimester pregnancy", "Foetal exposure during pregnancy", "High risk pregnancy", "Live birth", "Maternal exposure", "Multigravida", "Multiparous", "Normal foetus", "Normal labour", "Normal newborn", "Paternal exposure before pregnancy", "Planning to become pregnant", "Postpartum state", "Pregnancy", "Pregnancy test positive", "Pregnancy with advanced maternal age", "Second trimester pregnancy", "Term baby", "Term birth", "Third trimester pregnancy", "Twin pregnancy", "Ultrasound antenatal screen normal", "Unintended pregnancy", and "Unwanted pregnancy"), there were 132 serious pregnancy cases reporting 164 serious pregnancy-specific events.

Review of the serious pregnancy-specific events during this reporting period did not identify any new safety concerns. These cases reflect obstetric events observed in temporal association with elasomeran administration. Many of these cases had limited information about past medical and obstetric history, GA at time of vaccination, or onset of AE, diagnostics, treatment, and outcome. Where data were available, confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy [including advanced maternal age, in vitro fertilization, intrauterine insemination, concomitant medications, comorbidities (such as hypothyroidism, diabetes) and previous relevant obstetric history including fetal loss as well as prior history of a pregnancy with congenital anomalies] were present.

Fatal Pregnancy Cases– elasomeran)

During the review period, three pregnancy cases after elasomeran, were coded as fatal and are summarized in Table 16.25. Of the three fatal cases, there was one maternal death ([redacted]); the remaining two cases were fetal deaths of pregnancies with prenatal exposure to elasomeran (one spontaneous abortion with congenital anomaly ([redacted]), and one stillbirth with multiple congenital anomalies ([redacted]) and are discussed in the *Congenital Anomaly and Stillbirth* sections added below.

Table 16.25 Fatal Cases, Review Period– Elasomeran

Case ID	WW Identifier	Country	All PTs	Maternal Age	TTO Dose #	Pregnancy Outcome per Medical Review
[redacted]	[redacted]	PHILIPPINES	Hypovolaemic shock, Postpartum haemorrhage, Uterine atony	30	293 days after administration of an unspecified dose of elasomeran	Maternal Death, Neonatal outcome unknown
[redacted]	[redacted]	[redacted]	Foetal chromosome abnormality, Turner's syndrome	Unknown	Unknown	Spontaneous Abortion with Congenital Anomaly (Turner's syndrome)
[redacted]	[redacted]	[redacted]	Dysmorphism, Foetal growth restriction, heart disease congenital, Hypospadias, Multiple congenital abnormalities	Unknown	Experienced events at 23 weeks GA, 9 weeks after administration of unspecified dose of elasomeran	Stillbirth with multiple congenital anomalies

Cumulatively, there have been five cases of maternal mortality reported and summarized in previous PBRERs. The cases show no pattern or clusters on medical review.

- [redacted] – PBRER #1
- [redacted] – PBRER #2
- [redacted] – PBRER #2
- [redacted] – PBRER #3
- [redacted] – PBRER #4

During this reporting period, there was one case of maternal death, summarized below, which the MAH determined causality as unlikely given the long latency and lack of biological plausibility between elasomeran and uterine atony and postpartum hemorrhage.

[redacted] (PH-PH[redacted]: This is a regulatory case reported by a health-care professional concerning a 30-year-old female who experienced the unexpected and fatal outcome of hypovolaemic shock, uterine atony and postpartum haemorrhage. The events occurred 293 days after administration of an unspecified dose of elasomeran. The reported causes of death were "Hypovolemic shock, Postpartum hemorrhage and Uterine atony." It is unknown if an autopsy was performed. Information regarding her medical history, obstetrical history, concomitant medications, medical history, clinical course and treatment were not provided. According to the WHO causality assessment this case is considered unlikely, given the long latency and lack of biological plausibility between elasomeran and uterine atony and postpartum hemorrhage.

Cumulatively, there have been four cases of deaths of neonates/infants with prenatal exposure to elasomeran; no concerning pattern or clustering seen. One case was summarized in MSSR #12 and the remaining three cases were summarized in PBRER #3.

- [redacted] – MSSR #12
- [redacted] – PBRER #3
- [redacted] – PBRER #3
- [redacted] – PBRER #3

During this reporting period, there were no fatal cases reported of neonatal/infant death with prenatal exposure to elasomeran, when compared to the cumulative data, no safety concerns were identified from the review of serious and fatal cases received during the reporting period for the pregnancy subpopulation.

Fetal Deaths– Elasomeran

The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth" and are classified as spontaneous abortion if they occur before 20-weeks GA, and as stillbirth if they occur after 20 weeks gestational age. The threshold of 20 weeks is per the definitions applied in the United States [79,81].

Spontaneous and Missed Abortions – Elasomeran

Cumulatively, 674 pregnancy cases reported spontaneous abortion or missed abortion with 700 events of which 669 events were serious (some cases have more than one of the PTs used to identify this group). Of the 674 cases, 405 were medically confirmed, 648 cases were serious and three were coded as fatal (Appendix 11.6 [of the PSUR]).

During the review period, 50 pregnancy cases reported spontaneous abortion or missed abortion with 52 events of which 51 events were serious. Of the 50 cases, 24 were medically confirmed, 50 cases were serious, and no cases were coded as fatal. The mean age of the cases is 33.2 years (SD: 5.2), median age 33 years (range 21-44), and one (2.0%) case had missing age information. Of the cases with available data on the dose number prior to the event, there were more events reported after Dose 2 (9.6%) than Dose 1 (5.8%), Dose 3 (5.8%), and Dose 4 (1.9%). This must be interpreted with caution as one does not know how many pregnant women have received one versus two versus three or more doses; and, of note, 76.9% of events are missing dose information. Although the data are limited, when TTO and dose number were known, the majority of events (66.7%) occurred 30 or more days after vaccination. The median TTO was 42.0 days (range 6-231); there was no unusual clustering by dose or TTO.

Stillbirth – elasomeran)

Stillbirth has varying global definitions based on GA and fetal weight. For the purposes of this PBRER, and as described above, the MAH applied a definition of a fetal death after 20-weeks gestational are [79] [81]. Congenital anomalies, placental dysfunction associated with fetal growth restriction, and maternal medical diseases and obstetric complications (such as pre-eclampsia, chorioamnionitis, and infections such as group B *Streptococcus* and cytomegalovirus) are common causes of stillbirth. Advanced maternal age (over 40 years) has been associated with an increased risk of stillbirth as well. Evaluation of spontaneous, reports is limited due to a lack of complete information, such as medical and obstetric history as well as diagnostic evaluation and results performed to determine the cause of the stillbirth.

Cumulatively, 105 cases were coded as "foetal death" and/or "stillbirth". Upon medical review, 56 cases occurred ≥20 weeks GA (classified as stillbirth) and 45 cases occurred before 20 weeks (classified as spontaneous abortion). One case of "fetal death" did not have GA information and, thus, could not be classified. Of the 105 cases, two cases were mother-fetal linked cases with duplicate events (one coded as "Foetal death" and one coded as "stillbirth"). One case was a duplicate (both coded as "Stillbirth").

During the reporting period, eight cases were coded as "Foetal death" and/or "Stillbirth" (Table 16.26). Upon medical review, three cases occurred ≥20 weeks GA (classified as stillbirth) and five cases occurred before 20 weeks (classified as spontaneous abortion).

Table 16.26 MAH Fetal Death Case Classification of Reports with PTs "Fetal death" and/or "Stillbirth" – Reporting Period and Cumulative– elasomeran

MAH Medical Review Classification	Reporting Period		Prior to Reporting Period		Cumulative	
	# Cases	% Total Reporting Period Cases	# Cases	% Total Prior Cumulative Cases	#Cases	% Total Cumulative Cases
Stillbirth	3	37.5	53	54.6	56	53.3
Spontaneous abortion	5	62.5	40	41.2	45	42.9
Unknown	0	0	1	1.0	1	1.0
Duplicate (not classified)	0	0	3	3.1	3	2.9
Total	**8**	**100.0**	**97**	**100.0**	**105**	**100.0**

During the reporting period, five pregnancy cases that reported stillbirth were identified; three were identified through the medical review of cases that were coded as "foetal death" and/or "stillbirth" and the other two cases ([redacted] [incorrectly coded as SAB] and [redacted] [no pregnancy outcome was coded]) were identified from medical review of pregnancy cases with serious pregnancy-related events. These pregnancy cases noting a stillbirth are summarized in Table 16.27.

Table 16.27 Stillbirths, Review Period – elasomeran*

Case ID (WW Identifier)	All Preferred Terms	Company Comment	WHO-UMC Causality
[redacted]	Stillbirth	This is a regulatory case was reported by another health-care professional is concerning a 33-year-old female with no reported medical history, who experienced the unexpected, serious, event of stillbirth and occurred on an unknown interval (no vaccination date was provided) after receiving an unspecified dose of elasomeran. The delivery occurred on the same day of the onset of event which was reported as stillbirth. The outcome of the fetus was stillbirth NOS. No further information on last menstrual period, estimated due date, obstetrical and medical history, clinical course and management of the event was available in the report. It was reported that the outcome of the event has resolved.	Unassessable: This report has limited data and is missing critical information including timing of

[redacted]	COVID-19 immunization, Stillbirth	This is a regulatory case reported by consumer concerning a 31-year-old female, who experienced the unexpected, serious, event of stillbirth at 39+4weeks GA, 130 days after the third COVID-19 vaccination with the first dose of elasomeran (received at 21 weeks GA). The delivery occurred on the same day of the onset of event which was reported as stillbirth. The outcome of the fetus was stillbirth NOS. Her medical history includes laboratory confirmed COVID-19 during pregnancy at an unspecified time. She had previously completed her COVID-19 vaccination primary series with Comirnaty, with the last dose 203 days prior to receipt of the elasomeran. No further information on her obstetrical history, diagnostic evaluation and results and the clinical course and management of the event was available in the report. It was reported that the event has resolved.	Unassessable: This report is confounded by diagnosis of COVID-19 during pregnancy, as stillbirths have been reported among pregnancies complicated by COVID-19. Additionally, this case report has limited data and is missing critical information including maternal obstetrical history, history of the current pregnancy, concomitant medications, complete diagnostic evaluation, whether a fetal autopsy was performed and results if applicable, that is needed for an informed case and causality assessment.
[redacted]	Stillbirth	This is a regulatory case reported by physician concerning a 39-year-old female, who experienced the unexpected, serious, event of stillbirth at an unknown GA, 18 days after the third COVID-19 vaccination with the first dose of elasomeran (received at an unknown GA). The outcome of the fetus was reported as stillbirth NOS. Her obstetrical history includes two prior pregnancies resulting in live births with last pregnancy complicated by uterine rupture. She had previously completed her COVID-19 vaccination primary series with Comirnaty, with the last dose 238 days prior to receipt of the elasomeran. No further information on her medical history, diagnostic evaluation and results and the clinical course and management of the event was available in the report. It was reported that the event has not resolved at the time of the report.	Unassessable: Although there is temporal association, this case report has limited data and is missing critical information including GA when stillbirth happened, maternal medical history, history of the current pregnancy, concomitant medications, complete diagnostic evaluation, whether a fetal autopsy was performed and results if applicable, that is needed for an informed case and causality assessment.
[redacted]	Abortion spontaneous, Feeling abnormal	This regulatory case concerns a 29-year-old, gravid, female patient with no relevant medical history, who experienced the unexpected, serious (Medically significant, Hospitalization) event of Abortion spontaneous and unexpected, serious (Hospitalization) event of Feeling abnormal. The event Abortion spontaneous occurred 6 days after administration of third dose of	Possible: This meets the MAH criteria as a stillbirth (defined as loss ≥20 weeks GA) Causality is possible solely based on temporal association

		elasomeran, the exact date of onset of the event Feeling abnormal was not specified in respect to the administration of third dose of elasomeran, hence latency could not be assessed, there was no information provided regarding the initial two doses. It has been reported that the patient has miscarriage at 21 weeks of pregnancy and the child was not alive. Details of concomitant medications, medical history, clinical course and treatment were not provided. The outcome of the event Abortion spontaneous was unknown while the event Feeling abnormal has resolved at the time of the report. The benefit-risk relationship of elasomeran is not affected by this report. Events' seriousness retained as per Regulatory Authority's report.	given that this report is missing critical important information such maternal medical history including concomitant medications, prior obstetric history, diagnostic evaluation and results performed to evaluate the stillbirth, and clinical course needed to make an informed case and causality assessment.
[redacted]	Dysmorphism, Foetal growth restriction, Heart disease congenital, Hypospadias, Multiple congenital abnormalities	A female of unknown age experienced a stillbirth at an unknown GA. She had received an unspecified dose of elasomeran at 14 +4 weeks gestation and around 23 weeks gestation, the fetus was diagnosed with multiple congenital malformations, hypospadias, dysmorphism, fetal growth restriction and congenital heart disease. At an unknown time or interval after maternal vaccination or diagnosis of fetal anomalies, a stillbirth occurred, and the reported cause of death was the multiple congenital anomalies. It is unknown if an autopsy was performed. Maternal medical history of hypothyroidism on Levothyroxine was reported. Information regarding obstetric history, family history of congenital anomalies, ultrasound reports and genetic screening prior to vaccination, diagnostic workup/results related to congenital anomalies and stillbirth and treatment were not provided	Unassessable: Without knowing the full spectrum of congenital anomalies, causality regarding congenital anomalies is unassessable. Additionally, vaccination was at the tail end of period of fetal development where major defects in body structure can occur and the presence of anomalies affecting multiple organ systems a chromosomal anomaly is a plausible alternate cause that has not been ruled out based on the limited available data. Despite temporal association, causality regarding stillbirth is unassessable as this report is missing critical important information such as current and prior obstetric history, ultrasound reports,

			genetic screening prior to vaccination, diagnostic evaluation, results performed to evaluate the stillbirth, and clinical course.

* Stillbirth has varying global definitions based on GA and fetal weight. For the purposes of this safety report, the MAH applied a definition of a fetal death after 20-weeks GA per the definitions applied in the United States [79,81].

Based on medical review of the "stillbirth" and fetal death cases >20 weeks gestation age, there is no clear TTO pattern, some cases had clear alternate etiologies, and thus there was insufficient evidence to support causality or demonstrate an increased risk. Many reports had limited data and lacked crucial information to make a robust case and causality assessment; and in addition, it is well known that, typically, up to 60% of stillbirths cannot be attributed to an identifiable fetal, placental, maternal, or obstetric etiology due to lack of sufficient information or because the cause cannot be determined at the current level of diagnostic ability [81]. It was noted that for many of the pregnancy reports coded as "prospective", there was no evidence in the report to support this classification, thus this classification must be interpreted with caution as there is a high likelihood of coding errors.) Overall, cases of stillbirth and spontaneous abortion received during the reporting period was similar to the cumulative period and no safety concerns were identified.

A summary table of all pregnancy outcomes classified as retrospective and prospective and stratified by timing of exposure, as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/313666/2005)", is presented in Appendix 11.6 [of the PSUR]. It was noted that for many of the pregnancy reports coded as "prospective", there was no evidence in the report to support that classification, thus this classification must be interpreted with caution as there is a high likelihood of coding errors.

Congenital Anomaly– elasomeran

During the reporting period, 24 pregnancy cases that reported a PT from the Congenital, familial and genetic disorder SOC were identified and after medical review, no patterns and no safety concerns were identified. Of the 24 pregnancy cases, 14 occurred among fetuses and neonates from pregnancies exposed to elasomeran and 10 occurred in non-pregnancy cases and either represented medical history miscoded as an AE, or a pre-existing congenital anomaly detected in a nonpregnant person. The reported pregnancy outcome of the 14 cases was spontaneous or missed abortion in 1 (7.1%) case, stillbirth in 1 (7.1%) case, live birth in 9 (64.3%) cases, and unknown outcome in 3 (21.4%) cases. Further review of the congenital anomalies, considering the GA at vaccination and foetal development contributed to the assessment of causality. Many cases lacked GA at the time of vaccination and thus causality was unassessable. Although a meaningful comparison of congenital anomalies reported by pregnancy outcome is not possible, there was no clustering or safety concerns seen by pregnancy outcome. Cumulatively, there have been 140 reports of congenital anomalies. Upon medical review, 64 pregnancy reports (some contain parent-child duplicates) occurred in fetuses and neonates and the other 76 reports of congenital anomalies occurred in non-pregnancy cases for aforementioned reasons. Even when considering the cumulative data, there were no patterns and no safety concerns identified.

Subpopulation Analyzes:

Children <6 years of Age with with a medical history of maternal exposure to elasomeran during pregnancy

Cumulatively, there have been a total of 60 cases among children under the age of 6 years with a medical history of maternal exposure to elasomeran during pregnancy reported with 148 events of which 83 were serious. Of the 60 cases, 25 were medically confirmed, 41 cases were serious, and 6 cases had a fatal outcome. During the reporting period, 12 cases among children under the age of 6 years with a medical history of maternal exposure to elasomeran during pregnancy were identified with 33 events of which 20 were serious. Of the 12 cases, 4 were medically confirmed, 9 cases were serious, and no cases had a fatal outcome.

Given there was no notable difference in the most frequently reported PTs between the review and cumulative period data as well as the small number of cases reported during this reporting period, only the cumulative data for most frequently reported PTs are presented for children under the age of 6 years with prenatal exposure to elasomeran (Table 16.28). After excluding PTs that do not indicate an AE/outcome, the most frequently reported PTs cumulatively were: "Poor feeding infant", "Infantile vomiting", and "Low birth weight baby" reported by 17 cases and do not seem to represent a safety concern. See Table 16.28 for the most frequently reported PTs, with an event count of 2 or more, by seriousness among pregnancy cases under the age of 6 years.

Table 16.28 Most Frequently Reported PTs[1,2] by Seriousness Among Pregnancy- specific cases under the age of 6 years, Cumulative – elasomeran

PT	Non-Serious		Serious		# of Total Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Poor feeding infant	6	4.1	1	0.7	7	4.7
Infantile vomiting	5	3.4	0	0	5	3.4
Low birth weight baby	2	1.4	3	2.0	5	3.4
Premature baby	1	0.7	3	2.0	4	2.7
Atrial septal defect	0	0	3	2.0	3	2.0
Abdominal pain	1	0.7	1	0.7	2	1.4
Bradycardia neonatal	0	0	2	1.4	2	1.4
COVID-19	1	0.7	1	0.7	2	1.4
Death neonatal	0	0	2	1.4	2	1.4
Decreased appetite	1	0.7	1	0.7	2	1.4
Diarrhoea	2	1.4	0	0	2	1.4
Faeces discoloured	1	0.7	1	0.7	2	1.4
Fatigue	1	0.7	1	0.7	2	1.4
Neonatal aspiration	0	0	2	1.4	2	1.4
Pyrexia	1	0.7	1	0.7	2	1.4
Respiratory disorder neonatal	0	0	2	1.4	2	1.4
Transposition of the great vessels	0	0	2	1.4	2	1.4
Vomiting	1	0.7	1	0.7	2	1.4

[1] Only PT terms with a cumulative count of 2 or more are presented.

[2] This table excludes PTs that do not indicate an adverse pregnancy-specific event/outcome: "Exposure via breast milk" and "Foetal exposure during pregnancy".

During the review period, nine serious cases among children under the age of 6 years with a medical history of maternal exposure to elasomeran during pregnancy were identified with 23 events of which 20 were serious. Of the nine cases, three were medically confirmed and none had a fatal outcome. These nine cases are summarized below:

[redacted]: A 3-day-old term male neonate experienced bradycardia, 156 days after maternal third COVID-19 vaccination. Mother received 2 doses of Comirnaty and one dose of elasomeran at an unknown GA, and it is also unknown the order of these vaccinations. Bradycardia resolved 5 days later. Neonatal evaluation reported (chest X-ray, ECG, ECHO, head ultrasound) was normal except discrete sinus rhythm that was depressed for age with no indication of a rhythm disorder. Causality is "unassessable" because of the extremely limited data reported but this report is heavily confounded by the prolonged TTO. Critical data for case assessment and causality ascertainment are missing including obstetric history, maternal concomitant medications, medical history, status, and history of the pregnancy exposed to elasomeran.

[redacted]): A 2-month-old baby girl with relevant medical history of maternal exposure during pregnancy, and her mother received the first dose of elasomeran vaccine in her first pregnancy trimester, as well as a second dose on an unknown date who experienced events of Cleft palate, Eyelid disorder (Attached left eye lids) and Cerebral haemorrhage. Brain ultrasound of the patient showed a grade 2 haemorrhage. Patient had no history of cleft palate in both families of parents and mother did not take other medications during pregnancy. Mother was reported as healthy and non-smoker. It is reported that this infant was the third born with two healthy siblings. Information on pregnancy course including last menstrual period and due date, maternal and neonatal diagnostic tests/procedures, clinical course, and treatment were not provided. This case is unassessable given the inability to establish the timing of vaccination during pregnancy and temporal association.

[redacted]): A child of unknown age and gender, with maternal use of alprazolam and metformin for an unknown indication and maternal history of receipt of an unspecified dose of elasomeran during pregnancy. Fetal growth restriction was reported; however, temporal association cannot be assessed due to lack of information on onset date of the event and vaccination date. It is reported that the subject was delivered without any congenital anomalies and achieved all the developmental milestones at the time of the report, at an unknown age. No further clinical information was available for medical review. This case is "unassessable" given that temporal association cannot be established, and this report is missing critical information such as maternal history, obstetrical history, diagnostic evaluation and results which are needed for case and causality assessment.

[redacted]): This regulatory authority case reported by another health-care professional concerning a male infant of unknown age, who 18 months and 17 months after his mother received the first and second dose of elasomeran (Original), respectively experienced transposition of the great vessels. Reportedly, a prenatal screening test and prenatal visits did not show the congenital defect. The male infant had surgery 6 days after the detection of the congenital anomaly. No further information on maternal and infant medical history, infant diagnostic evaluation and results and the clinical course and management of the event was available. Outcome was reported as unknown, and patient was hospitalized at the time of the report. Causality is unlikely, the long latency makes a relationship improbable given that the last dose of elasomeran vaccine were received approximately 7 months prior to conception. This case report is missing critical information including maternal medical and obstetrical history, maternal concomitant medications, infant medical history, complete diagnostic evaluation of the infant, that is needed for an informed case and causality assessment.

[redacted]: A female infant, who experienced the unexpected serious (hospitalization and medically significant) events of bronchiolitis at 5.5 months of age, approximately 6 months after maternal receipt of the third dose of COVID-19 vaccine with the first dose of elasomeran at 37+5 weeks GA. Reportedly, the patient's mother was vaccinated with two doses of COVID-19 VACCINE NRVV AD (CHADOX1 NCOV-19) with first vaccine administered 3 days after last menstrual period and second dose administered at 11+4 weeks GA. The infant was delivered at term weighing 2,834 grams (6lbs 4oz) and the mother spent three days at hospital for the delivery. Causality is unassessable because although there is temporal association, critical information about neonatal medical history, concomitant medications, diagnostic tests or laboratory results and clinical course regarding the event of bronchiolitis was not provided. However, the long latency, the timing of elasomeran during the pregnancy (two weeks prior to delivery) and lack of biological plausibility makes another explanation more likely.

[redacted]: This is a regulatory authority case concerning a 1-day-old, male neonate whose mother received an unspecified dose of elasomeran at 4+1 weeks gestation. The exact date and GA of the onset of the events after vaccination was not specified, events reported ~6 months after vaccination The diagnosis of respiratory disorder neonatal, kidney duplex, prematurity ("33 to 36 weeks"), atrial septal defect, congenital inguinal hernia, infantile apnoea, and bradycardia neonatal was reported. No further details on the pregnancy course, infant clinical course, diagnostic evaluation, and results as well as treatment received were reported. Maternal medical history reported Hypothyroidism and factor V Leiden mutation and pregnancy-related complications reported were cholestasis of pregnancy and preeclampsia. Causality is possible regarding the congenital anomalies given the timing of vaccination during early fetal development. However, given the presence of anomalies affecting multiple organ systems a chromosomal anomaly is a plausible alternate cause that has not been ruled based on the limited available data.

[redacted]: This is a regulatory authority case concerning a 1-day-old female neonate, whose mother received an unspecified dose of elasomeran at 2+3 weeks gestation. Atrial septal defect was detected at an unknown exact date or GA, event reported ~9 months later. It is reported that maternal medical history included "prophylaxis of neural tube defect and labour induction. Further information regarding Last menstrual period and estimated due data, pregnancy course including prenatal scans, obstetrical history as well as neonatal evaluation and treatment was not provided. Causality is possible given the timing of vaccination during early fetal development. However, septal defects, especially small ones, are a relative frequent finding and this report is missing critical information such as prior obstetric history, neonatal evaluation, and treatment for atrial septal defect, needed to make an informed case and causality assessment.

[redacted]): An infant of unknown age and gender whose mother received an unspecified dose of elasomeran during pregnancy at an unknown date. The infant is described to have experienced the non-serious event of "Foetal exposure during pregnancy" at an unknown GA and the serious event of "COVID-19" at an unknown timing or age. No further information was available for medical review. The case is "unassessable" given the extremely limited data available.

[redacted]): A child of unknown age and gender who experienced the unexpected, serious (Hospitalization) events of rhinovirus infection and metapneumovirus infection at an unknown date. Maternal history of receipt of an unspecified dose of elasomeran during pregnancy was reported but timing and GA at administration us unknown. The report mentioned the subject was hospitalized for two days; however, no further clinical details were provided for medical review. The outcome of the events was unknown at the time of the report. Although temporal association cannot be established, causality is "unlikely" as these are common viral infections

and elasomeran is a nucleoside modified vaccine that does not contain any virus capable of causing viral infection.

Pregnancy Cases Among Children 6-11 Years of Age – elasomeran)

There are no reported pregnancy cases among children 6-11 years of age.

Pregnancy Cases Among Adolescents (12-17 Years of Age – elasomeran)

Cumulatively, 20 pregnancy cases were reported among adolescents (12-17-years of age) with 47 events of which 10 events were serious. Of the 20 cases, 17 were medically confirmed, 4 were serious cases and none had a fatal outcome.

During the reporting period, there was one pregnancy case ([redacted]) reported among adolescents (12-17 years of age) which noted only the non-serious event of "Caesarean section" in a 16-year-old female with no reported medical history or concomitant medication at an unknown GA, ~ 7months after a second COVID-19 vaccination with elasomeran at an unknown GA. It is reported that caesarean section was scheduled.

Cumulatively, most of the reports had PTs: "Product administered to patient of inappropriate age", "Maternal exposure during pregnancy", or "Exposure during pregnancy". No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period; however, the data are limited.

Pregnancy Cases Who Received Three or More Doses of elasomeran)

Cumulatively, 278 pregnancy cases with 758 events (of which 403 were serious events) after receipt of three or more doses of elasomeran have been reported. Of the 278 cases, 70 cases were medically confirmed, 150 were serious cases and none had a fatal outcome.

During the review period, 55 pregnancy cases with 136 events (of which 52 events were serious) after receipt of three or more doses of elasomeran were identified. Of the 55 pregnancy cases, 25 cases were confirmed, 33 were serious cases and none had a fatal outcome.

During the reporting period, after excluding PTs that do not indicate an adverse pregnancy-specific event/outcome, similar to the events reported by pregnancy cases for all doses, the majority of the most frequently reported PTs represent expected reactogenicity for elasomeran. The most frequently reported PTs indicating an adverse pregnancy-specific event/outcome were "Foetal growth restriction" (4 events) and "Abortion spontaneous" (3 events)". The types and distribution of the most frequently reported events during this reporting period is similar to the cumulative period. Overall, based on current available information, regardless of the type of COVID-19 vaccines used for the primary series, no unusual patterns or pregnancy-specific safety concerns were identified.

Pregnancy After Receiving Booster Dose with elasomeran/imelasomeran

During the reporting period, 17 pregnancy cases (66 events) with 4 serious cases (22 serious events) after exposure to a booster dose of elasomeran/imelasomeran have been reported; there were no pregnancy cases with a fatal outcome, stillbirth, or fetus/infant with congenital anomalies after receipt of elasomeran/imelasomeran There were five case reports medically confirmed, the most frequently reported clinical events/PTs represent expected reactogenicity for elasomeran. Of the 66 events reported, 16 were pregnancy-specific events and the only pregnancy-specific event reported in order of

decreasing frequency are "Maternal exposure during pregnancy," "Exposure during pregnancy," and "Morning sickness."

See Appendix 11.6 [of the PSUR] for all pregnancy cases who received a booster with elasomeran/imelasomeran).

Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified.

Pregnancy After Receiving Booster Dose with elasomeran/davesomeran

During the reporting period, 11 pregnancy cases (42 events) with 1 serious case (5 serious events) events after exposure to a booster dose of elasomeran/davesomeran have been reported; there were no pregnancy cases with a fatal outcome, stillbirth, or fetus/infant with congenital anomalies after receipt of elasomeran/davesomeran. There were six medically confirmed cases. The most frequently reported events/PTs represent expected reactogenicity for elasomeran. The only pregnancy-specific PT reported by all 11 cases is "Maternal exposure during pregnancy."

See Appendix 11.6 [of the PSUR] for all of pregnancy cases who received a booster dose with elasomeran/davesomeran.

Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified.

Literature Summary of Safety of elasomeran During Pregnancy

The literature reviewed have not identified any maternal, fetal, or neonatal immunization safety concerns with the administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. From the search, 2,622 articles were captured during the reporting period. After exclusion of articles on COVID-19 during pregnancy or neonatal period or lactation, COVID-19 vaccination coverage during pregnancy or lactation, COVID-19 vaccination acceptability by pregnant or lactating persons, safety of other COVID-19 vaccines apart from elasomeran during pregnancy or lactation, case reports and case series of safety of COVID-19 vaccines including elasomeran during pregnancy or lactation, 680 articles underwent full length review and of the 680 articles identified to include regarding safety of elasomeran during pregnancy and lactation, 40 of them were among pregnant persons and of these, two articles [82,83] will be discussed below because they contain new and substantiative findings that positively impact the benefit/risk profile of the use of elasomeran during pregnancy.

1. COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry,

an observational prospective cohort study [83]

Abstract and Company Comment: This observational prospective cohort study assesses early AEs and perinatal outcomes in pregnant woman who received at least one dose of mRNA vaccine between 01 Mar and 01 Dec 2021 in Switzerland, using the COVI-PREG registry. Among 1,012 vaccinated women, 894 (88.3%) received both primary series injections during pregnancy. Localized pain was the most frequently reported AE (81.3% and 80.5% after the first and second dose, respectively). Events of fatigue and headache were the most frequently reported systemic reactions, particularly after the second dose of elasomeran. There were four severe early AEs: pulmonary embolism, preterm premature rupture of membranes, isolated fever with hospitalization, and herpes zoster. One early spontaneous abortion (8 weeks GA) was reported among 107 patients vaccinated prior to 14 weeks GA. One late spontaneous abortion (16 weeks GA) was reported among 228 patients vaccinated before 20 weeks GA. There were 33 preterm delivery reported in 513 patients who were vaccinated prior to 37 weeks GA. Among the 530 patients exposed during pregnancy, there were no reports of stillbirth, and 25 neonates were admitted

to the intensive care unit. This study data indicated that the most frequently reported events among pregnant women vaccinated with mRNA COVID-19 vaccines were reactogenicity events which is consistent with the product safety profile of these vaccines. Data also indicated that severe events were rare and pregnant women vaccinated with mRNA COVID-19 vaccines did not experience higher adverse pregnancy or neonatal outcomes when compared to historical data on background risks in the obstetric population. These findings provide continued evidence that supports the favorable benefit/risk profile of maternal mRNA COVID-19 immunization including during the first trimester.

2. Maternal immune response and placental antibody transfer after COVID-19 vaccination across trimester and platforms [82]

Abstract and Company comment: This cohort biorepository study conducted from January 2021 to September 2021 examined how different COVID-19 vaccine platforms and timing of vaccination during pregnancy may impact maternal and neonatal immunity. The study characterized the antibody profile in 158 pregnant individuals who were vaccinated with one of three COVID 19 vaccines: Ad26.COV2.S, BNT162b2, or elasomeran. This analysis revealed higher vaccineinduced functions and Fc receptor-binding after mRNA vaccination when compared to Ad26.COV2.S, revealed subtle advantages in titer and function with elasomeran when compared to BN162b2, and showed mRNA vaccines demonstrated higher titers and functions against SARSCoV-2 variants of concern. The study also evaluated transplacental antibody transfer by profiling maternal and umbilical cord blood in 175 maternal-neonatal dyads. This analysis demonstrated first, and third trimester vaccination resulted in enhanced maternal antibody dependent NK-cell activation, cellular and neutrophil phagocytosis, and complement deposition relative to second trimester; and demonstrated that higher transplacental transfer ratios following first and second trimester vaccination may reflect placental compensation for waning maternal titers. These findings provide evidence that supports both the efficacy of mRNA COVID-19 vaccines in pregnant women and how the timing of maternal vaccination can positively impact the maternal-neonatal dyad antibody mediated immunity generated by mRNA COVID-19 vaccines.

Discussion

During the reporting period, the pattern of the reports remained generally consistent when compared with the cumulative data, and review of the reporting period serious pregnancy-specific events and non-pregnancy-specific events did not identify any safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Reported cases reflect obstetric events observed after administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of AE, Diagnostics, treatment and/or outcome. Where data was available, noted confounding factors for spontaneous abortion/foetal deaths and complications of pregnancy included advanced maternal age, invitro fertilization, intrauterine insemination, concomitant medications, comorbidities (such as hypothyroidism), previous relevant obstetric history, and congenital anomalies which predated the vaccination.

Spontaneous abortion was the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster was identified. Cumulatively there are 53 reports classified as stillbirth. Considering that some cases have clear alternate etiologies, there is an absence of a clear TTO cluster, and published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth after COVID vaccination, there is insufficient evidence to support a causal relationship between elasomeran and stillbirth.

The MAH will continue to review and evaluate cases of spontaneous abortion, foetal death and stillbirth, using routine surveillance as well as post-authorization safety studies.

Review of the 14 cases of congenital anomalies received during the reporting period as well as the cumulative data did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with elasomeran.

Review of 9 serious cases received during the reporting period concerning children under 6-years of age who were exposed during gestation did not identify any unusual patterns or safety concerns. There was one pregnancy-related case among adolescents received during the reporting period, and there continues to be an increasing number of pregnancy-related cases following receipt of three or more doses of elasomeran (278 pregnancy cases reporting receipt of three or more doses of elasomeran). Overall, based on current available information there are no unusual patterns or pregnancy-related safety concerns identified among these subpopulations.

Cumulatively, 28 pregnancy cases were reported to the MAH with an exposure to a booster dose of Spikevax bivalent vaccines [17 cases reported an event after elasomeran/imelasomeran, and 11 cases reported an event after elasomeran/davesomeran. Most events reflect expected reactogenicity. The most frequently reported pregnancy-specific event was "Maternal exposure during pregnancy"]. There were no reports of PTs that indicate an adverse pregnancy event/outcome, or fatal outcomes. No unusual patterns or pregnancy-specific safety concerns have been identified; MAH will continue to review cases that received the bivalent vaccines using routine surveillance.

In-depth literature reviews performed have not identified any safety concerns for the use of elasomeran during pregnancy; however. Thus far, published literature has not identified any evidence of an increased risk of pregnancy, foetal or neonatal complications related to elasomeran maternal immunization. Furthermore, literature demonstrates that there is transfer of maternal antibodies, reduction in COVID-19 in vaccinated pregnant women and early evidence that that infants benefit from passive protection from SARS-CoV-2 infection and severe disease following maternal COVID-19 vaccination, recognition that COVID-19 may be more serious and cause complications for both the mother and the fetus; and thus, in sum, published literature supports the favorable benefit/risk profile of maternal elasomeran immunization. Data on use of Spikevax bivalent vaccines during pregnancy, continues to provide supporting evidence for Has recommendations for the use of COVID-19 vaccines including elasomeran during pregnancy.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in Pregnancy and while Breastfeeding, the benefit-risk profile for elasomeran remains favorable.

• The MAH has monitored use in Pregnancy and while breastfeeding in each MSSRs as well as PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found: Review of the congenital anomalies reported in the GSDB indicates that the anomalies are varied in type, etiology,

and critical GA at exposure; this data would seem to indicate that the anomalies have occurred as part of the background incidence rather than as a result of vaccine exposure.

• Review of the post-marketing safety data does not support a causal relationship between elasomeran, and the birth defects reported to the GSDB.

• It remains difficult to interpret the significance of malformations when they are rare.

• All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug or vaccine exposure.

• At the request of the EMA the following recommendations are included in the SmPC: "elasomeran can be used during pregnancy" and "elasomeran can be used during breastfeeding".

• Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines.

• The MAH continues to evaluate the pregnancy outcomes in reports of elasomeran and bivalent Boosters use during pregnancy via routine pharmacovigilance activities as well as through post-authorization safety studies.

• Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

• Use of the vaccine in pregnant individuals is already included in the product's labeling, and it is embedded in clinical practice and has been recommended by major public HAs.

• There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to 'use in pregnancy and while breast-feeding' as long-term safety is being kept.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals during pregnancy and while breastfeeding in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of "Use in pregnancy and while breastfeeding" as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals during pregnancy and while breastfeeding through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Conclusion

After review of all new safety data received during the reporting period and cumulatively, the MAH did not identify any safety concerns for maternal immunization and, thus, there is no change to the benefit-risk profile for pregnant woman or their fetuses and neonates. The benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable for use during pregnancy. The MAH will continue to monitor pregnancy-specific reports through routine surveillance and post-authorization safety studies.

Rapporteur assessment comment:

The MAH proposed removal of the missing information 'use in pregnancy and while breast-feeding' from the EU-RMP, which is not accepted (see section 3.1.4.1.2.). In line with this, it shall remain in the PSUR list of safety concerns and an evaluation of new information on this topic is required with future PSURs.

No new significant safety information was identified.

2.3.3.2. Use in Breastfeeding

Source of the New Information

Information presented below includes analyzes performed on spontaneous reports from lactating women who were vaccinated and their children who were exposed to breastmilk from mothers who had been vaccinated (referred to as lactation cases) received by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for COVID-19 ModernaTx, Inc. vaccines: elasomeran and bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran). Cumulative data, also considered in the analyses, cover the period from 18 Dec 2020 to 17 Dec 2022. The Company GSDB was queried for valid clinical and spontaneous case reports in lactating women, who were vaccinated, and their children who were exposed to breastmilk from mothers who had been vaccinated with elasomeran and Spikevax bivalent COVID-19 vaccines. These case reports were received from HCP, HA, consumers, and the literature, cumulatively and for the reporting period, worldwide.

Background Relevant to the Evaluation

The use of ModernaTx, Inc. COVID-19 vaccines among breastfeeding women is an area of missing information in the RMP; no CTs were conducted among lactating women. Developmental and reproductive toxicology showed maternal to rat pup transfer of antibodies; however, no data were available on vaccine excretion in human breast milk. Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during breastfeeding to prevent COVID-19 [66]. However, there was recognition that in absence of CTs, vigilant post-EUA passive report monitoring, and real-world evidence was needed to continue monitoring the safety of COVID vaccination among breastfeeding women.

There have been no specific safety concerns identified for vaccinated breast-feeding women and/or their breastfed children. Epidemiological studies have not indicated any increased risk of side-effects in the mother or the breastfed child after vaccination with elasomeran, or decreased milk production [84] [85] [86] [87] [88]. More specifically, a large series of 17,525 women vaccinated with a COVID-19 vaccine of which 6,815 were lactating women (2,596 received elasomeran), 7,809 pregnant, and 2,901 women of reproductive age planning to get pregnant, found that there was no difference in rate of AEs by vaccine type across all groups and the AEs were transient, mild and consistent with reactogenicity events [84] [85] [86] have shown similar findings that elasomeran is well tolerated by lactating women and their children, and side-effects experienced are similar to side-effects in the general population.

Regarding the side-effects among infants exposed to breastmilk from mothers who had been vaccinated with elasomeran, studies show no increased risk in short-term adverse effects. In the large case series by Kachikis et al [84] where only 3% and 4.4% of breastfeeding mothers reported to have concerns about the infant after the first dose and second dose, respectively. Few infant events are reported; and the most common side-effects seen among nursing children are transient, non-serious poor sleep and irritability [85] [86].

Regarding impact of vaccination on breastmilk production, most studies have shown that only a small percentage of lactating vaccine recipients report a transient reduction in breastmilk production post-vaccination [84,85,89] surveyed 4,455 breast-feeding mothers (1,714 received elasomeran) determined that 90.1% of mothers reported no change, 3.9% of mothers reported an increase in milk supply and 6.0% of mothers reported a decrease. In the large case series by Kachikis et al [84], 339 (5.0%) and 434 (7.2%) participants reported a decreased milk supply for less than 24 hours after the first and second dose, respectively.

Another topic of interest after vaccination during lactation is presence or absence of COVID-19 vaccine components in breast milk. A study by Golan et al [87] analyzed breastmilk samples from seven breastfeeding mothers (two received elasomeran) to determine if PEGylated protein was detectable in human milk after vaccination and they found no increased PEGylated protein concentrations in a subset of samples post-vaccination. A similar study by Golan et al [88] detected no mRNA in breastmilk of six breastfeeding mothers (one received elasomeran) 4-48 hours postvaccination. Another study of 11 lactating persons who received an mRNA COVID-19 vaccine (five received elasomeran) within six months after delivery, showed the sporadic presence and trace quantities of COVID-19 within 48-hours after vaccination were detected in seven samples from five different participants; however, it was unknown if the detected mRNA is translationally active. ModernaTx, Inc. COVID-19 vaccines do not contain infectious virus and the minimal amount of vaccine components that might cross into breastmilk is likely to be inactivated by the infant's digestive system.

The literature also demonstrates robust secretion and transfer of maternal SARS-CoV-2 antibodies (mainly Immunoglobulin (Ig) A and IgG) induced by vaccination through breast milk, and some studies have showed these antibodies have neutralizing activity indicating potential passive protection to the infant, although the effectiveness is not yet established [90-94]. Although, there is still limited published data regarding elasomeran/imelasomeran and elasomeran/davesomeran during breastfeeding, the available data shows no increased risk of adverse outcomes among people vaccinated against SARS-CoV-2 during breastfeeding, supporting recommendations for vaccination of breastfeeding people against SARS-CoV-2. Post-marketing safety data with elasomeran are relevant to the Spikevax bivalent vaccines because these vaccines are manufactured using the same process. Clinical trials and post-marketing pharmacovigilance thus far demonstrate that the reactogenicity and safety profile of the bivalents are similar and to date, no new safety concerns for the bivalents elasomeran/imelasomeran and elasomeran/davesomeran have been identified.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals during pregnancy and while breastfeeding in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in pregnancy and while breastfeeding as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals during pregnancy and while breastfeeding through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports in ModernaTx, Inc. GSDB:

Reports of vaccinated lactating women, and children exposed to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran through breast milk (referred to as lactation cases) were identified from the ModernaTx, Inc. GSDB and are described in this PBRER#4. Data were reviewed by the following time periods: cumulative (18 Dec 2020–17 Dec 2022) and PBRER #4 reporting period (19 Jun 2022–17 Dec 2022).

Lactation cases were identified as any case containing at least one lactation-specific event or PT term identified in the SMQ: "Lactation-specific topics (including neonatal exposure through breast milk)" described in the PSSF 9.0 (Appendix 11.29 [of the PSUR]). Identified lactation cases were pulled by case identification numbers to obtain all PTs reported; the PTs that are captured in the Lactation-specific topics (including neonatal exposure through breast milk) SMQ are referred to as lactation-specific events, and those that are not, are referred to as non-lactation-specific events.

The MAH reviewed and performed descriptive analyzes of all events reported for the reporting and cumulative period by type of vaccine (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). These analyses were also performed for lactation cases who received third or subsequent doses of elasomeran, lactation cases among 12-17 years old (adolescents) and 6-11 years old, as well as lactation cases among children younger than 6 years of age (breastfed children). For the calculation of TTO and the attribution of Dose Number to individual events an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a dose was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number. All fatal cases were medically reviewed and summarized; deaths among lactating women within one year of pregnancy completion is considered a pregnancy-specific death and will be discussed in Section-Pregnancy. Deaths among lactating women occurring more than one year after pregnancy completion or breastfed infants only with a possible exposure to a ModernTx, Inc a COVID-19 vaccine through breastmilk will be discussed here. However, the MAH receives reports in which fetal deaths among breastfeeding mothers are coded as fatal cases, originating from regulatory reports or due to coding discrepancies. These fetal deaths will be summarized in the Section 16.3.5.1 [of the PSUR].

Finally, serious lactation-specific cases among children younger than 6 years were medically reviewed and summarized in Appendix 11.7 [of the PSUR].

Literature Search Methodology:

A targeted literature search for relevant publications on pregnancy and lactation and mRNA COVID vaccines was conducted on a weekly basis during the PBRER#4 reporting period (19 Jun 2022–17 Dec 2022) using PubMed of the National Library of Medicine; search strategy is documented in Appendix 12.1dAppendix 12.1dAppendix 12.1d [of the PSUR]. Review of the abstracts and titles was performed to identify articles relevant to the safety and benefit/risk profile of vaccination with, elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during pregnancy and lactation. Articles that were excluded were those regarding COVID-19 during pregnancy or lactation, COVID-19 infection of fetuses/neonates, COVID-19 vaccination coverage during pregnancy or lactation, outcomes including safety after COVID-19 vaccination during pregnancy or lactation that did not include a Moderna COVID-19 vaccine, acceptance of COVID-19 vaccination among pregnant or lactating persons, safety of non-COVID-19 vaccinations during pregnancy or lactation, and case reports or case series regarding the use of a Moderna COVID-19 vaccine during pregnancy or lactation. Only articles with information regarding the safety and benefit/risk profile of vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during pregnancy and lactation were reviewed and only those with new information or substantiative findings that affect the benefit/risk profile of the use of a Moderna COVID-19 vaccine during pregnancy are discussed in this PBRER.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Lactation Cases Who Received Elasomeran

Cumulatively, ModernaTx, Inc. has received 2,036 lactation cases (6,922 events) of which 527 were serious cases (2,026 serious events); no cases reported a fatal outcome. There were 508 cases medically confirmed.

During the reporting period, 145 lactation cases (502 events) were identified with 20 serious cases (49 serious events): no cases reported a fatal outcome. There were 63 medically confirmed. A higher percentage (86.2%) of the cases reported during this reporting period were non-serious compared to the cumulative period (74.1%).

No changes have been observed in the age distribution of the cases of lactating women and their breastfeeding children, cumulative and during the reporting period and it is consistent with the expected age of lactating women and their breastfeeding children (Table 16.29). Note there are some cases that describe mastitis in non-breastfeeding individuals, particularly older women. Additionally, cases coded as males likely represent children who were exposed to breastmilk from mothers who had been vaccinated with Moderna COVID-19 vaccines or data entry and/or coding error.

Table 16.29 Age Distribution for Lactation Cases (Including Breastfed Children) - elasomeran

Age Group All (11)	Prior to Review Period		Review Period		# of Total Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
0-5 months*	88	4.6	8	5.5	96	4.7
6 months - <2 years*	85	4.5	11	7.6	96	4.7
02-05 years	15	0.8	1	0.7	16	0.8
16-17 years**	1	0.1	0	0	1	0.0
18-24 years	32	1.7	1	0.7	33	1.6
25-39 years	1,085	57.2	69	47.6	1,147	56.3
40-49 years	144	7.6	8	5.5	152	7.5
50-64 years	20	1.1	3	2.1	23	1.1
65-74 years	4	0.2	2	1.4	6	0.3
75 years+	4	0.2	0	0	4	0.2
Missing	420	22.1	42	29.0	462	22.7
Grand total	**1,898**	**100.0**	**145**	**100.0**	**2,036**	**100.0**

* The cases under 5 years of age most likely represent children with exposure to elasomeran through breast milk or are a result of data entry and/or coding error.

** Cases in this age group will be discussed in the *Adolescent* section below.

The most frequently reported PTs during this reporting period were consistent with reactogenicity events and common breastfeeding issues such as suppressed lactation and mastitis. Although the frequency and ranking differed, the most frequently reported PTs are generally similar between the reporting period and the cumulative period.

After excluding the PTs that are not lactation-specific (i.e., not included in the SMQ: "Lactation-specific topics [including neonatal exposure through breast milk]), there were 144 lactation cases that had 166 lactation-specific events (13 serious) with 62 cases medically confirmed. Common breastfeeding-related issues such as "Suppressed lactation," "Mastitis," and "Lactation disorder" remain the most frequently reported events for the reporting and cumulative period after exclusion of PTs that do not indicate an adverse lactation-specific event or outcome. There has not been a significant change in the pattern of PTs reported during the reporting period compared to cumulative period. Most of the lactation-related events were transient occurring within two days after vaccination.

Medical review of the HLT "Lactation Disorders" as performed for the reporting period and the data are similar with the previous cumulative experience; no concerning patterns or notable trends were identified.

All of the serious lactation cases identified as lactation-specific from this reporting period were medically reviewed; many cases lack information on clinical course, outcome, medical history, alternate etiologies/concurrent clinical events. To date, no concerning patterns or notable trends were identified.

Fatal Cases–elasomeran)

Cumulatively, there have been no reported fatal cases of vaccinated lactating women or of children under 6 years of age exposed to breastmilk from mothers who had been vaccinated with elasomeran. One fetal death case ([redacted]) had previously been coded as a fatal lactation case in BSSR 03 and that coding error has been corrected.

Subpopulation Analyzes

Lactation Cases Under 6 Years of Age–elasomeran)

Cumulatively, among children under 6 years of age with exposure to breastmilk from mothers who had been vaccinated with elasomeran (referred to as lactation cases among children under 6 years of age) a total of 208 lactation cases (503 events), with 31 serious cases (86 serious events) were reported; there were no cases reporting a fatal outcome. There were 46 cases medically confirmed. When restricted to only lactation-specific events, 208 cases were reported with 216 lactation-related events of which 23 were serious.

During the reporting period, among children under 6 years of age with exposure to breastmilk from mothers who had been vaccinated with elasomeran there were 20 cases (64 events) reported, with all the cases and events classified as non-serious. There were no fatal outcomes reported during the reporting period. When restricted to only lactation-specific events, the same 20 non-serious cases were included with 20 non-serious lactation-specific events.

Given there was no notable difference in the age, gender and most frequently reported PTs between the reporting and cumulative period as well as the small number of lactation cases among children under 6 years with exposure to breastmilk from mothers who had been vaccinated with elasomeran reported during this reporting period, only the cumulative data will be presented.

Cumulatively, the mean age of lactation cases among children under 6 years is 0.7 years (SD 0.6) and median age is 0.5 years (range 0.0 to 3.0). There were no differences in the number of reports involving males (67; 32.2%), and females (65; 31.3%); there were 76 cases (36.5%) with missing gender information. After excluding PTs that do not indicate an adverse lactation event/outcome, the most frequently reported clinical events were pyrexia, diarrhoea, and vomiting, which are consistent with reactogenicity events expected for elasomeran.

When TTO was known, most of the lactation-related events occurred within two days after vaccination and were transient Appendix 11.7 [of the PSUR].

Cumulatively, three cases of seizures occurring in infants exposed to elasomeran via breast milk were reported. Of the 3 cases, only one ([redacted]) reported experiencing pyrexia and seizures 26 days after the mother received Dose 1 of elasomeran. The other 2 cases ([redacted] and [redacted]) experienced seizures on the same day the mother received Dose 1 of elasomeran. There is limited information for all three reports and no additional information on outcomes have been received.

Lactation Cases Among Adolescents (12-17 Years of Age)

Cumulatively, one non-serious lactation-specific case ([redacted]) aged 17 years has been reported (previously reported in the PBRER #2). No clinical AEs were reported, and the case has two events: "Maternal exposure during breast-feeding", and "Product administration to patient of inappropriate age". There were no lactation cases among adolescents reported during this review period.

Lactation Cases with Third or Subsequent Doses of elasomeran

Cumulatively, 244 lactation cases were reported with 663 events of which 351 events were serious, after a third, fourth, or fifth dose of elasomeran. Of these 244 lactation cases, 23 were medically confirmed, 115 were serious cases, no case had a fatal outcome, and 61 cases (25%) had a lactation-specific event.

During the reporting period, 23 lactation cases were reported with 55 events of which 12 events were serious, after a third or fourth dose of elasomeran. The vast majority (92.7%) of events were reported after the third dose and 4 events after the fourth dose. Of the 23 cases, three were medically confirmed, six were serious cases, no case had a fatal outcome, and 14 (60.9%) had a lactation-specific event. Of the 14 lactation cases with a lactation-specific event, there was only one serious case with one serious lactation-specific event of "Suppressed Lactation" after Dose 3 that was transient and short-lived.

Several of the cumulative cases reported represent the use of a heterologous booster dose or do not mention the vaccine type received as the primary series. The majority of events reported, regardless of the vaccine regimen originally received, are consistent with expected reactogenicity seen with elasomeran. No concerning patterns or notable trends were identified.

Lactation Cases After Receiving Booster Dose with elasomeran/imelasomeran

During the reporting period, five non-serious lactation cases who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran/imelasomeran were reported with 22 non-serious events (Table 16.30) of which six were lactation-specific events. When restricted to only lactation-specific events, the PTs reported in decreasing order were "Maternal exposure during breast-feeding", "Mastitis", and "Exposure via breast milk".

Table 16.30 Lactation Cases Who Received or Were Exposed to Breastmilk from Mothers Who Had Been Vaccinated with a Booster with elasomeran/imelasomeran, 19 Jun 2022 to 17 Dec 2022

Case ID	WW Identifier	Case Seriousness	Age	All Preferred Terms	Medical History	Concomitant Medications
[redacted]		Non-Serious	21 years	Erythema, Maternal exposure during breast-feeding, Pain of skin, Skin swelling	Breast-feeding	Not reported
		Non-Serious	17 months	Exposure via breast milk, Pyrexia, Rash	PFIZER-BIONTECH COVID-19 VACCINE	Not reported
		Non-Serious	39 years	COVID-19 immunisation, Feeling abnormal, Interchange of vaccine products, Malaise, Maternal exposure during breast-feeding, Vaccination site rash	Not reported	Not reported
		Non-Serious	37 years	Mastitis, Maternal exposure during breast-feeding	Breast-feeding	Not reported
		Non-Serious	Reported as	Chills, Fatigue, Headache, Malaise,	PFIZER-BIONTECH	Not Reported

			"elderly"	Mastitis, Myalgia, Nausea	COVID-19 VACCINE	

There has been no fatal lactation case after receipt of elasomeran/imelasomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/imelasomeran.

Lactation Cases After Receiving Booster Dose with elasomeran/davesomeran

During the reporting period, three non-serious lactation cases who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran/davesomeran were reported with eight non-serious events (Table 16.31) of which three were lactation-specific events. When restricted to only lactation-specific events, the PTs reported were "Exposure via breast milk" and "Maternal exposure during breast-feeding".

Table 16.31 Lactation Cases Who Received or Were Exposed to Breastmilk from Mothers Who Had Been Vaccinated with a Booster with elasomeran/davesomeran, 19 Jun 2022 to 17 Dec 2022

Case ID	WW Identifier	Case Seriousness	Age	All Preferred Terms	Medical History	Concomitant Medications
[redacted]		Non-Serious	Not reported	Maternal exposure during breast-feeding, No adverse event	Not reported	Not reported
		Non-Serious	3 years	Erythema, Exposure via breast milk, Pain, Rash	Not reported	Not reported
		Non-Serious	Not reported	Exposure via breast milk, Immunisation reaction	Not reported	Not reported

There has been no fatal lactation case after receipt of elasomeran/davesomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/davesomeran.

Literature Findings

Literature Summary of Safety of elasomeran During Lactation

The literature reviewed have not identified any elasomeran immunization safety concerns for lactating persons and/or children exposed via breast milk. Two-thousand, six hundred and twenty-two (2,622) articles were captured during the reporting period. After exclusion of articles on COVID-19 during pregnancy or neonatal period or lactation, COVID-19 vaccination coverage during pregnancy or lactation, COVID-19 vaccination acceptability by pregnant or lactating persons, safety of other COVID-19 vaccines apart from elasomeran during pregnancy or lactation, case reports and case series of safety of COVID-19 vaccines including elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy or lactation, 680 articles underwent full length review. Of the 680 articles identified to include regarding safety of elasomeran during pregnancy and lactation, five of them were among lactating

persons. The findings from the 5 articles pertinent to safety of elasomeran for lactating persons and/or children exposed to breast milk during this reporting period did not provide new data to impact the benefit-risk profile of the use of elasomeran during lactation for both women and their children. Articles identified continue to reveal no significant safety concerns among vaccinated breastfeeding women and/or their breastfed children or new information about the transfer of maternal SARS-CoV-2 antibodies induced by vaccination to infants via breastmilk, supporting the favourable benefit-risk profile of the use of elasomeran during lactation for both women and their children.

Discussion

During the reporting period, ModernaTx, Inc. received 145 lactation cases, of which 20 were among children under 6 years of age with exposure to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran via breastmilk. There were no reported fatalities. While vaccination can induce cytokines, which can be passed via breast milk, vaccination while breast-feeding has not been linked to AEs in infants [95]. In fact, women with fever and illness are encouraged to continue breast-feeding given the positive impact of the transfer of antibodies, which has also been reported for COVID vaccines, as well as to support infant nutritional needs [96].

There was no lactation case reported among the 12-17 age group during this reporting period and there were 23 lactation cases reporting receipt of third or subsequent doses, with 60.9% reporting a lactation-specific event. Among the serious lactation-specific events, there was no clustering by dose or TTO and no concerning patterns or notable trends of events reported were identified. Reported events were mild and transient. The pattern of reports remained generally consistent during the reporting period when compared with the cumulative data. No new safety concerns were identified.

Where duration and outcome are available, many of the events (such as decreased lactation) occur within a day after vaccination, and most events were mild/moderate, transient events where information is available. Both in the GSDB and in the literature, reports of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhea, and pyrexia are consistent with the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran or what is expected in the general population [97] [96,98]. Review of the literature to date has not identified any safety concerns related to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccination during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated breast-feeding women and/or their breastfed children as well as transfer of maternal SARS-CoV-2 antibodies induced by vaccination to infants via breastmilk, supporting the favorable benefit/risk profile of COVID vaccination during lactation which continues to provide supporting evidence for HAs recommendations for the use of COVID-19 vaccines including Moderna COVID-19 vaccines during lactation.

The MAH is closely monitoring the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in this population through routine pharmacovigilance [66,99-101]. The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in Pregnancy and while Breastfeeding, the benefit-risk profile for elasomeran remains favorable.

• Review of the reports of exposure to elasomeran while breastfeeding reported in the GSDB indicates no increased risk in short-term adverse effects. In several epidemiological studies of breastfeeding mothers, very few reported to have concerns about the infant after the first dose and second dose. Few infant events are reported, with the majority of them nonserious and the most common side-effects seen among nursing children are poor sleep and irritability, which indicates they may have occurred as part of the background incidence rather than as a result of vaccine exposure.

• Review of the post-marketing safety data does not support a causal relationship between elasomeran, and AEs reported in breastfed infants to the GSDB.

• SmPC states "elasomeran can be used during pregnancy" and "elasomeran can be used during breastfeeding".

• Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines.

• The MAH continues to evaluate reported outcomes in infants while breastfeeding in reports of elasomeran and bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies.

• Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

• Use of the vaccine in breastfeeding individuals is already included in the product's labeling, and it is embedded in clinical practice and included in relevant health guidelines.

• There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to Use in pregnancy and while breast-feeding.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals with Use in pregnancy and while breast-feeding in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in pregnancy and while breast-feeding as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals with Use in pregnancy and while breast-feeding through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Conclusion

Based on the review of all new safety data received during the reporting period, compared to the cumulative data, for the cases of AEs in breastfeeding women and their children, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The safety of the use of Moderna COVID-19 vaccines among lactating people and events occurring in their breastfed children will continue to be monitored using the routine pharmacovigilance measures.

Rapporteur assessment comment:

The MAH proposed removal of the missing information 'use in pregnancy and while breast-feeding' from the EU-RMP, which is not accepted (see section 3.1.4.1.2.). In line with this, it shall remain in the PSUR list of safety concerns and an evaluation of new information on this topic is required with future PSURs.

No new significant safety information was identified.

2.3.3.3. Long-Term Safety

Source of the New Information

As of the DLP of this PBRER, 26 CTs were ongoing 11 of which are sponsored by ModernaTx, Inc. Two CTs that assessed long-term safety completed during the reporting period. Cumulatively, 52,530 subjects have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.617.2, mRNA-1273.529), in conjunction with mRNA-1283 (including its variants mRNA-1283.211), or placebo in the mRNA clinical development program sponsored by ModernaTx, Inc. The 52,530 represents unique subjects.

Background Relevant to the Evaluation

Per protocols, the clinical development program has a safety follow-up period of 12 months in the ongoing studies that will assess long-term safety: mRNA-1273-P101 (DMID 20-0003), mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P903, and mRNA-1273-P904, and the completed study that assessed long-term safety: mRNA-1273-P201. Subjects are followed up for 24 months in the Phase 3 Study mRNA-1273-P301. In Study mRNA-1273-P301 the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183 days (range: 1 to 218 days), or approximately 6 months. The follow-up time is through Day 209 for the Phase 1 Study mRNA-1273-P101 (DMID 20-0003) and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The long-term safety profile remains to be characterized through continued trial follow-up, active surveillance for safety, a European post-authorization safety study, and routine pharmacovigilance.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

No results to date.

Discussion

The long-term safety profile remains to be characterized. In addition to routine pharmacovigilance activities, results from the following studies will be used to evaluate long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Ongoing Studies:

- Study mRNA-1273-P903 (final CSR: 30 Jun 2023)
- Study mRNA-1273-P904 (final CSR: 31 Dec 2023)
- Study mRNA-1273-P203 (final CSR: 31 Jul 2024)
- Study mRNA-1273-P204 (final CSR; 31 Mar 2024)
- Study mRNA-1273-P205 (final CSR: 31 Dec 2023)

• Study mRNA-1273-P301 (final CSR: 31 Dec 2023)

Completed Studies:

• Study mRNA-1273-P201 (final CSR: 30 Sep 2022)

• Study mRNA-1273-101/ 20-0003 (final CSR Main Study: 01 Nov 2022)

Conclusion

As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor the 2 completed studies (mRNA-1273-P201 and mRNA-1273-P101) which are being assessed to characterize long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Rapporteur assessment comment:
The MAH reports no significant safety findings in the ongoing or completed studies, which aim to characterise long term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.
The information provided is acknowledged.

2.3.3.4. Use in immunocompromised subjects

Source of the New Information

New information presented below includes analysis performed on cases received into the GSDB for immunocompromised individuals by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022.

Background Relevant to the Evaluation

Immunocompromised and/or Immunosuppressed people were excluded from CTs, thus this subpopulation constitutes missing information in the Spikevax RMP. The MAH has been monitoring the safety profile in this subpopulation through routine pharmacovigilance. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, countries are recommending a booster dose (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in immunocompromised individuals, especially now with the bivalent vaccines. The third dose of elasomeran recommended for immunocompromised patients is 100 ug dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 ug dose [102,103].

In general, public health and professional groups recommend COVID-19 vaccination for patients immunocompromised. These recommendations highlight the likely potential benefits of COVID vaccines in this population with the potential risk of more severe COVID infections, sequelae, and impact on underlying immune-mediated diseases [104-107]. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals immunocompromised after vaccination with elasomeran, and they have indicated that the safety/tolerability profile in those individuals studied is

consistent with that observed in general populations receiving elasomeran [108] [109]. Analyzes have found a higher risk of hospitalization or death from COVID-19 in those with a variety of immunocompromising conditions, including rheumatic diseases, hematological malignancies, solid organ transplants, and HIV [110,111]. Factors that increase the risk of severe COVID-19 in the general population, such as older age, chronic kidney disease, cardiovascular disease, and other comorbidities, are significant drivers of risk in immunocompromised individuals. Moreover, some immunodeficiencies seem to increase the risk above and beyond traditional risk factors [112]. Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in immunocompromised individuals in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of use in immunocompromised individuals as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in immunocompromised individuals through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for valid, clinical, and spontaneous case reports for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in immunocompromised individuals, received from health-care providers, HAs, consumers, and literature, for the review period (19 Jun 2022–17 Dec 2022) and cumulatively (18 Dec 2020–17 Dec 2022).

For the purposes of this PBRER#4, the following operational definitions were applied in the analysis of the immunocompromised/immunosuppressed subpopulation:

The "Immunocompromised Subpopulation": Specifically, cases were identified in the MAH GSDB for immunocompromised and immunosuppressed individuals using a past medical history of hematological malignant tumors SMQ, transplantation, primary/innate and acquired immunodeficiency syndromes (including Human Immunodeficiency Virus [90]) and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs.

The "General Population" (all elasomeran data in the ModernaTx, Inc. GSDB: This refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the ModernaTx, Inc's. GSDB. This data is used to compare the AEs and safety profile in the immunocompromised population vs. the general population.

Literature Search Methodology:

The MAH performed a focused search of PubMed for elasomeran/imelasomeran and elasomeran/davesomeran and immunocompromised subjects to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 11.8 [of the PSUR].

A total of 75 literature articles were retrieved using these search criteria. There was no published information from these articles that described new and potentially important safety information on the safety profile of elasomeran.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases Reported for elasomeran

Cumulatively, there were 7,559 cases (31,444 events) in immunocompromised individuals, of which 2,936 were serious cases (11,514 serious events); there were 199 cases reporting a fatal outcome; 3,829 cases were medically confirmed.

There was a higher number of cases reported cumulatively in females (4,785; 63.3%) when compared to males (2,567;34.0%), with 207 cases (2.7%) missing gender information. Among the reported cases, the median age was 60.0 years with a range of 0.3 year to 101.0 years. Five hundred and seventy-one (571) cases had missing age information. The distribution of cases by age group is presented in Table 16.33 below.

Cumulatively, most of the events reported a resolved/ resolving outcome (13,482; 42.9%), with 8,482 events (30.2%) reported as not resolved. The majority of the cases continue to be reported by regulatory authorities (5,433;71.9%), with most of the cases coming from the United States (50.2%), UK (21.6%) and the Netherlands (8.0%).

During this review period, there were 812 cases (2,931 events) reported in immunocompromised individuals, of which 378 cases were serious (1,287 serious events); there were 12 cases reporting a fatal outcome. There were 269 cases medically confirmed.

Similar to the prior reporting period, during this reporting period there were more cases involving females (483 59.9%) compared to males (292;36.0%), with 37 cases (4.6%) missing gender information. The median age of reported cases was 59.0 years (range: 12.0 years – 95.0 years). Ninety-eight (98) cases had missing age information. The distribution of cases by gender (Table 16.32) and by age group (Table 16.33) is presented below.

Table 16.32 Distribution of Cases by Gender in the Immunocompromised Subpopulation (Review Period and Cumulative) – elasomeran

Patient Gender	Prior to Review Period		Review Period		Total of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Female	4,335	63.8	483	59.5	4,785	63.3
Male	2,293	33.7	292	36.0	2,567	34.0
Unknown	170	2.5	37	4.6	207	2.7
Grand total	**6,798**	**100.0**	**812**	**100.0**	**7,559**	**100.0**

During this review period, as in the previous reporting period, the distribution of cases by age showed that most events reported in the immunocompromised subpopulation occurred in individuals >50 years of age (606; 74.6%) (Table 16.33).

Table 16.33 Distribution of Cases by Age Group in the Immunocompromised Subpopulation (Review Period and Cumulative)

Age Group	Prior to Review Period		Review Period		Total # of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2	1	0.0	0	0	1	0.0
02-05Y	8	0.1	0	0	8	0.1
06-11Y	13	0.2	0	0	13	0.2
12-15Y	7	0.1	7	0.9	9*	0.1
16-17Y	12	0.2	3	0.4	15	0.2
18-24Y	175	2.6	12	1.5	183	2.4
25-39Y	840	12.4	93	11.5	931	12.3
40-49Y	842	12.4	91	11.2	921	12.2

50-64Y	1,909	28.1	244	30.0	2,139	28.3
65-74Y	1,564	23.0	158	19.5	1,716	22.7
75Y+	953	14.0	106	13.1	1,052	13.9
Missing	474	7.0	98	12.1	571	7.6
Grand total	**6,798**	**100.0**	**812**	**100.0**	**7,559**	**100.0**

Note: Some data changes between prior reporting period and current may result due to case processing, including receipt of follow- up information

*of the cumulative 9 cases, there are five cases ([redacted], [redacted], [redacted], [redacted] and [redacted]) in 12-15Y age group which were reported during the Prior to Review Period but also captured in review period due to case processing changes. Overall, all there are nine cases cumulatively in this age group

During the review period, similar to the cumulative period, the most frequently reported PT in the immunocompromised subpopulation included fatigue, headache, pyrexia, chills, myalgia and nausea. These PTs were comparable to that reported in the general population and reflected expected reactogenicity (Table 16.34). Events of COVID-19 infection is included on the top 10 PTs reported during this reporting period (66; 2.3%) only for the immunocompromised subpopulation. This may be due to a decreased immunogenicity of vaccination and/or the susceptibility to constantly changing variants. This was observed only in individuals receiving elasomeran.

Table 16.34 Top 10 MedDRA Preferred Terms (PT) in the Immunocompromised Subpopulation vs. General Population elasomeran (Review Period and Cumulative)

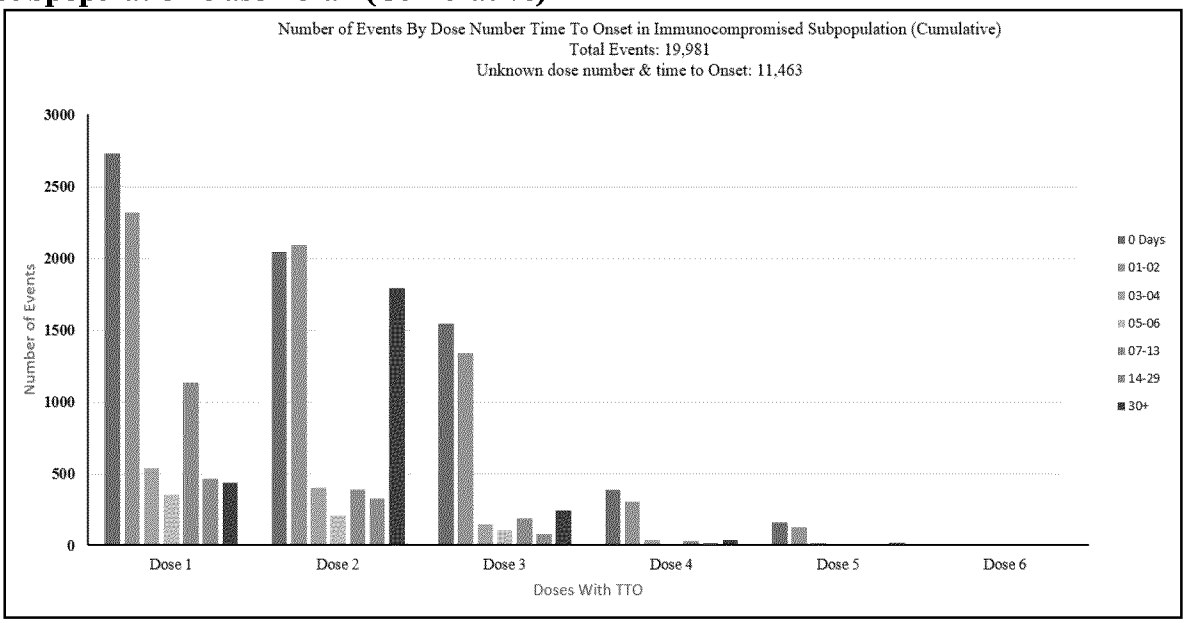
Review Period						Cumulative					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Fatigue	138.00	4.7	Headache	20,326	6.2	Fatigue	1,502	4.8	Headache	146,039	5.8
Headache	121.00	4.1	Fatigue	19,244	5.9	Headache	1,423	4.5	Pyrexia	139,460	5.5
Pyrexia	110.00	3.8	Pyrexia	18,726	5.7	Pyrexia	1,401	4.5	Fatigue	127,184	5.1
Nausea	78.00	2.7	Myalgia	13,373	4.1	Chills	981	3.1	Chills	97,683	3.9
Pain in extremity	74.00	2.5	Chills	11,127	3.4	Myalgia	841	2.7	Myalgia	91,510	3.6
Chills	70.00	2.4	Malaise	10,449	3.2	Nausea	837	2.7	Injection site pain	70,431	2.8
Myalgia	66.00	2.3	Injection site pain	10,156	3.1	Pain in extremity	691	2.2	Nausea	69,913	2.8
COVID-19	66.00	2.3	Arthralgia	8,647	2.6	Arthralgia	670	2.1	Malaise	67,283	2.7
Arthralgia	61.00	2.1	Nausea	8,346	2.5	Malaise	576	1.8	Arthralgia	55,998	2.2
Dizziness	52.00	1.8	Dizziness	8,036	2.5	Pain	548	1.7	Pain in extremity	53,606	2.1

= events, and % = % of events

When dose number was known, during the review period, more events were reported after dose 4 (349; 11.9%) and dose 3 (313; 10.7%). This may reflect the general trend of increased uptake of booster

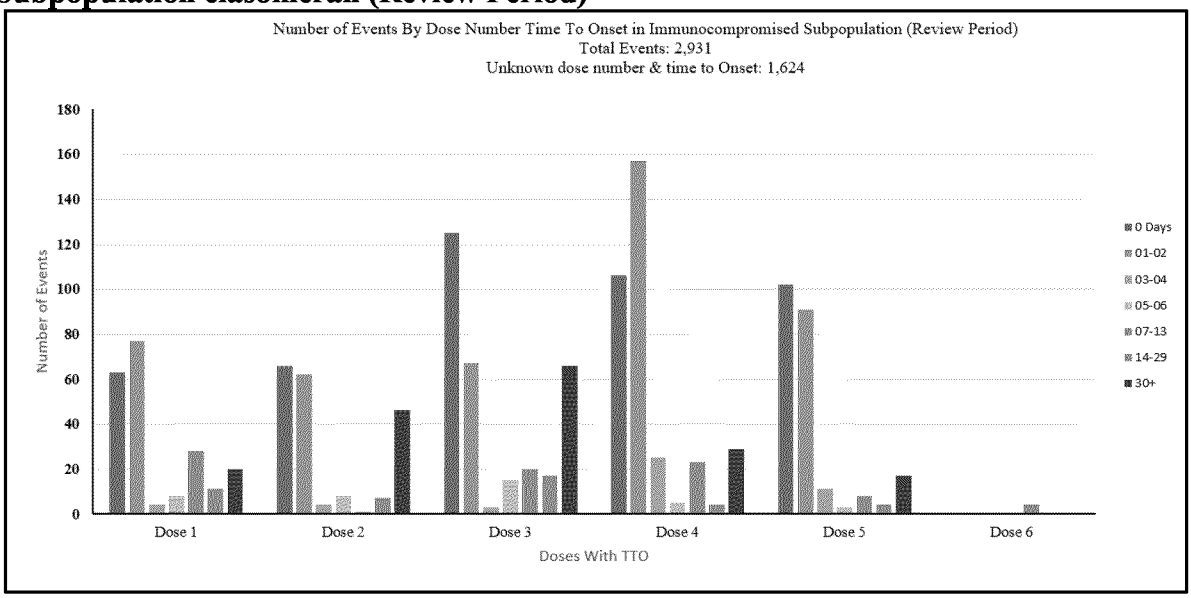
doses. Another consideration for this difference was the high percentage of events that were missing dosing information (55.4%) during the reporting period (Figure 16-7 and Figure 16-8). When dose and TTO were known, events most frequently occurred within 2 days of any dose, both cumulatively (41.0%) and during the review period (31.3%), except for events reported after dose 2 that had a bimodal peak within 2 days and 30 days and beyond. Medical review showed that events reported after 30 days were associated with multiple morbidities.

Figure 16-7. Event Distribution by Dose Number and Time to Onset Immunocompromised Subpopulation elasomeran (Cumulative)



Source: ModernaTx, Inc. GSDB – PBRER 4 Spotfire dashboard

Figure 16-8. Event Distribution by Dose Number and Time to Onset Immunocompromised Subpopulation elasomeran (Review Period)



Source: ModernaTx, Inc. GSDB – PBRER 4 Spotfire dashboard

Note that cumulatively, a total of 2,020 cases (including 867 serious and 38 fatal cases) overlap between the subpopulation of those with a medical history of autoimmune/inflammatory diseases (MedHx autoimmune or inflammatory disorders (AI)/ID) and immunocompromised/immunosuppressed subpopulations, as many people with AI/ID are on immunosuppressive therapies. During the reporting period, 274 cases (including 130 serious and 2 fatal cases) overlapped. (Please also refer to the Section 16.3.5.7 [of the PSUR].

Serious Cases and Events in the Immunocompromised Subpopulation – elasomeran

Cumulatively, there were 2,936 serious cases (11,514 serious events) in immunocompromised individuals with 199 cases reporting a fatal outcome; 1,431 serious cases were medically confirmed. Cumulative there were more serious reports involving females (1,736; 59.1%) than males (1,142; 38.9%), and 2.0% had missing gender information. Among the serious cases, the median age was 59.0 years (range: 13 years-98 years), with 180 cases were missing age information.

Cumulative the majority of the serious cases were reported by regulatory authorities (85.9%), with the three countries to countries being the UK (39.1%), the United States (38.1%) and France (4.2%).

During the review period, there were 378 serious cases (1,287 serious events) reported in immunocompromised individuals, 116 cases were medically confirmed. There were no changes in the gender distribution of reports with more serious cases involving females (224; 59.3%) than males (142; 37.6%); 12 serious reports (3.2%) had missing gender information. The median age of reported cases was 60.0 years (range 13 years-89 years).

Similar to the prior period, the majority of the serious cases were reported by regulatory authorities (79.4%), with the same top three reporting countries: UK (56.6%), the United States (13.2%) and France (3.2%).

The top 3 SOCs during this reporting period were general disorders and administration site conditions (25.5%), nervous system disorders (12.8%), and musculoskeletal and connective tissue disorders (11.4%). The most frequently reported PTs were in line with those seen in the general population (including pyrexia, headache, fatigue, chills and myalgia), and reflect expected vaccine reactogenicity. COVID-19 infection was the most reported PT (1,509; 4.1%) for serious events in the general population during the reporting period, a difference with all events during the reporting period where COVID-19 infection was identified on the top 10 events for immunocompromised individuals. (Table 16.35).

Serious events must be interpreted with caution, as not all events truly meet the definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases).

Table 16.35 Top 10 Preferred Terms (PT) for Serious Events in Immunocompromised Subpopulation vs. General Population elasomeran (Review Period and Cumulative)

Review Period - Serious Events						Cumulative - Serious Events					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Fatigue	65	5.1	COVID-19	1,509	4.1	Pyrexia	484	4.2	Pyrexia	16,087	3.8
Headache	57	4.4	Vaccination failure	1,151	3.1	Fatigue	452	3.9	Headache	15,358	3.7
Pyrexia	47	3.7	Fatigue	1,118	3.0	Headache	437	3.8	Fatigue	13,569	3.2

Nausea	35	2.7	Headache	1,070	2.9	Nausea	294	2.6	COVID-19	11,402	2.7
Pain in extremity	35	2.7	Pyrexia	967	2.6	Dyspnoea	287	2.5	Nausea	8,974	2.1
Myalgia	29	2.3	Syncope	889	2.4	COVID-19	254	2.2	Dyspnoea	8,772	2.1
Chills	28	2.2	Arrhythmia	797	2.1	Chills	253	2.2	Chills	8,454	2.0
Arthralgia	26	2.0	Myalgia	694	1.9	Dizziness	200	1.7	Myalgia	7,732	1.8
Dizziness	25	1.9	Dizziness	637	1.7	Pain in extremity	182	1.6	Syncope	7,428	1.8
Chest pain	25	1.9	Nausea	577	1.5	Myalgia	181	1.6	Dizziness	6,947	1.7

= serious events, and % = % of Total Serious Events

When dose number was reported, most serious events were reported after dose 4 (240;14.9%), and within 2 days post-vaccination, regardless of vaccine dose and reporting periods.

Fatal Cases in Immunocompromised Subpopulation – elasomeran

Cumulatively, reported cases with a fatal outcome (119 cases; 675 events) in immunocompromised individuals after elasomeran presented with a different demographic distribution when compared to all reported cases with more cases reported for males (119; 59.8%) than females (79; 39.7%), and one case missing gender information. Median age of reported fatal cases was 72.0 years (Range: 21.0 years - 98.0 years), with six cases missing age information. There were more fatal reports among individuals >65years old (141; 70.9%), after dose 2 (323; 47.9%) and after >30 days (292; 43.1%) regardless of dose number.

Cumulative, the top three PT with a specify term in fatal cases were COVID-19 (48; 7.1%), dyspnea (18; 2.7%) and COVID-19 Pneumonia (14; 2.1%. Of the 119 fatal cases, 111 were classified as "frail" (from past medical history and criteria (PT) included in "frail"), indicating that most of fatal cases had multiple risk factors and comorbidities (such as cardiovascular, diabetic, neurological disorders).

Most fatal case reports in immunocompromised individuals after elasomeran were from the United States (69.3%).

During the review period, the 12 fatal cases (21 serious events) reported for immunocompromised individuals, followed the same gender and age distribution as cumulative reports. There were no important differences related to dose number and TTO. There were only 3 specific PTs associated with the fatal reports received during the reporting period, including COVID-19 infection, cardiac arrest and vaccination failure. Four cases were classified as "frail" due to their past medical history and criteria PTs included in "frail", indicating that many of fatal cases had multiple comorbidities (such as cardiovascular, diabetic, or neurological disorders) (Table 16.36).

Table 16.36 Top 10 Fatal Events/Preferred Terms (in Fatal Cases in Immunocompromised Subpopulation (Reporting Period vs. Cumulative) - elasomeran

Report Period			Cumulative		
PT	# of Events	% of Total Events	PT	# of Events	% of Total Events
Death	5	23.8	Death	82	12.1
COVID-19	3	14.3	COVID-19	48	7.1
Cardiac arrest	2	9.5	Dyspnoea	18	2.7

Vaccination failure	2	9.5	COVID-19 pneumonia	14	2.1
			Respiratory failure	14	2.1
			Asthenia	12	1.8
			Cardiac arrest	12	1.8
			Hypoxia	12	1.8
			Pyrexia	12	1.8
			Vaccination failure	11	1.6

Evaluation of the fatal reports in immunocompromised individuals during the reporting period showed that they are heavily confounded by the patient's concurrent comorbidities, including hematologic disorders, cardiovascular disorders, diabetes, COPD, etc., which in almost all the fatal reports where information is provided, are important contributors to the fatal outcome. The medical review of all fatal cases received during the review period is presented in Appendix 11.8 [of the PSUR]. Refer to Section 16.3.6.7.6 [of the PSUR] and Section 16.3.5.6 [of the PSUR].

Of the 12 fatal cases reported during the reporting period, 5 cases ([redacted], [redacted], [redacted], [redacted] and [redacted]) included a COVID-19-related diagnoses around the time of death which likely caused or contributed to the fatal outcomes. Table 16.37 summaries the seven fatal cases not associated with COVID-19 that were received during this reporting period in the immunocompromised subpopulation.

Table 16.37 Non-COVID-19 Fatal Cases in the Immunocompromised Subpopulation (Review Period) - elasomeran

Case ID/Age (Years) /Gender	ALL Preferred Terms	Medical History	Case Summary
[redacted]/ 57-Years (Male)	Acute kidney injury, Adrenal insufficiency, Anaemia, Cardiac arrest, Cardiac failure, Diarrhoea, Encephalopathy, Haemolysis, Hypofibrinogenaemia, Hypotension, Hypothermia, Kaposi's sarcoma, Liver injury, Malaise, Mycobacterium avium complex infection, Nausea, Respiratory failure, Shock, Thrombocytopenia	[redacted] infection(C); Left ventricular failure(C); Chronic kidney disease(C); Atrial fibrillation(C)	Comorbidities are strong confounders
[redacted]/ 86-Years/ Female	Cardiomyopathy, Chest pain	Chronic lymphocytic leukaemia (CLL)	Case confounded by medical condition
[redacted]/ 85-Years (Male)	Death	Atrial fibrillation(C); Cardiac assistance device user(C); Disease risk factor(C); Hypertension(C); Hypercholesterolaemia(C); Chronic lymphocytic leukaemia stage 1(C); Cerebrovascular accident(H); Peripheral venous disease(H); Osteoporotic	Multiple comorbidities are strong confounders

		fracture(C); Fractured sacrum(H); Camptocormia(H); Olfacto genital dysplasia(H); Cognitive disorder(C); Bladder neoplasm(H); Transurethral bladder resection; Bradycardia(H); Arrhythmia(H); Atrioventricular block first degree(H); Bundle branch block right(H); Osteoporosis(C); Asthma(C)	
[redacted] / 54-Years (Male)	Chronic lymphocytic leukaemia recurrent, Renal cancer recurrent	Chronic lymphocytic leukaemia (C); Renal cancer(C); Hypercalcaemic nephropathy(C); JANSSEN COVID-19 VACCINE	Case confounded by medical condition
[redacted] / 43-Years (Male)	Death	Drug abuser(H); HIV infection(C)	Confounded by immunosuppressive condition.
[redacted] / 63-Years (Female)	Death, Thrombotic thrombocytopenic purpura	Hypertension(C); DM(C); Chronic kidney disease (C); HIV infection(C); Thrombotic thrombocytopenic purpura(C); RITUXIMAB(H)	Multiple immunosuppressive conditions are strong confounders
[redacted] / 58-Years (Male)	Acute kidney injury, Altered state of consciousness, Cardiac arrest, Inappropriate schedule of product administration, Respiratory failure, Thrombotic thrombocytopenic purpura, Ventricular fibrillation	Hypertension(C); Obesity(C); HIV infection(C); Antiretroviral therapy	Case confounded by medical conditions

H: Historical Condition; C: Concurrent Condition

Subpopulation Analyzes

Use in Immunocompromised Children (<12 years old) – elasomeran)

Cumulatively, there were 22 cases (59 events) reported in immunocompromised individuals 0-11 years old. All cases were non-serious.

Cumulatively, in the age group 0-5 years, there were 9 cases with 28 events (all non-serious events). One case was reported as exposure via breastmilk in a child less than 2 years of age. Medical review of the cases showed that the height and weight information provided suggested these were adults and thus represented age miscoding errors. There were no reports in this age groups received during this reporting period.

Cumulatively, in the age group 6-11 years, there were 13 non-serious cases with 31 events All 13 cases were medically confirmed. Most of the reported cases involved males (10;76.9%), compared to females (3; 23.1%). The mean age of reported cases was 7.0 years (SD 0.6). All reported events were related to product administration issues. There were no reports in this age groups received during this reporting period.

Review of reports in immunocompromised children (<12 years of age) did not identify any new safety concerns in this subpopulation.

Use in Immunocompromised Adolescents (12-17 years y/o) – elasomeran

Cumulatively, there were reported 24 cases (66 events) of which 6 were serious cases (19 serious events) with no reports of fatal outcome; 19 cases were medically confirmed. Most of the reports involved males (12; 50.0%) compared to females (8; 33.3%) with 4 reports (16.7%) missing gender information. The mean age of reported cases was 15.3 years (SD: 1.5 years) Fifteen (62.5%) of cases were 16-17-year-olds, and 9 cases (37.5%) were 12-15-year-olds.

During this reporting period, there were 10 cases (22 events) reported in immunocompromised adolescents, of which 2 were serious cases (1 serious event); there were cases reporting a fatal outcome; 10 cases were medically confirmed. There were more reports involving males (6; 60%) than females (1; 10.0%) with 3 reports (30.0%) missing gender information. The mean age of reported cases was 14.5 years (SD: 1.5 years). When the outcome of the reports was known, most of them (12; 54.5%) were reported as resolved.

Both cumulatively and during the reporting period, the most frequently reported PT for immunocompromised adolescents was "Product administered to a patient of inappropriate age" most of those reports did not include an AE. Additional PTs included reactogenicity events including pyrexia, myalgia, nausea, headache, dizziness, etc. There were no reports of COVID-19 in the adolescent subpopulation.

Review of reports in immunocompromised adolescents (12–17 years of age) did not identify any new safety concerns in this subpopulation.

Elasomeran Dose 3 and Booster in Immunocompromised Patients

Cumulatively, 1,708 cases (4,797 events) were reported for immunocompromised individuals receiving a 3rd dose or a booster dose; there were 911 serious cases (2,766 serious events), and 19 cases reporting a fatal outcome. There were 491 cases medically confirmed. There were more reports involving females (1,101; 64.5%) than males (556; 32.6%), with 51 reports (3.0%) missing gender information. Most of the reports were in individuals >50 years of age (1,020; 59.7%). The median age of reported cases after dose 3 was 56.5 years, ranging from 7.4 years to 92.0 years.

During the reporting period, there were 332 cases (902 events) reported for immunocompromised individuals after a 3rd dose or a booster dose; there were 170 serious cases (516 serious events), with 2 cases reporting a fatal outcome; there were 86 medically confirmed cases. The reporting pattern of cases regarding age, and gender was similar to that seen in the cumulative period. (See Table 16.38).

Table 16.38 Distribution of Cases by Age in the Immunocompromised Subpopulation, elasomeran Dose 3 or Booster (Report Period and Cumulative)

Age Group	Prior to Review Period		Review Period		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
06-11Y	1	0.1	0	0	1	0.1
12-15Y	0	0	1	0.3	1	0.1
16-17Y	1	0.1	1	0.3	2	0.1
18-24Y	36	2.6	2	0.6	38	2.2
25-39Y	222	16.0	38	11.4	260	15.2
40-49Y	216	15.6	39	11.7	254	14.9
50-64Y	373	27.0	110	33.1	480	28.1
65-74Y	244	17.6	70	21.1	312	18.3
75Y+	176	12.7	54	16.3	228	13.3

Missing	115	8.3	17	5.1	132	7.7
Grand total	**1,384**	**100.0**	**332**	**100.0**	**1,708**	**100.0**

With the exception of COVID-19, the most common PTs reported in immunocompromised individuals after Dose 3 or a booster dose with elasomeran are reflective of expected reactogenicity (Table 16.39).

No differences were noted in serious cases in immunocompromised individuals after a 3rd dose or a booster dose of elasomeran.

Table 16.39 Top 10 Events/Preferred Terms (PTs) in the Immunocompromised Subpopulation vs. General Population, elasomeran Dose 3 and above (Reporting Period and Cumulative)

Review Period – Dose 3 and above						Cumulative - Dose 3 and above					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Headache	51	5.7	Pyrexia	3,581	6.6	Headache	263	5.5	Headache	13,919	6.5
Fatigue	45	5.0	Headache	3,495	6.5	Pyrexia	255	5.3	Pyrexia	13,004	6.1
Pyrexia	40	4.4	Fatigue	3,057	5.7	Fatigue	218	4.5	Fatigue	11,040	5.1
Dizziness	28	3.1	Myalgia	2,489	4.6	Nausea	146	3.0	Chills	9,069	4.2
Nausea	27	3.0	Chills	2,229	4.1	Chills	144	3.0	Myalgia	7,947	3.7
Pain in extremity	26	2.9	Malaise	2,013	3.7	Pain in extremity	127	2.6	Nausea	6,024	2.8
COVID-19	25	2.8	Dizziness	1,411	2.6	Myalgia	126	2.6	Expired product administered	5,503	2.6
Myalgia	23	2.5	Arthralgia	1,396	2.6	Arthralgia	115	2.4	Lymphadenopathy	5,459	2.5
Chills	20	2.2	Nausea	1,344	2.5	Dizziness	106	2.2	Malaise	5,018	2.3
Arthralgia	19	2.1	Lymphadenopathy	1,304	2.4	Expired product administered	105	2.2	Dizziness	4,839	2.3

Fatal Cases and Events - elasomeran 3rd dose or booster

During the reporting period, there were two cases with fatal outcomes reported in males in Switzerland and Taiwan (1 each). Their mean age was 64.0 (SD: 29.7).

During the reporting period, both fatal cases in the immunocompromised subpopulation occurred after dose 4, with TTO of 1-2 days and 14-29 days. This differs from the earlier reported TTO of 1-2 days in the general population, after Dose 3 or booster.

Use in Immunocompromised Subjects After Booster Dose with elasomeran/imelasomeran

Cumulatively there were 88 cases (323 events) reported in immunocompromised individuals after receiving a booster dose with elasomeran/imelasomeran. All these reports were received during the reporting period for this PBRER 4. There were 54 serious cases (173 serious events), with one case (4 events) reporting a fatal outcome; 9 cases were medically confirmed. Most of the events were reported as resolved/ resolving (176; 54.5%). There were more reports involving females (54; 61.4%) than males (31; 35.2%), with 3 reports (3.4%) missing gender information. Most of the cases reported in immunocompromised individuals were in individuals >50 years of age (73; 83.0%%). The distribution of cases by age group is presented in Table 16.40 below.

Table 16.40 Distribution of Cases by Age Group in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/imelasomeran (Report Period and Cumulative)

Age Group	Prior to Review Period		Review Period		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-24Y	0	0	1	1.1	1	1.1
25-39Y	0	0	8	9.1	8	9.1
40-49Y	0	0	6	6.8	6	6.8
50-64Y	1	100.0	16	18.2	16	18.2
65-74Y	0	0	22	25.0	22	25.0
75Y+	0	0	13	14.8	13	14.8
Missing	0	0	22	25.0	22	25.0
Grand total	**1**	**100.0**	**88**	**100.0**	**88**	**100.0**

The most frequently reported PTs in immunocompromised individuals receiving a booster dose with elasomeran/imelasomeran were considered reactogenicity event (fatigue, headache, pyrexia, chills, and Arthralgia) were comparable to the general population receiving a booster dose with elasomeran/imelasomeran. There was no difference in the PTs reported for the serious cases in immunocompromised individuals after elasomeran/imelasomeran (Table 16.41).

Table 16.41 Top 10 Preferred Terms (PT) in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/imelasomeran vs. General Population (Cumulative)

Cumulative Booster Dose with elasomeran/imelasomeran					
Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%
Fatigue	27	8.4	Headache	1,773	8.2
Headache	25	7.7	Malaise	1,612	7.5
Pyrexia	19	5.9	Fatigue	1,507	7.0
Chills	16	5.0	Myalgia	1,491	6.9
Arthralgia	12	3.7	Chills	1,426	6.6
Limb discomfort	12	3.7	Pyrexia	1,209	5.6
Nausea	11	3.4	Arthralgia	1,001	4.6
Malaise	10	3.1	Nausea	999	4.6
Injection site pain	9	2.8	Injection site pain	998	4.6

Myalgia	9	2.8	Injection site inflammation	455	2.1

When dose and TTO were known, events most frequently occurred within 2 days regardless of vaccine dose (57; 17.6%).

Table 16.42 Event Distribution by Dose Number and Time to Onset (TTO) in Patients Receiving Booster Dose with elasomeran/imelasomeran

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 3	***Subtotal***	***15***	***4.6***
	0 days	4	1.2
	01-02	4	1.2
	30+	7	2.2
Dose 4	***Subtotal***	***79***	***24.5***
	0 days	42	13.0
	01-02	26	8.0
	03-04	8	2.5
	07-13	3	0.9
Dose 5	***Subtotal***	***66***	***20.4***
	0 days	26	8.0
	01-02	27	8.4
	03-04	1	0.3
	05-06	6	1.9
	07-13	6	1.9
Unknown	***Subtotal***	***163***	***50.5***
	0 days	2	0.6
	01-02	8	2.5
	05-06	2	0.6
	14-29	2	0.6
	Event onset prior to first dose reported	1	0.3
	Missing	148	45.8
Grand total		**323**	**100.0**

Fatal Reports in Immunocompromised Individuals after receiving elasomeran/imelasomeran Vaccination:

Cumulatively, there was only one (1) fatal case reported in an immunocompromised individual after elasomeran/imelasomeran. Details of this case is described below:

Case# [redacted] **(TW-**[redacted]: This is a spontaneous case concerning a 50-year-old male patient with medical history of multiple myeloma and bone marrow transplant, who two days after receiving a fifth dose with elasomeran/imelasomeran experienced, dizziness, cold sweat, abdominal bloating and cardiac arrest. He was dead before arriving hospital (reported as out-of-hospital cardiac arrest). The reported cause of death was cardiac arrest. An autopsy was not performed. No

further clinical information was provided. The medical history of multiple myeloma and bone marrow transplant are strong confounders. This case is missing relevant information for concomitant medications and clinical course of events, hence assessed as WHO-UMC Unassessable due to the lack of information.

Use in Immunocompromised Subjects After Receiving Booster Dose with elasomeran/davesomeran

Cumulatively, there were 21 cases (69 events) reported in immunocompromised individuals after receiving a booster dose with elasomeran/davesomeran. All these reports were received during the reporting period of this PBRER 4. There were 3 serious cases (3 serious events); there were no cases reporting a fatal outcome. There were 11 cases medically confirmed. There were more reports involving females (13; 61.9%) than males (7; 33.3%) with 1 case (4.8%) missing gender information. Most events of the cases reported in the immunocompromised individuals occurred in individuals >50 years of age (15; 71.4%). The median age of reported cases was 66.0 years, with range from 23.0 years to 83.0 years

The distribution of cases by age group is presented in Table 16.43 below.

Table 16.43 Distribution of Cases by Age Group in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/davesomeran (Review Period and Cumulative)

Age Group	Review Period		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases		
18-24Y	1	4.8	1	4.8
25-39Y	1	4.8	1	4.8
50-64Y	6	28.6	6	28.6
65-74Y	6	28.6	6	28.6
75Y+	3	14.3	3	14.3
Missing	4	19.0	4	19.0
Grand total	**21**	**100.0**	**21**	**100.0**

The most frequently reported PTs in immunocompromised individuals receiving a booster dose with elasomeran/davesomeran were considered reactogenicity event (fatigue, headache, pyrexia, chills, and Arthralgia). When compared to the general population these events were reported at a higher proportion.

Table 16.44 Top 10 Preferred Terms (PT) in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/davesomeran vs. General Population (Cumulative)

Cumulative Booster Dose with elasomeran/davesomeran					
Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%
Pyrexia	6	8.7	Pyrexia	108	1.6
Fatigue	4	5.8	COVID-19	105	1.6
Headache	4	5.8	Pain in extremity	90	1.4
Accidental underdose	3	4.3	Vaccination site pain	88	1.3
Dizziness	3	4.3	Headache	81	1.2
Pain	3	4.3	Fatigue	80	1.2

Chills	2	2.9	Chills	72	1.1
Decreased appetite	2	2.9	Underdose	69	1.0
Vaccination site erythema	2	2.9	Myalgia	68	1.0
Vaccination site swelling	2	2.9	Pain	64	1.0

When dose number was reported, there were more reports after dose 4 (20;29.0%), followed by dose 5 (15;21.7%) Table 16.45). When TTO was known, events most frequently occurred within 2 days after any dose.

Table 16.45 Event Distribution by Dose and Time to Onset (TTO) in Patients Receiving Booster Dose with elasomeran/davesomeran

Dose Number	TTO All Doses (Days)	Review Period		Grand total of # Events	Grand total of % of Total Events
		# Events	% of Total Events		
Dose 3	Subtotal	1	1.4	1	1.4
	0 days	1	1.4	1	1.4
Dose 4	Subtotal	20	29.0	20	29.0
	0 days	18	26.1	18	26.1
	01-02	2	2.9	2	2.9
Dose 5	Subtotal	15	21.7	15	21.7
	0 days	9	13.0	9	13.0
	01-02	6	8.7	6	8.7
Unknown	Subtotal	33	47.8	33	47.8
	Missing	33	47.8	33	47.8
Grand total		**69**	**100.0**	**69**	**100.0**

Discussion

A review of the data received during the reporting period of this PBRER, showed that events reported in immunocompromised individuals continue to primarily occur in individuals >50 years of age, with a higher number of reports involving females, as it is seeing in the general population, with a TTO of less than 7 days.

Review of the safety information included in the MAH's GSDB as well as the literature received during the reporting period of this PBRER did not identify any new safety concerns in immunocompromised individuals. Frequently reported events in the immunocompromised subpopulation were generally comparable to those seen in the general population and were related to reactogenicity events commonly seeing after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. During this reporting period, reports of COVID-19 infection were lower in the immunocompromised subpopulation compared to the general population. This might be due to a higher rate of booster administration in the immunocompromised subpopulation.

Currently, some countries have approved/authorized/recommend a third dose in the primary series as well as a fourth "booster" dose and fifth "second booster" in severely immunocompromised individuals, as well as a third booster dose in mildly immunosuppressed individuals (and the general population) due to waning of immunity and the emergence of new variants. A higher percentage of reports for Dose 3 and

Dose 4 during the review period compared to the cumulative likely reflects increased booster vaccination uptake and reporting of booster cases in the immunocompromised subpopulation during this period.

Cumulative review of the safety information has not identified any patterns/trends or specific safety concerns in the immunocompromised population. Serious events and fatal reports are heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported AEs in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population. As of the DLP of this PBRER (17 Dec 2022), the review of the post-marketing safety data has not identified any patterns or specific safety concerns in the immunocompromised population.

The large scale use of elasomeran (and other COVID-19) vaccines through EUA is without historical precedent. As of the end of the reporting period of this PBRER, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in Immunocompromised individuals, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable.

• Review of the safety data in immunocompromised subjects reported in the GSDB indicates that the general pattern of commonly reported AEs in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population, rather than as a result of vaccine exposure.

• The MAH continues to evaluate "Use in Immunocompromised subjects" in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies.

• Throughout the world all the EUA received for elasomeran includes recommendations for additional doses for immunocompromised subjects

• Use of elasomeran in immunocompromised subjects is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

• Extended use of the elasomeran vaccines in immunocompromised individuals has provided extensive safety information in this subpopulation group to no longer be considered missing information.

• Use of the vaccine in immunocompromised individuals is already included in the product's labeling, and the use of elasomeran in immunocompromised subjects is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

• There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to 'use in immunocompromised subjects' as long-term safety is being kept as missing information.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in immunocompromised individuals in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in immunocompromised individuals as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in immunocompromised individuals through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Conclusion

Given that this population is at an increased risk for severe COVID-19 infection, based on the analysis of all the safety data available as of 17 Dec 2022, the MAH considers cases included under the immunocompromised subpopulation to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and the benefits for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran far outweigh any possible vaccine-associated risks.

Based on the analysis of all the safety data received during the reporting period and cumulatively in the immunocompromised subpopulation, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The MAH will continue to monitor use in immunocompromised individuals using routine surveillance.

Rapporteur assessment comment:

The MAH proposed removal of the missing information 'use in immunocompromised subjects' from the EU-RMP, which is currently not accepted (see section 3.1.4.1.3.). Regardless of the outcome on the RMP, the topic shall remain in the PSUR list of safety concerns and an evaluation of new information on this topic is required with future PSURs.

No new significant safety information was identified.

2.3.3.5. Interactions with Other Vaccines

Source of the New Information

The Company (herein referred to as ModernaTx, Inc.) GSDB was queried for valid, clinical, and spontaneous case reports received from HCP, HA, consumers, and literature, from 19 Jun 2022 through 17 Dec 2022, reported for elasomeran (including boosters and recent bivalent approvals) for cases of vaccine coadministration with all other vaccines (not including COVID 19 products).

Background Relevant to the Evaluation

The safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when co-administered with non-COVID-19 vaccines is being monitored, including their use with the new Spikevax bivalent vaccines.

Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show increased AEs. Therefore, WHO considers that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

As COVID-19 vaccines become available to children who are also being vaccinated against childhood infectious diseases, the safety and efficacy of coadministration is being evaluated with routine surveillance activities.

As of the DLP of this PBRER (17 Dec 2022), the review of post-approval/EUA data has not identified any patterns or specific safety concerns in individuals receiving concomitant vaccines with elasomeran.

Literature Review for Interactions with Other Vaccines Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and interactions with other vaccines (non-COVID-19) to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d. A total of 16 literature articles were retrieved using these search criteria.

There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

[Please refer to the PSUR for sections on methodology and results]

Discussion

Overall, cumulatively, AEs reported for individuals receiving non-COVID-19 vaccines concomitantly with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran were generally comparable to those seen in the general population after vaccination with non-COVID-19 vaccines and were related to reactogenicity events commonly seeing after vaccination with elasomeran elasomeran/imelasomeran and elasomeran/davesomeran. A review of the data received cumulative and during the reporting period of this PBRER, showed that events reported in individuals receiving concurrent vaccines with elasomeran continue to primarily occur in individuals >50 years of age, with a higher number of reports involving females, as it is seeing in the general population, with a TTO of less than 7 days. Reports in the pediatric population comprised mainly product administration errors. The highest reported events were seen with coadministration with the influenzae vaccine.

Cumulative review of the safety information has not identified any patterns/trends or specific safety concerns in individuals receiving concurrent vaccines with elasomeran elasomeran/imelasomeran and elasomeran/davesomeran. Serious events and fatal reports are heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported AEs in those individuals receiving concurrent vaccines with elasomeran is comparable to the general population.

As of the DLP of this PBRER (17 Dec 2022), the review of post-approval/EUA data has not identified any patterns or specific safety concerns in individuals receiving concomitant vaccines with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. No interactions between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and other non-COVID-19 vaccines have been observed.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of

110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Interaction with other vaccines, the benefit-risk profile for elasomeran remains favorable.

The MAH has monitored interactions with other vaccines in each MSSRs as well as in PSURs since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found:

• Review of the safety data on individuals receiving concurrent vaccines with elasomeran reported in the GSDB indicates that the general pattern of commonly reported AEs is consistent with expected reactogenicity events and are comparable to events observed in the general population receiving other widely used vaccines.

• Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show an increase in reporting of AEs. Health authorities consider that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

• Use of elasomeran with other vaccines, including childhood immunization vaccines is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

• Extended use of the elasomeran vaccines in conjunction with other vaccines has provided extensive safety information for "Interactions with other vaccines" no longer be considered missing information.

• Concomitant use of other vaccines with elasomeran is included in the Summary of Products Characteristics: High dose quadrivalent influenza vaccine can be concomitantly administered with elasomeran.

• The MAH continues to evaluate "Interaction with other vaccines" in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through postauthorization safety studies.

• Concomitant use of the vaccine with the influenza vaccine is already included in the product's labeling, and the use of with other vaccine is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

• There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to Interaction with other vaccines' as long-term safety is being kept as missing information.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events for "Interactions with other vaccines" in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of "Interactions with other vaccines" as Missing Information from the Spikevax EU-RMP, and to continue monitoring "Interactions with other vaccines" through routine surveillance.

Conclusion

After careful review of all new safety data received during the reporting period and cumulatively for interactions of non-COVID-19 vaccines co-administered with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and

elasomeran/davesomeran remains favorable. The MAH continues to evaluate "Interaction with other vaccines" in reports of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran via routine pharmacovigilance activities as well as through postauthorization safety studies.

2.3.3.5.1. Interaction with Other COVID-19 vaccines (Heterologous Vaccine Schedule)

Source of the New Information

European Medicines Agency/PRAC requested that in this PSUR, the MAH present data, including literature, and discuss the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in relation to heterologous COVID-19 vaccines schedule. The data and discussion should be presented in relevant sections e.g., off-label use, or in addition to the already presented PSUR headline "Interaction with other vaccines (Heterologous Vaccine Schedule)".

Background Relevant to the Evaluation

Several vaccines have demonstrated efficacy against SARS-CoV-2 mediated disease (herein referred to as "COVID-19"), yet there are limited clinical data on the efficacy/safety or immunogenicity of heterologous vaccine regimens (including those employing different vaccine platforms, such as vectored vaccines) [113,114]. Currently, various heterologous combinations of COVID-19 vaccines are being used under post- EUA, or post-market authorization, either as heterologous priming (heterologous-prime-boost) or heterologous boost. The heterologous primeboost vaccination technique is not new as it has a history of deployment in previous outbreaks [115]. However, the difference for the COVID-19 vaccines is that there are different vaccine constructs as well as interchangeability of the mRNA vaccines.

Heterologous priming is also referred to as the "interchangeability" of vaccine products. In a scenario of heterologous priming schedules (commonly referred to as "mix and match" schedules), the second dose uses a different vaccine product than the first dose administered. According to the WHO, reasons for the utility of heterologous priming include "reducing reactogenicity," "increasing immunogenicity," and "enhancing vaccine effectiveness" [116]. However, the WHO also notes that "the most common reason for considering a heterologous COVID-19 vaccine as a second priming dose is lack of availability of the same vaccine in settings with limited vaccine supply or unpredictable supply" [116], the WHO advised that heterologous priming should only be implemented if there is documented "supporting evidence." In the case of heterologous boosting, a vaccine from a different vaccine platform is administered other than the vaccine used to complete the primary vaccine series [116]. In May 2022, WHO has continued with the recommendation of dosing with the heterologous schedule [117].

In 2021, the United States FDA and other developed countries recommended the use of a booster dose for COVID-19 vaccines in eligible populations. In the case of heterologous use in the United States, the FDA had authorized the Moderna COVID-19 Vaccine for use in eligible individuals "as a heterologous booster dose following completion of primary vaccination with a different available COVID-19 vaccine. For example, Pfizer-BioNTech COVID-19 Vaccine and Janssen COVID-19 vaccine recipients 18 years of age and older may receive a single booster dose of the Moderna COVID-19 Vaccine" [117].

COVID-19 vaccines emerging from different platforms differ in efficacy, duration of protection, and side-effects. This 'Mix and Match" landscape will become increasingly complex over time, with increasing number of booster doses. Heterologous prime-boost immunization strategies have the potential to augment COVID-19 vaccine efficacy. Kaku et al examined the immunity induced by either prime and boost with the adenoviral-vectored vaccine ChAdOx1 or prime with ChAdOx1 and boost with a messenger RNA (mRNA) vaccine and reported that heterologous mRNA booster immunization induced higher serum neutralizing antibody and memory B-cell responses against SARS-CoV-2 variants of concern (VOCs) compared with that of homologous ChAdOx1 boosting [118]. The focus of this review for "Interaction with

Other COVID-19 Vaccines/Heterologous Vaccines" data is on 1) Heterologous COVID-19 vaccine administration (i.e., interchange of vaccines ("Mix and Match") and booster; 2) Heterologous vaccine interactions (and other reported interactions, if any; and 3) Safety profile of elasomeran, elasomeran/imelasomeran and elosameran/davesomeran in relation to heterologous COVID-19 vaccines schedule.

Literature Search and Review

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and (Interaction with heterologous vaccines) to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d [of the PSUR].

A total of 690 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTx, Inc. queried GSDB for the review period from 19 Jun 2022 to 17 Dec 2022, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following criteria: Heterologous interchange of vaccines.

A cumulative review of potential interaction of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran with other COVID-19 vaccines from other manufacturers was performed using the PT "Interchange of vaccine products" with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran including 4 criteria:

1. PT: 'Interchange of vaccine products'

2. Medical history of manufacturer's vaccine (AstraZeneca, Janssen, Pfizer-BioNTech, Other)

3. Concomitant Medication as in manufacturer's vaccine (AstraZeneca, Janssen, Pfizer-BioNTech, ModernaTx, Inc., Other)

4. Co-suspect as in manufacturer's vaccine (AstraZeneca, Janssen, Pfizer-BioNTech, ModernaTx, Inc., Other).

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more information about cases involving interaction with other COVID-19 vaccines (heterologous vaccine schedule) refer to Appendix 11.9 [of the PSUR].

Overview of Cases - Review Period (19 Jun 2022 to 17 Dec 2022) – Elasomeran

During the review period, there were 13,329 cases (66,025 events, 3,097 serious cases). There were 81 cases (208 events) with fatal outcomes. The majority of reported cases were by regulatory authorities (11,971; 89.8%); originated from the EEA (9,927; 74.5%) followed by the UK (1,625, 12.2%). A high proportion of reported cases were in females (9,170; 68.8%) as compared to males 3,940 (29.6%) and 220 (1.7) has unknown gender information. The most frequent age group for reported cases in the 25-39 years (3,489; 26.2%). The median age of reported cases was 47 years. There were only 65 (0.5%) reported cases in the pediatric age group (less than 12 years) and 43 (0.3%) reports for adolescent subpopulations (12-17 years) (Table 16.46). Of the 66,031 events, 19,718 events (29.9%) Not

recovered, 16,021 events (24.3%) had resolved, while 11,612 events (17.6%) had resolving. There were 16,986 (25.7%) events with unknown/missing outcome (Table 16.49).

Table 16.46 Age and Gender Distribution "Interchange of Vaccine Product" Cases (Review Period: 19 Jun 2022 to 17 Dec 2022) – elasomeran

Age Group	Review Period							
	Female		Male		Unknown		Total	
	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases
< 2 years	8	0.1	9	0.1	2	0.0	19	0.1
2-4 years	3	0.0	7	0.1	2	0.0	12	0.1
5-11 years	21	0.2	13	0.1	0	0.0	34	0.3
12-17 years	19	0.1	21	0.2	3	0.0	43	0.3
18-24 years	504	3.8	130	1.0	6	0.1	640	4.8
25-39 years	2,643	19.8	826	6.2	20	0.2	3,489	26.2
40-49 years	1,960	14.7	692	5.2	6	0.1	2,658	20.0
50-64 years	2,132	16.0	1,021	7.7	24	0.2	3,177	23.8
65-74 years	901	6.8	555	4.2	17	0.1	1,473	11.1
75+ years	485	3.6	371	2.8	18	0.1	874	6.7
missing	494	3.7	295	2.2	122	1.0	911	6.8
Grand Total	**9,170**	**68.8**	**3,940**	**29.6**	**220**	**1.7**	**13,330**	**100.0**

Note- There is overlapping of one case in two age groups

In the review period, The European Economic Area (EEA) reported the highest proportion of cases (9,927; 74.5%). This is due to Europe spearheading the massive global campaign to boost its population with COVID-19 vaccines. Case distribution by region is presented below in Table 16.47.

Table 16.47 Distribution of Interchange Vaccine Product Cases Reported by Region (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

Region	Review period cases	% Total Cases
European Economic Area	9,927	74.5
United Kingdom	1,625	12.2
Asia	543	4.1
Australia	514	3.9
United States	486	3.6
Canada	145	1.1
Latin America	46	0.3
Switzerland	40	0.3
Middle East	3	0.0
Grand Total	**13,329**	**100**

During the reporting period, the most frequently reported preferred terms (PT) for interchange vaccines were Fatigue 4752 (7.2%), Headache 4251 (6.4%) and Injection site pain 3554 (5.4%). These are all consistent with reactogenicity reactions expected after COVID-19 immunization. The top reported PTs (>2%) during the review period for "Interchange of Vaccines Products" continue to be consistent with those seeing in the previous reporting periods as well as cumulative and are presented in Table 16.48.

Table 16.48 Top PTs (>2%) for the Interchange of Vaccines by Events (Review Period: 19 June 2022 to 17 Dec 2022) elasomeran

PT	Event Counts	% Events
Fatigue	4,752	7.2
Headache	4,251	6.4
COVID-19 immunization	3,911	5.9
Injection site pain	3,554	5.4
Pyrexia	2,906	4.4
Myalgia	2,785	4.2
Malaise	2,371	3.6
Arthralgia	1,787	2.7
Dizziness	1,653	2.5
Chills	1,573	2.4
Nausea	1,495	2.3

In the review period, while a high proportion of reported events for "Interchange of Vaccines" were after Dose 3 (12,185; 18.5%), more than half (45,424; 68.8%) of the reported events had missing dose numbers. Most of the events during the reporting period were reported as recovered/recovering (27,633; 41.8%) at the time of the report (Table 16.49). There were 83 cases (208 events) reported with a fatal outcome (0.3%)

Table 16.49 Number and Percentage of Events Reported after Interchange of Vaccines (Heterologous Vaccination) by Dose Number, Outcome (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

	Review Period	
	Events	
	N	%
Total	66,031	100
Dose number prior to onset		
Dose 1	1,078	1.6
Dose 2	5,252	8.0
Dose 3	12,185	18.5
Dose 4	1,767	2.7
Dose 5	318	0.5
Dose 6	5	0.0
Dose 7	2	0.0

	Review Period	
	Events	
	N	%
Unknown	45,424	68.8
Outcome		

Fatal	208	0.3
Not Recovered/Not Resolved	19,718	29.9
Recovered/Resolved	16,021	24.3
Recovered/Resolved with Sequelae	1,486	2.3
Recovering/Resolving	11,612	17.6
Unknown	16,986	25.7

Overview of Heterologous Vaccines Serious Cases by Manufacturer elasomeran

Of the 13,329 cases heterologous vaccines reported in the review period, 3,097 cases (23.2%, 15,391 events) were assessed as serious and 81 (2.6%) reported serious cases had fatal outcome. Among the serious cases reported, the highest number of cases were from Pfizer-BioNTech (2,381; 76.9%), AstraZeneca (435; 14.0%), Janssen (115; 3.7%) and other manufacturers (327; 10.6%). There was a female preponderance during the review period reported in serious cases (1,881; 60.7%) than males (1,154, 37.3%), while 62 (2.0%) reported cases were missing gender data values with most cases reported in the 50-64 years age group (872; 28.2%). Of the 15,391 serious events reporting during the review period, 2,856 events (18.6%) were resolved. Most events were seen after dose 3 (3,433; 22.3%) (Table 16.51).

Age distribution among serious interchange vaccine products is presented in Table 16.50; details by MAH further are described in their respective sections below under fatalities by interchange vaccine products (MAH).

Table 16.50 Age Distribution of Serious Cases by Manufacturers (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

Age	Pfizer-BioNTech		AstraZeneca		Janssen		Other	
	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases
< 2 years	3	0.1	1	0.2	0	0.0	0	0.0
2-4 years	0	0.0	0	0.0	0	0.0	0	0.0
5-11 years	1	0.0	1	0.2	0	0.0	1	0.3
12-17 years	11	0.5	0	0.0	0	0.0	0	0.0
18-24 years	79	3.3	8	1.8	1	0.9	2	0.6
25-39 years	453	19.0	49	11.3	17	14.8	33	10.1
40-49 years	420	17.6	39	9.0	20	17.4	33	10.1
50-64 years	620	26.0	156	35.9	40	34.8	107	32.7
65-74 years	312	13.1	85	19.5	14	12.2	68	20.8
75+ years	266	11.2	60	13.8	3	2.6	60	18.4
missing	216	9.1	36	8.3	20	17.4	23	7.0
Total	**2,381**	**100.0**	**435**	**100.0**	**115**	**100.0**	**327**	**100.0**

Note: There is overlap of cases between different age groups.

Serious events for interchange vaccines by dose and outcome are presented in Table 16.51. While a high proportion of reported events for "Interchange of Vaccines" were after dose 3, (9,475; 61.6%) of the reported events had missing dose numbers. A high proportion of the reported events had not resolved at the time of the report (5,188, 33.7%).

Table 16.51 Serious Events by Dose Number and Outcome Interchange Vaccine Products (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

	Review Period	
	Events	
	N	%
Total	15,391	100
Dose number prior to onset		
Dose 1	455	3.0
Dose 2	1,069	7.0
Dose 3	3,433	22.3
Dose 4	749	4.9
Dose 5	208	1.4
Dose 6	0	0.0
Dose 7	2	0.0
Unknown	9,475	61.6
Outcome		
Fatal	208	1.4
Not Recovered/Not Resolved	5,188	33.7
Recovered/Resolved	2,856	18.6
Recovered/Resolved with Sequelae	740	4.8
Recovering/Resolving	2,362	15.3
Unknown	4,037	26.2

There were no differences among the serious cases, when compared to the non-serious cases, regarding the most frequently reported PT (>2%events) with fatigue (770, 5.0%), headache (587, 3.8%), dizziness (403, 2.6%) and pyrexia (388, 2.5%) being the most commonly reported PTs. Most of the events reflect common and well-described reactogenicity of ModernaTx, Inc. elasomeran and other COVID-19 vaccines and were comparable or lower than the respective percentage of these events in the general population with elasomeran. Table 16.52 presents the top serious PTs by events/cases and their percentages for the reporting period.

Table 16.52 Top Serious PTs (>2%) by Number of Serious Events and Percentages for Heterologous Interchange During the Review Period (Review Period: 19 Jun 2022 to 17 Dec 2022)

PT	Event Counts	% Events
Fatigue	770	5.0
Headache	587	3.8
COVID-19 immunization	541	3.5
Dizziness	403	2.6
Pyrexia	388	2.5
Myalgia	362	2.4
Interchange of vaccine products	360	2.3
Malaise	327	2.1

Table 16.53 presents the top five (5) events reported. Pfizer-BioNTech primary series with ModernaTx, Inc. boosters had the highest cases across all doses and higher serious cases compared to other vaccines. The trend noted is an increasing rate of serious cases with increasing dose, which tapered by dose 7. Top

PTs and their reporting rates were similar across all vaccines, except for AZ which had a higher rate of COVID-19 infection.

Table 16.53 Overview of Co-Administered COVID-19 Vaccines by Top 5 Reported Preferred Terms, and Dose Number, and Number of Reported Serious Cases (Review Period 19 Jun 2022 to 17 Dec 2022) elasomeran

Heterologous Co-Suspect	Top 5 PTs (# events; %)	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Unknown	# of Serious Cases
Pfizer-BioNTech COVID-19 vaccine	COVID-19 immunization (895; 8.2%) Pyrexia (610, 5.6%) Headache (557, 5.1%) Fatigue (535; 4.9%) Myalgia (363; 3.3%)	234	1496	3120	485	73	2	1	8401	2381
AstraZeneca COVID-19 vaccine	COVID-19 (294; 23.6%) Headache (37, 3.0%) Fatigue (32, 2.6%) Pyrexia (24, 2.0%) Arthralgia (22, 1.8%)	42	45	286	121	29	0	0	922	435
Janssen COVID-19 vaccine	COVID-19 (29, 7.4%) Fatigue (18; 4.6%) Headache (12; 3.1%) Injection site pain (10; 2.5%) Myalgia (10, 2.5%) Suspected COVID-19 (10, 2.5%)	12	133	41	7	0	0	1	270	115
Other vaccine Manufacturers	Arthralgia (21, 1.9%) Headache (21; 1.9%) Fatigue (20, 1.8%) Myalgia (20, 1.8%) COVID-19 (18; 1.6%)	29	112	133	181	68	0	0	762	327

Note: There is overlapping of cases between multiple doses for all manufacturers

Overview of Fatalities for Interchange Vaccine Products elasomeran

During this review period, a total of 81 cases (208 events) of vaccine interchange with fatal outcomes were reported. Pfizer-BioNTech interchange had the highest fatal outcome (57; 0.5%). However, the outcomes are independent of doses distributed. Table 16.54 presents interchange fatalities by manufacturer.

Table 16.54 Frequency and Number of Reported Fatal Cases by Manufacturers of COVID Vaccines (Reporting Period 19 Jun 2022 to 17 Dec 2022) elasomeran

Manufacturer/ Co-Suspect	Total Cases	Fatal Cases	% per Vaccine
Pfizer-BioNTech	10,939	57	0.5
AstraZeneca	1248	17	1.4
Janssen	393	5	1.3
Other	1130	6	0.5

Note: There is overlapping of cases between different manufacturers

Overview of Cases for Interchange Vaccine Products after Dose 3+/booster elasomeran

During the reporting period, a review of cases including events after dose 3+/booster dose reported with co-suspect manufacturers' of COVID vaccines showed that the highest events were seen in age groups 25-39 for Pfizer-BioNTech and Other vaccines; 50-64 for AZ and Janssen. This may be explained by the demographics of administration of each vaccine product. The highest reports after dose 3+/booster were reported with Pfizer-BioNTech (10,829) followed by AstraZeneca (5,078) (Table 16.55).

Table 16.55 Number of Cases after Heterologous Vaccination by Age for Dose 3+ by Manufacturers of COVID Vaccines- elasomeran

Manufacturers	Co-Suspect Subpopulations	Case Counts
Pfizer-BioNTech COVID-19 vaccine	< 2 years	6
	2-4 years	2
	5-11 years	14
	12-17 years	59
	18-24 years	545
	25-39 years	3,404
	40-49 years	2,245
	50-64 years	2,333
	65-74 years	844
	75+ years	783
	missing	594
	Total Booster/3rd +Dose	10,829
AstraZeneca COVID-19 vaccine	<2 years	1
	2-4 years	0
	5-11 years	2

	12-17 years	0
	18-24 years	74
	25-39 years	542
	40-49 years	1,142
	50-64 years	2,024
	65-74 years	574
	75+ years	245
	missing	474
	Total Booster/3rd +Dose	5,078
Janssen COVID-19 vaccine	<2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	0
	18-24 years	15
	25-39 years	53
	40-49 years	46
	50-64 years	98
	65-74 years	37
	75+ years	25
	Missing	17
	Total Booster/3rd +Dose	291
Other COVID-19 vaccine	< 2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	1
	18-24 years	38
	25-39 years	345
	40-49 years	239
	50-64 years	336
	65-74 years	223
	75+ years	174
	Missing	56
	Total Booster/3rd +Dose	1,412

Heterologous Interchange Vaccine Schedule with Booster Dose elasomeran/imelasomeran - Review Period (19 Jun 2022 to 17 Dec 2022)

During the review period, there were 88 cases (295 events) reported with 43 serious cases. There was 1 case with a fatal outcome. In this case ([redacted]) involving concomitant administration of influenza vaccine, alternative etiology is suspected of the reported events of myocardial infarction and acute kidney injury, given the patients advanced age (89-year-old female patient), multiple underlying relevant comorbidities (including hypertension, breast cancer, osteoporosis; pernicious anaemia) and polypharmacy which provide a more likely explanation for the reported events potentially leading to a fatal outcome.

The majority of reported cases were by regulatory authorities (68; 77.3%); originated from the UK (61; 69.3%) followed by the Asia (13, 14.8%) (Table 16.57). A high proportion of reported cases were in females (51; 58.0%) than males (34, 38.6%) and (3, 3.4%) were reported with unknown age. The most frequent age group for reported cases in the 65-74 years (24; 27.3%). The median age of reported cases was 67 years. There were only 1 (1.1%) reported cases in the pediatric age group (less than 12 years) and no reports for adolescent subpopulations (12-17 years) (Table 16.56). Of the 295 events, 46 events (15.6%) Not recovered, 143 events (48.5%) had resolved, while 39 events (13.2%) had resolving. There were 61 (20.7%) events with unknown/missing outcome (Table 16.59).

Table 16.56 Age and Gender Distribution "Interchange of Vaccine Product" Cases (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Age Group	Review Period							
	Female		Male		Unknown		Total	
	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases
< 2 years	1	1.1	0	0.0	0	0.0	1	1.1
2-4 years	0	0.0	0	0.0	0	0.0	0	0.0
5-11 years	0	0.0	0	0.0	0	0.0	0	0.0
12-17 years	0	0.0	0	0.0	0	0.0	0	0.0
18-24 years	0	0.0	0	0.0	0	0.0	0	0.0
25-39 years	7	8.0	2	2.3	0	0.0	9	10.2
40-49 years	4	4.6	4	4.6	0	0.0	8	9.1
50-64 years	12	13.6	2	2.3	0	0.0	14	15.9
65-74 years	13	14.8	10	11.4	1	1.1	24	27.3
75+ years	9	10.2	14	15.9	0	0.0	23	26.1
missing	5	5.7	2	2.3	2	2.3	9	10.2
Grand Total	**51**	**58.0**	**34**	**38.6**	**3**	**3.4**	**88**	**100.0**

Table 16.57 Distribution of Interchange Vaccine Product Cases Reported by Region (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Region	Review period cases	% Total Cases
United Kingdom	61	69.3
Asia	13	14.8
Canada	7	8.0
European Economic Area	7	8.0
Grand Total	**88**	**100**

In the reporting period, the most frequently reported preferred terms (PT) for interchange vaccines were fatigue (21, 7.1%), headache (17, 5.8%) and limb discomfort (16, 5.4%). These are all consistent with reactogenicity reactions seen in the general population; Limb discomfort is usually associated with the vaccinated arm and may represent vaccination site pain. The top PTs (>2%) reported for "Interchange of Vaccines Products" are presented in Table 16.58.

Table 16.58 Top PTs (>2%) event counts and percentages for the Interchange of Vaccines by Events (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

PT	Event Counts	% Events
Fatigue	21	7.1
Headache	17	5.8
Limb discomfort	16	5.4
COVID-19 immunisation	11	3.7
Interchange of vaccine products	11	3.7
Arthralgia	9	3.1
Pain in extremity	9	3.1
Malaise	7	2.4
Myalgia	7	2.4
Nausea	7	2.4
Pyrexia	7	2.4

In the review period, while a high proportion of reported events for "Interchange of Vaccines" were Dose 4 (89; 30.2%), more than half (155; 52.5%) of the reported events had missing dose numbers. Of the 295 reported events, 143 (48.5%) were resolved and 46 (15.6%) were not resolved at the time of the report (Table 16.59). Some of the underlying medical conditions that were noted included rheumatoid arthritis, hypertension etc., Refer to Appendix 11.8 [of the PSUR].

Table 16.59 Number and Percentage of Events Reported after Interchange of Vaccines (Heterologous Vaccination) by Dose Number and Outcome (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

	Review Period	
	Events	
	N	%
Total	295	100
Dose number prior to onset		
Dose 1	0	0.0
Dose 2	1	0.3
Dose 3	12	4.1
Dose 4	89	30.2
Dose 5	38	12.9
Dose 6	0	0.0
Dose 7	0	0.0
Unknown	155	52.5
Outcome		
Fatal	2	0.7
Not Recovered/Not Resolved	46	15.6
Recovered/Resolved	143	48.5
Recovered/Resolved with Sequelae	4	1.4
Recovering/Resolving	39	13.2
Unknown	61	20.7

Overview of Heterologous Vaccines Serious Cases by Manufacturer Elasomeran/imelasomeran

Of the 88 cases heterologous vaccines reported in the review period, 43 cases (48.9%; 162 events) were assessed as serious and 1 (2.3%) reported serious cases had fatal outcome. Among the serious cases reported, the highest number of cases were from Others (20, 46.5%), Pfizer-BioNTech (17; 39.5%), Astrazeneca (6; 14.0%). There was a female preponderance during the review period reported in serious cases (25; 58.1%) than males (16, 37.2) while 2 (4.7%) reported cases were missing gender data values with most cases reported in the 75+ years age group (14; 32.6%). Of the 162 serious events reporting during the review period, 73 events (45.1%) were resolved and 28 (17.3%) had unreported outcome. Most events were seen after dose 4 for the interchange of vaccine products (62; 38.3%) (Table 16.61). Almost half of the events had an unreported dose number (72, 44.4%).

Age distribution among serious interchange vaccine products is presented in Table 16.60; details by MAH further are described in their respective sections below under fatalities by interchange vaccine products (MAH).

Table 16.60 Age Distribution of Serious Cases by Manufacturers (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Age	Pfizer-BioNTech		AstraZeneca		Other	
	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases
< 2 years	0	0.0	0	0.0	1	0.0
2-4 years	0	0.0	0	0.0	0	0.0
5-11 years	0	0.0	0	0.0	0	0.0
12-17 years	0	0.0	0	0.0	0	0.0
18-24 years	0	0.0	0	0.0	0	0.0
25-39 years	1	5.9	0	0.0	1	5.0
40-49 years	2	11.8	1	16.7	1	5.0
50-64 years	3	17.7	2	33.3	4	20.0
65-74 years	5	29.4	2	33.3	4	20.0
75+ years	5	29.4	1	16.7	8	40.0
Missing	1	5.9	0	0.0	1	5.0
Total	**17**	**100.0**	**6**	**100.0**	**20**	**100.0**

Serious events by dose and outcome are presented in Table 16.61. The outcome for serious events that resolved were 73 events (45.1%), and that were not resolved were (27; 16.7%). There were 1 (1.2%) reported cases with fatal outcomes in the review period. An overview of the fatalities is described below.

Table 16.61 Serious Events Overview by Dose Number and Outcome for Interchange Vaccine Products (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

	Review Period	
	Events	
	N	%
Total	162	100
Dose number prior to onset		
Dose 1	0	0.0
Dose 2	1	0.6
Dose 3	2	1.2
Dose 4	62	38.3
Dose 5	25	15.4

Dose 6	0	0.0
Dose 7	0	0.0
Unknown	72	44.4
Outcome		
Fatal	2	1.2
Not Recovered/Not Resolved	27	16.7
Recovered/Resolved	73	45.1
Recovered/Resolved with Sequelae	4	2.5
Recovering/Resolving	28	17.3
Unknown	28	17.3

Among the serious cases, the most frequently reported serious PT (>2%) in the group of Interchange of vaccine products were fatigue (12, 7.4%), headache (7,4.3%), myalgia (6, 3.7%) and arthralgia (5, 3.1%). Most of the events reflect common and well-described reactogenicity of ModernaTx, Inc. elasomeran/imelasomeran and other COVID-19 vaccines. The percentage of all events of fatigue, headache, pyrexia, myalgia, and arthralgia were comparable or lower than the respective percentage of these events in the general population with elasomeran/imelasomeran. Table 16.62 presents the top serious PTs by events and their percentages for the reporting period.

Table 16.62 Top Serious PTs (>2%) by Number of Events and Percentages for Heterologous Interchange During the Review Period (19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

PT	Event Counts	% Events
Fatigue	12	7.4
Headache	7	4.3
Myalgia	6	3.7
Arthralgia	5	3.1
COVID-19	5	3.1
Dizziness	5	3.1
Nausea	5	3.1
Chest Pain	4	2.5
Dyspnea	4	2.5
Malaise	4	2.5

Table 16.63 Overview of Co-Suspect Manufacturers of COVID Vaccines by Dose Number and Serious Cases (Review Period 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Heterologous Co-Suspect	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Unknown	# of Serious Cases
Pfizer-BioNTech	0	0	3	20	5	0	0	35	17
AstraZeneca COVID-19 vaccine	0	0	1	5	0	0	0	6	6
Janssen COVID-19 vaccine	0	0	0	0	0	0	0	1	0
Other Manufacturers	0	1	1	8	9	0	0	14	20

Note: There is currently insufficient data to stratify by vaccine type and corresponding PT and there can be overlap of cases between the manufacturers.

During this review period, a total of 1 case (discussed above) of vaccine interchange with fatal outcomes were reported, However, the outcomes are independent of doses distributed. Table 16.64 presents interchange fatalities by manufacturer.

Table 16.64 Frequency and Number of Reported Fatal Cases by Manufacturers of COVID Vaccines (Reporting Period 19 June 2022 to 17 Dec 2022) elasomeran/imelasomeran

Manufacturer/Co-Suspect	Total Cases	Fatal Cases	Fatal %
Pfizer-BioNTech	47	0	0.0
AstraZeneca	11	0	0.0
Janssen	1	0	0.0
Other	29	1	3.4

Note: There is overlapping of cases between different manufacturers

During the reporting period, a review of cases including events reported with co-suspect manufacturers' of COVID vaccines is presented below. The demographics of administration of each vaccine product described below (Table 16.65). The highest events were seen in age groups 65-74 for Pfizer-BioNTech and Astrazeneca; 75+ for other vaccines. This may be explained by the demographics of administration of each vaccine product. The highest reports after dose 3+/booster were reported with Pfizer-BioNTech (28) followed by Janssen (23).

Table 16.65 Cases Distribution by Age by Manufacturers of COVID Vaccines (Reporting Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Manufacturers	Co-Suspect Subpopulations	Subpopulation Case Counts
Pfizer-BioNTech COVID-19 vaccine	< 2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	0

Manufacturers	Co-Suspect Subpopulations	Subpopulation Case Counts
	18-24 years	0
	25-39 years	7
	40-49 years	6
	50-64 years	3
	65-74 years	8
	75+ years	4
	missing	0
	Total Cases	28
Janssen COVID-19 vaccine	< 2 years	1
	2-4 years	0
	5-11 years	0
	12-17 years	0
	18-24 years	0
	25-39 years	5
	40-49 years	6
	50-64 years	2
	65-74 years	6
	75+ years	3
	missing	0
	Total Cases	23
AstraZeneca COVID-19 vaccine	< 2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	0
	18-24 years	0
	25-39 years	0
	40-49 years	1
	50-64 years	2
	65-74 years	3
	75+ years	0
	missing	0
	Total Cases	6
Other COVID-19 vaccine	<2 years	1
	2-4 years	0

Manufacturers	Co-Suspect Subpopulations	Subpopulation Case Counts
	5-11 years	0
	12-17 years	0
	18-24 years	0
	25-39 years	1
	40-49 years	1
	50-64 years	4
	65-74 years	3
	75+ years	7
	missing	0
	Total Cases	17

Note: There is overlap of cases between the age groups

Heterologous Interchange Vaccine Schedule with Booster Dose elasomeran/davesomeran - Review Period (19 Jun 2022 to 17 Dec 2022)

During the review period, there were 8 cases (18 events). All the reported cases were spontaneous of which 17 originated from the United States. The case distribution was higher in males (4, 50.0%) than in females (3, 37.5%). The median age of reported cases was 55.5 years. There were no cases in adolescents and pediatric patients. Of the 8 cases, 6 cases were almost evenly distributed amongst the adult age groups and for 2 case the patient age was unknown. Of the 18 events, 7 events (38.9%) were Not recovered. There were 11 (61.1%) events with unknown/missing outcome. There are no cases with fatal outcome. The reported PTs with the use of elasomeran/davesomeran contained isolated reports of each event only and no specific safety patterns were seen.

Discussion

The landscape of heterologous/interchange vaccine increasingly is becoming complex over time, with increasing number of booster doses administered. Overall, case reports after heterologous "Mix and Match" booster with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccine have increased globally, due to the massive scale up of COVID-19 vaccination and advocacy for boosting. Based on the currently available safety data, the AE profile reported after booster dose in vaccine interchange has been generally similar to that seen in the general population and noted to be of similar reactogenicity events compared with the safety profile established in the primary series of elasomeran.

Notably, there has been an increasing trend in the use of interchange of vaccine products (Mix &Match and booster) for the global COVID-19 mass vaccination campaign, especially for the booster or more than 2 doses. Hence, a significant proportion of reported events were noted after dose 3+. However, the most frequently reported AEs raised no notable safety concerns and did not show any specific new patterns.

The analysis of the review period safety data reported for heterologous vaccines interchange did not find any new safety issue and showed that the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran is not different when used with other heterologous vaccines.

Conclusion

The data provided in this PBRER sufficiently describes the review period safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when used with other heterologous vaccines.

Based on the analysis of the review period safety data available as of 17 Dec 2022 for heterologous interchange of COVID-19 vaccines, including primary series vaccination as well as boosting, the MAH considers that heterologous priming schedule/Mix & Match and boosting-related events do not presently constitute a safety issue of concern.

The benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when used with other heterologous vaccines remains favorable. The MAH will continue to evaluate heterologous priming schedule/Mix & Match and boosting-related events using routine surveillance.

Rapporteur assessment comment:

The MAH proposed removal of the missing information 'interaction with other vaccines' from the EU-RMP, which is endorsed (see section 3.1.4.1.4. . Furthermore, the MAH proposed to continue monitoring interaction with other vaccines through routine surveillance. The PRAC Rapporteur wants to specify that, based on the cumulative evidence, the knowledge gaps regarding this area of missing information have been filled and interaction with other vaccines has not been shown to constitute an important risk. Therefore, it is no longer considered important in the context of the RMP **and** the PSUR. I.e. it should be removed from the PSUR list of safety concerns and an evaluation of new information on this topic in future PSURs is not expected.

No new significant safety information has been identified.

2.3.3.6. Use in frail subjects with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders

Source of the New Information

New information presented below includes analysis performed on cases received into GSDB by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022. ModernaTx, Inc. queried the GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran.

Background Relevant to the Evaluation

Frail patients are considered at higher risk of complications due to coronCOVID-19 infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. Since frail subjects with unstable health conditions and comorbidities were excluded from the registration trials, ModernaTx, Inc. is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Frailty refers to a state of vulnerability to stressors characterized by a decreased physiological reserve, resulting in poor health outcomes compared to individuals of the same chronological age [119].

There is growing evidence supporting the safety profile of the COVID-19 vaccine in immunocompromised patients, such as HIV-infected patients, diabetics, and patients with cardiopulmonary diseases, is similar to that in the general population. Presently, the US Centers for Disease Control and Prevention, British Society for Immunology, and various other governmental and professional societies and organizations endorse COVID-19 vaccination in the immunocompromised population. Overall, recommendations for use in patients with immunocompromising medical conditions and immunosuppressing medications on the efficacy of the vaccine may support the extrapolation into the frail subpopulation indicating potential benefits to outweigh theoretical risks. The frail population was the first subpopulation group vaccinated with elasomeran and other COVID-19 vaccines given that this population was recognized to have the

potential for more severe complications due to COVID-19 infection. This same recommendation is still in place for vaccination against SARS-CoV2 and its variants.

Lupo-Staghellini et al [120] in a prospective, multicenter, national VAX4FRAIL study (NCT04848493) which evaluated vaccines in a large trans-disease cohort of patients with solid or hematological malignancies, and/or neurological, and/or rheumatological diseases demonstrated that frail patients who are candidates for mRNA COVID-19 vaccination should be reassured about the safety profile of vaccine strategy. They noted that AEs were in line with the reporting from the healthy cohort of subjects and national observatories, no evidence of worsening of the underlying disease was reported, and no concern on the adherence to the treatment program of the disease itself emerged from the prospective multicenter national study [120].

Connolly et al [121] is an observational cohort study examining approximately 325 frail patients with rheumatic and musculoskeletal diseases and taking immunomodulatory therapy; 51% received BNT-162b2 and 49% were vaccinated with elasomeran. The most common diagnoses were inflammatory arthritis (38%), systemic lupus erythematous (28%) and overlap connective tissue disease (19%). Observed AEs were mild local and systemic reactions consistent with expected vaccine reactogenicity and occurred at a similar frequency as in the non-frail population [121].

Cavanna et al [122] is an observational study of 257 frail participants with solid tumor malignancies who received two doses of either elasomeran or BNT-162b2; 85.21% of subjects were taking active anti-cancer therapy. Mild local or systemic reactions consistent with symptoms of reactogenicity such as weakness, headache, fever, and muscle pain were reported by 33.46% of patients, with more severe AEs after the second dose, in line with AE reports in the healthy population [122].

Thus far, there have been no specific safety concerns identified for use of elasomeran in frail subjects with unstable health conditions and comorbidities. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals after vaccination with elasomeranor elasomeran/imelasomeran or elasomeran/davesomeran and they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran.

As of the DLP of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in frail individuals. Serious events and fatalities reported after vaccination are heavily confounded or may have been caused by underlying medical conditions. Otherwise, the general pattern of commonly reported AEs in those considered frail individuals or with unstable health conditions and comorbidities is comparable to the general population.

Based on all the information provided, the MAH is requesting to discontinue presenting analysis of events in frail subjects with unstable health conditions and comorbidities in each PSUR and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in frail subjects with unstable health conditions and comorbidities as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in frail subjects with unstable health conditions and comorbidities through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/ imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for reports of frail individuals using "Frail" custom search as defined in the ModernaTx, Inc. PSSF (see Appendix 11.29 [of the PSUR]), which included subjects of all ages with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders).

Literature Review

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeranand the frail subpopulation to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d [of the PSUR].

A total of 60 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran in the frail subpopulation.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on Frail cases please refer to Appendix 11.10 [of the PSUR].

Overview of Cases

Cumulatively, as of 17 Dec 2022, a total of 54,153 cases (246,375 events) were reported in frail subjects, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these, 37,792 cases (69.8%) were medically confirmed, 19,708 (36.4%) were serious, and 2,457 cases (4.5%) had a fatal outcome. The median age of frail subjects was 61.0 years (range: less than 1 year – 121.0 years); 1,161 reports were missing age information. There was a higher proportion of cases reported in females (36,452; 67.3%) compared to males (17,330; 32.0%) and 371(0.7%) were missing gender descriptor. The majority of cases were reported by regulatory authorities (83.0%) in the United States (70.9%), followed by France (6.6%), the UK (4.5%), and Germany (2.4%).

During the reporting period, there was approximately a 19% decrease in the number of reported cases in the frail subpopulation, compared to the prior period. There was a total of 5,078 cases (21,917 events) reported, representing 6.3% of the 80,461 cases reported in all populations in this reporting period. Of these 5,078 cases, 1,382 (27.2%) were medically confirmed, 1,671 cases (32.9%) were serious, and 103 cases (2.0%) had a fatal outcome. There were disproportionately more cases reported in females (3,304; 65.1%) compared to males (1,722; 33.9%), and gender was unknown in 52 cases (1.0%). The median age was 55.0 years, ranging from 0.2 years to 99.0 years.

Most cases in this reporting interval were reported by regulatory authorities (81.1%), with the highest contributors from Sweden (25.7%), Germany (22.4%), and the United States (11.6%).

Of the 5,078 frail cases in this interval period, 1,533 cases (30.2%) were in the elderly age group 65 years and older. See Table 16.66 below for age distribution.

Table 16.66 Age Distribution of Reports in the Frail Subpopulation this Reporting Period

Age Group	Review Period	
	# Cases	% of Total Cases
<2	3	0.0
02-05	2	0.0
06-11	5	0.1
12-15	24	0.5
16-17	22	0.4
18-24	135	2.7
25-39	874	17.2
40-49	836	16.5

50-64	1,452	28.6
65-74	867	17.1
75+	666	13.1
Missing	192	3.8
Grand total	**5,078**	**100.0**

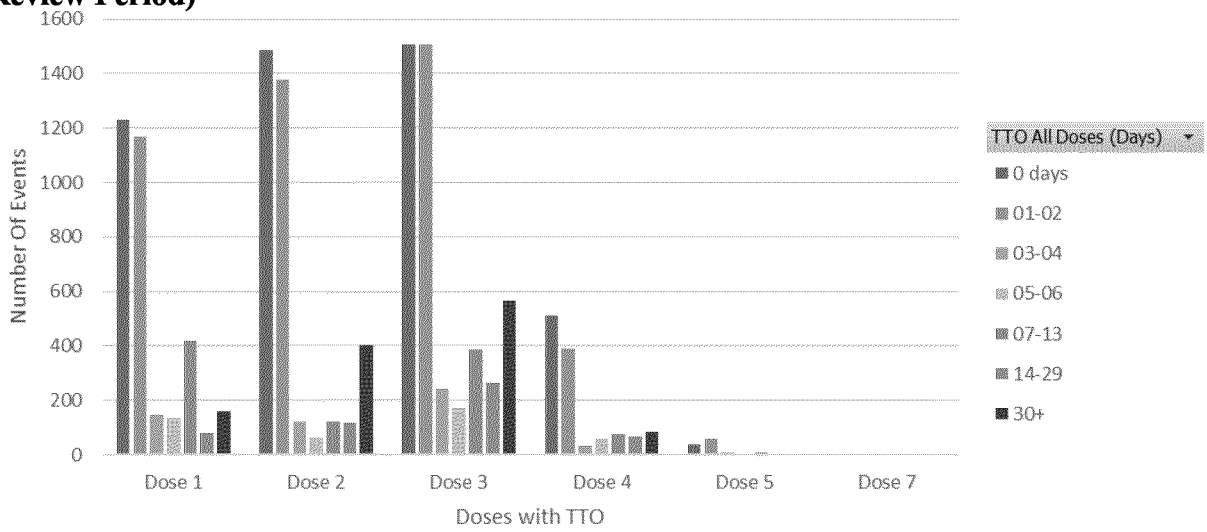
The most frequently reported events in frail subjects by PT were in line with those seen in the general population and in line with expected reactogenicity with elasomeran. The most frequently reported PTs are listed below (Table 16.67).

Table 16.67 Most Frequently Reported Events by Preferred Term in Frail Subjects >=2% (Review Period)

PT	# Events	% of Total Events
Fatigue	1,161	5.3
Pyrexia	1,061	4.8
Headache	1,004	4.6
Myalgia	754	3.4
Chills	696	3.2
Malaise	593	2.7
Vaccination site pain	562	2.6
Arthralgia	547	2.5
Nausea	530	2.4
Dizziness	528	2.4

During this review period, dose number was not reported for 40.6% of events. When reported, events were most frequently reported after dose 3 (4,643; 21.2%), followed by dose 2 (3,688; 16.8%). When TTO was known, clusters of events were frequently reported in the first two days (9,273; 42.3%) regardless of the dose number (Figure 16-9).

Figure 16-9 Number of Events by Dose Number Time to Onset in the Frail Subpopulation (Review Period)



Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard.

Outcomes

During the review period, 103 cases (2.0%) were reported with fatal outcome. When event outcomes were reported, 26.0 % (5692) of events had resolved, 16.0% (3511) events were resolving, and 32.4% (7104) events had not resolved. The outcome of 21.3% (4664) events was unknown as at the time of report. The category "Not recovered/Not resolved" is an overestimate as it reflects information submitted at the time of the report (generally without additional follow-up). Fatal cases are reviewed below.

Serious Cases in the Frail Subpopulation (Review Period)

There were 1,671 serious cases (7,438 events) in the frail subpopulation in this reporting period, of which 716 (42.9%) were medically confirmed. Serious cases in the frail subpopulation were most frequently reported in the elderly age 65 and over (39.1%), followed by in the 50 to 64-year-old age group (28.8%).

The age distribution of frail subpopulation in serious cases are presented below in Table 16.68.

Table 16.68 Age Distribution of Serious cases in the Frail Subpopulation in the Review Period

Age Group	Review Period	
	# Cases	% of Total Cases
<2	1	0.1
2-5	1	0.1
6-11	0	0
12-15	6	0.4
16-17	8	0.5
18-24	36	2.2
25-39	189	11.3
40-49	209	12.5
50-64	482	28.8
65-74	320	19.2
75+	333	19.9
Missing	86	5.1
Grand total	**1,671**	**100.0**

Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard.

Events in serious cases were missing dose or TTO information in 50.5% of instances. When known, most events were reported following the third dose (20.6%) followed by the second dose (11.9%), the first dose (7.9%) and the fourth dose (7.7%). The most frequently reported events terms in serious cases in the frail subpopulation were fatigue (3.7%), Headache (2.9%), Pyrexia (2.7%), and Dizziness and Dyspnoea (2.3% each). There were 113 events of arrhythmia (1.5% of all serious events), and 111 cases of chest pain (1.5%).

The 113 events of arrhythmia were reported in 101 cases, including one case with fatal outcome.

Gender distribution showed 65.3% of cases reported in females compared to 34.7% cases in males. The median age was 56.0 years (ranging from 27.0 years to 87.0 years). Most events of arrhythmia were reported following dose 3 (51 events), with 20 of these events occurring within 3 days of vaccination and 12 events occurring 30 or more days later. Most cases were confounded by underlying cardiovascular conditions, or respiratory disorders, type 2 diabetes, autoimmune diseases, or concomitant medications, or did not contain information regarding dose or TTO. No trends were seen with reported incidence of arrhythmia and age, dose number, or time of occurrence after vaccination.

The one case ([redacted]) with fatal outcome for arrhythmia was a report from a health authority of an 87-year-old female patient who experienced arrhythmia, bradycardia, and atrioventricular block complete after vaccination with elasomeran (TTO not known). She was previously vaccinated with tozinameran for her previous dose. The patient died within 7 days of vaccination; reported cause of death was bradycardia and cardiac arrest. No further information with regards to other medical history, concomitant medications or clinical course was provided. Case was confounded by underlying type 2 diabetes and advanced age.

Chest pain was reported in 111 events in 106 cases, including two cases with fatal outcome. Gender distribution showed slightly more cases in males (52.8%) than females (46.2%). The median age was 43.0 years (range from 13.0 years to 94.0 years). Most events of chest pain were reported following dose 3 (22 events) and dose 2 (17 events). Most events were reported within 5 days of vaccination. Cases were confounded by concomitant medications or underlying medical conditions also associated with chest pain, including cardiac disorders such as pericarditis, acute coronary syndrome, and myopathy, respiratory disorders such as asthma and COPD, chest injury, and upper gastrointestinal conditions such as gastrooesophageal reflux disease. No trends were noted among these reported cases with TTO, age, or dose number.

There were two cases with fatal outcomes reporting chest pain. One case ([redacted]) was a 53-year-old male patient with a history of myocardial infarction who experienced acute myocardial infarction, chest pain, and malaise an unknown time after a booster dose of elasomeran (as dose 3). The patient died 3 months and 17 days following vaccination. The second case ([redacted]) was reported in a 94-year-old female patient who experienced cough, pleural effusion, and chest pain 10 days after vaccination with her first dose of elasomeran. The patient died in the hospital two days later; no information was provided on course of treatment, autopsy results or cause of death. The event chest pain was confounded by the patient's advanced age and underlying hiatal hernia.

On reviewing the events outcome for serious cases in the frail subpopulation, 19.2% had resolved, 14.8% were resolving, while 34.7% had not resolved as at the time of report. Event outcome was unknown for 23.0% of events. The reported outcome "not recovered" is an overestimate as it reflects information submitted at the time of the report (generally without additional follow-up).

Fatal Cases in the Frail Subpopulation: Review Period

There were 103 cases with fatal outcome (266 events) in the frail subpopulation in this reporting period, of which 80 cases were medically confirmed, and 68.0% were in the elderly population 65 years of age or older. The median age in fatal cases was 75.5 years (range: 23.0 years - 99.0 years). Fatal cases were reported slightly higher (58.3%) in male than in females (41.7%). A high proportion of the fatal cases was reported by regulatory authorities (73.8%) in Japan (19.4%), the UK and France (11.7% each), and Germany (10.7%). The most frequently reported event terms in the fatal cases in the frail subpopulation were death (6.8%), cardiac arrest (3.8%), and COVID-19 (2.6%). Exceptionally, myocarditis was reported at a higher frequency in frail subpopulation (2.3%) compared to the general population (0.2%). Medical review of these cases of myocarditis revealed strong confounders/multiple risk factors and comorbidities, including COVID-19 infection, inflammatory diseases, and cardiovascular diseases.

Frail patients also have comorbidities or unstable health conditions which are subject to worsening and can lead to fatal outcomes. The most frequently reported concurrent diseases and concomitant medications cumulatively are presented Table 16.69 and Table 16.70. The most commonly reported concomitant medications are those that would be expected to be taken by those having the common comorbidities of cardiovascular disease and DM.

Table 16.69 Most Frequently Reported Comorbidities (Cumulative period)

Medical History	Cases	% Cases
Asthma	17,470	32
Drug hypersensitivity	15,557	28.5
Hypertension	13,911	25.5
Diabetes mellitus	10,819	19.8
Type 2 diabetes mellitus	5,274	9.7
Food allergy	4,335	7.9
Chronic obstructive pulmonary disease	4,188	7.7
Atrial fibrillation	4,011	7.3
Seasonal allergy	3,206	5.9
Hypothyroidism	3,082	5.6
Hypersensitivity	3,009	5.5
Gastrooesophageal reflux disease	2,913	5.3
Hyperlipidaemia	2,868	5.3
Obesity	2,411	4.4
Depression	2,291	4.2
Coronary artery disease	2,214	4.1
COVID-19	2,151	3.9
Anxiety	1,786	3.3
Multiple sclerosis	1,527	2.8
Chronic kidney disease	1,496	2.7
Arthritis	1,485	2.7
Osteoarthritis	1,465	2.7
Migraine	1,340	2.5
Rubber sensitivity	1,340	2.5

Note: Frequently reported 2.5% &above comorbidities

Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard

Table 16.70 Most Frequent Reported Concomitant medications (Cumulative period)

Concomitant Medication	Cases	Percent
ATORVASTATIN	5,882	4.4
LEVOTHYROXINE	4,554	3.4
LISINOPRIL	4,442	3.3
AMLODIPINE	3,853	2.9
METOPROLOL	3,549	2.6
CALCIUM	3,390	2.5

LOSARTAN	3,386	2.5
VITAMIN D3	3,167	2.3
METFORMIN	3,093	2.3
OMEPRAZOLE	3,065	2.3
SIMVASTATIN	2,525	1.9
MULTIVITAMIN [VITAMINS NOS]	2,375	1.8
SYNTHROID	2,297	1.7

Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard.

Subpopulation Analyzes: Review Period

Frail Subpopulation Children 0-5 years

During the reporting period, there were 5 cases (12 events) in the frail subpopulation in the age group 0-5 years, of which 2 cases were medically confirmed and serious, with no fatal outcomes. A slightly higher proportion 3 (60%) was reported spontaneous and 2 (40%) cases were reported by regulatory authorities. There were 3 cases reported from the United States and 1 each from Argentina and Sweden. Five events were reported following dose 1, two events after dose 2, and dose number was unknown for five events.

Two cases do not refer to children who received elasomeran but rather maternal exposure: one case ([redacted]) described a 2-month-old baby with a non-serious case of exposure via breast milk with reported diarrhea the same day as mother was vaccinated, which resolved after 3 days. The second case ([redacted]) was serious and described a congenital defect in a full-term infant, born one year and five months after mother's last dose. Mother was not pregnant at the time of the last dose of elasomeran. The other serious case ([redacted]) reported febrile convulsion in a four-year-old male child one day after his second dose. Patient symptoms were consistent with complex febrile seizures with lowered seizure threshold secondary to fever following COVID vaccination. Patient was admitted but no outcome information was available.

Frail Subpopulation Children 6-11 years

During the reporting period, in the age group 6-11 years of the frail subpopulation, there were five cases reported, of which all were medically confirmed, (16 events), none of the cases were serious or had a fatal outcome. Reported cases were predominantly in males (4; 80%); Three (60%) of these cases were reported by regulatory authorities in Argentina, and the other two cases were reported spontaneously in the United States. Four cases reported medication errors (administered to wrong age, accidental overdose, or expired vaccine given), one in which the child experienced pyrexia and diarrhea the same day as vaccination with little other information ([redacted]), one in which the concurrent non-serious events included feeling abnormal, illness, neck pain, and respiration abnormal, with no reported TTO, and a temporal relationship could not be determined ([redacted]), and two with no associated clinical AEs ([redacted]; [redacted]). The fifth case reported non-serious symptoms consistent with reactogenicity one day post-vaccination ([redacted]).

Frail Subpopulation Adolescents 12-17 years

During the reporting interval, there were 46 cases (164 events) in frail adolescents 12 – 17 years of age, of which 38 were medically confirmed, 14 were serious, and none had a fatal outcome. Similar to the 6 to 11-year-old frail age group, a large proportion of cases (56.5%) were reported from Argentina. Reported cases were similarly distributed among males and females (45.7% and 52.2% respectively). The most frequently reported medical history in these frail adolescents was asthma, reported in 34 of the 46 cases. The most frequently reported preferred terms (PTs) in frail adolescents 12 to17 years were mostly in line

with expected reactogenicity for elasomeran (pyrexia, fatigue, headache etc), and similar to those seen in the general population, and in the entire frail subpopulation. Myo/pericarditis was the exception and was reported in eight of the 14 serious cases in frail adolescents (five male and three female). See Section 16.3.1.2 [of the PSUR].

Five of the six remaining serious cases were confounded by medical history/concomitant medications, describes events consistent with known reactogenicity with vaccines including elasomeran, or lack information on clinical course of treatment, outcome, or TTO.

The remaining case ([redacted]) describes a 17-year-old female patient with medical history of asthma and polycystic ovarian syndrome, no reported concomitant medications, who reportedly experienced pain, haematoma, and thrombocytopenia four days after her second dose of elasomeran. Patient was brought to the hospital after reported metrorrhagia, punctiform skin lesions in the neck and trunk, and spontaneous epistaxis. Platelet count was reported to be 50,000 (low). Patient was hospitalized and no information about ongoing clinical course of treatment or outcome of events was provided. According to the WHO-UMC causality assessment, this case is assessed as possible, based on temporal association, abnormal laboratory test, with reasonable time relationship to the product. However, information on concomitant medication is lacking.

Frail Patients After Dose 3 and above of elasomeran

During this reporting period, there was a 14% reduction in the number of cases reported after dose 3 and above, compared with the prior period. There were 1,664 cases (5,984 events, 419 (25.2%) medically confirmed), reported after dose 3 elasomeran, of which 611 cases (36.7%) were serious, and 41 cases (2.5%) had fatal outcome. Most events were reported after dose 3 (4,643; 77.6%) and dose 4 (1,217; 20.3%). Events after dose 3 and above in the frail subpopulation were most frequently reported with a TTO of less than 3 days.

The most frequently reported PTs after dose three and above in the frail subpopulation (Table 16.71) were in line with expected reactogenicity with elasomeran and similar to those reported in the immediate period after dose 1 and 2. About 24% of reported events had resolved as at the time of reporting.

Table 16.71 Most Frequently Reported Preferred Terms after Dose 3 and above of elasomeran in the Frail Subpopulation (Review Period)

PT	# Events	% of Total Events
Fatigue	350	5.8%
Pyrexia	312	5.2%
Headache	300	5.0%
Myalgia	245	4.1%
Dizziness	205	3.4%
Chills	199	3.3%
Malaise	164	2.7%
Arthralgia	151	2.5%
Nausea	142	2.4%
Dyspnoea	130	2.2%

Source: ModernaTx, Inc. GSDB - PBRER Spotfire Dashboard.

Serious Cases After Dose 3 and above

During the review period, 611 serious cases (1507 serious events, 216 [35.4%] medically confirmed cases and 41 cases [6.7%] with fatal outcome) were reported in receipts of elasomeran dose 3 and above. A high proportion of these serious cases were reported by regulatory authorities (82.2%), mostly in Germany (31.8%), the UK (24.1%) and Japan (10.3%). There were more serious cases reported in females (55.3%), compared to males (43.5%). The median age was 63.0 years (range: 19.0 years to 99.0 years). Most serious cases were reported in elderly patients 65 years and older (275 cases; 45.0%), followed by age group 50-64 years (196 cases; 32.1%). Of the 1,507 serious events reported, a high proportion (60.1%) were after dose 3, and 32.7% after dose 4. Most events in serious cases with dose 3 and above were reported to have occurred less than 3 days post-vaccination.

Events outcomes in serious cases in the frail subpopulation were most frequently reported as "not recovered (40.1%) while 18.2% had recovered as at the time of reporting. The most frequent events reported in serious cases after dose 3 or above are more of reactogenicity that is known to be associated with elasomeran and other vaccines and are presented below (Table 16.72).

Table 16.72 Most Frequently Reported Preferred Terms (PT) in Serious Cases after Dose 3 and above elasomeran in the Frail Subpopulation (Reporting Period)

PT	# Events	% of Total Events
Fatigue	92	4.2%
Dizziness	88	4.0%
Headache	78	3.5%
Pyrexia	77	3.5%
Arrhythmia	52	2.3%
Dyspnoea	47	2.1%
Myalgia	45	2.0%
Nausea	44	2.0%
Malaise	44	2.0%

Fatal cases after booster (dose 3 or above) of elasomeran

There were 41 fatal cases (84 serious events) reported after dose 3 or above of elasomeran, of which 35 fatal cases were medically confirmed. There were more cases reported among males (68.3%) compared to females (31.7%), and most of the cases (31; 75.6%) occurred in elderly 65 years and older. The median age of reported fatal cases after dose 3 and above was 77.5 years (range: 23.0 years – 99.0 years). The most frequently reported events in these fatal cases were death (8 events; 9.5%), cardiac arrest (4; 4.8%), cardiorespiratory arrest, respiratory arrest, pyrexia, and sudden death (3 events; 3.6% each). The same number of events in these fatal cases occurred after dose 3 and dose 4 (41 events each), with two cases reported with dose 5. Fatal cases after dose 3 and above were strongly confounded by comorbidities (including DM, neoplasms/cancers, cardiovascular diseases, and COPD), and concomitant medications, such as anti-cancer therapies.

Overview of Cases in the Frail Subpopulation After Receiving Booster Dose with elasomeran/imelasomeran

During this reporting period, 305 cases (1,128 events, of which 396 were serious) were reported in the frail subpopulation with elasomern/imelasomeran, of which 166 cases (54.4%) were assessed as serious, 75 (24.6%) cases were medically confirmed, and 10 cases (3.3%) reported fatal outcomes. Cases were disproportionately reported in females compared to males (57.7% vs 40.3%, respectively) and were most

frequently reported via regulatory authority (85.9%) from the UK (42.0%) and the Netherlands (39.0%). These cases reported a median age of 67.0 years (range from 0.0 to 99.0 years).

In this reporting interval, TTO was not reported for 58.1% of events. Of all 1,128 events, most were reported after the fourth and fifth dose (240 cases and 106 cases, respectively). This is expected as most patients receiving the bivalent booster have already received three or four previous doses. Most events were reported within less than 3 days post-vaccination, regardless of vaccine dose.

Case reports in the frail subpopulation represented 5.8% of all elasomern/imelasomeran cases (5,230 cases) across all populations in this reporting period, and serious cases in the frail subpopulation comprised 42.1% of all elasomeran/imelasomeran serious cases (940 cases) in all age groups during the reporting period.

The most frequently reported events in the frail subpopulation who received elasomern/imelasomeran were representative of expected reactogenicity (such as headache, fatigue, malaise, and chills) and were similar to those reported after elasomeran and in the general population.

Serious Cases After Receiving Booster Dose with elasomern/imelasomeran)

In this review period, 166 serious cases (396 serious events) were reported in frail patients receiving a booster dose with elasomern/imelasomeran. Of these 166 serious cases, 47 (28.3%) cases were medically confirmed, and ten cases (6.0%) had fatal outcomes. There were more cases reported in females (90; 54.2%) than in males (73; 44.0%), and three cases had missing gender information. These serious cases reported a median age of 69.0 years (ranging from 23.0 years to 99.0 years).

The PTs reported most frequently in serious cases after booster elasomeran dose(s) in the frail subpopulation were largely consistent with symptoms of expected reactogenicity, except for 15 events of dyspnoea, all of which reported confounding medical history of respiratory or cardiac disorders.

Among serious cases during the reporting period, events were most frequently reported after dose 4 (150 events; 37.9%), followed by dose 5 (64 events; 16.2%), and dose 3 (6 events;1.5%). Events in these serious cases occurred on average within three days of vaccination.

Overview of Fatal Cases with elasomern/imelasomeran

During the reporting interval, there were 10 cases with fatal outcomes (20 serious events) reported among frail recipients of elasomern/imelasomeran. The majority of these cases were medically confirmed (80.0%) and reported by regulatory authorities (80.0%). Most fatal cases were from Taiwan (60.0%). Of the 20 events reported in fatal cases, nine events were reported after dose 5 and six events after dose 4, with an additional 5 events not reporting dose number. Time to onset for fatal cases with elasomern/imelasomeran varied from 1 to 18 days post-vaccination; average TTO was 6.7 days (SD 6.3).

A review of the 10 fatal cases reported in the frail subpopulation found them all to be strongly confounded by medical history of respiratory disorders, such as pulmonary fibrosis and COPD, cardiovascular disorders, including atrial fibrillation, acute coronary syndrome, CAD, and hypertension, diabetes, and renal disorders. There was no safety concern observed for reported events in fatal cases after administration of elasomern/imelasomeran in the frail subpopulation.

Overview of Cases in the Frail Subpopulation After Receiving Booster Dose with elasomern/davesomeran

During this reporting period, 120 cases (531 events, of which 41 were serious) were reported in the frail subpopulation after vaccination with elasomeran/davesomeran, of which 25 (20.8%) were assessed as serious, 54 (45.0%) cases were medically confirmed, and one case (0.8%) reported a fatal outcome. Cases were disproportionately reported in females compared to males (58.3% vs 39.2%, respectively),

and a majority were reported spontaneous (99.2%), in the United States (91.7%), and fewer cases were reported in Puerto Rico (6.7%), with one case each reported in Canada and Japan. A higher proportion of cases were reported in females than males (58.3% vs 39.2% respectively). These cases reported a median age of 71.0 years, with a range from 4.0 years to 100.0 years.

In this reporting interval, most events were reported after dose 5 (130 events; 24.5%) and dose 4 (94 events; 17.7%). This is expected, as most patients receiving the bivalent booster .222 have already received three or four previous doses. Events were most frequently reported within 3 days of vaccination, regardless of dose number. Case reports in the frail subpopulation represented 5.1% of all elasomeran/davesomeran cases (2,348 cases) across all populations in this reporting period, and serious cases in frail patients comprised 21.0% of all elasomeran/davesomeran serious cases (119 cases) in all populations during the reporting period.

The most frequently reported events in the frail subpopulation who received elasomeran/davesomeran were representative of expected reactogenicity and were similar to those reported after elasomeran and in the general population. As elasomeran/davesomeran was more recently authorized, the data are limited.

Serious Cases After Receiving Booster Dose with elasomeran/davesomeran

In this review period, 25 serious cases (41 serious events) were reported in frail patients receiving a booster dose with elasomeran/davesomeran. Of these 25 serious cases, 48.0% of cases were medically confirmed, and one case reported a fatal outcome. A similar number of cases was reported in females (12 cases) and males (13 cases), though overall case counts were low. These serious cases reported a median age of 74.0 years (ranging from 42.0 years to 90.0 years).

The event terms reported most frequently in serious cases in the frail subpopulation after elasomeran/davesomeran were consistent with expected reactogenicity, except for atrial fibrillation (4 events), insomnia (3 events), and peripheral swelling (3 events) Most of these cases are confounded by reported underlying comorbidities, concomitant medications, and advanced age (average age of patients experiencing these three events was 75.5 years). There was no trend noted with dose number or temporal relationship. Medical review of the cases including events of atrial fibrillation found the events to be confounded by the patients' advanced age and underlying cardiovascular disease, including one patient with a history of atrial fibrillation. The three cases of insomnia refer to subjective "trouble sleeping" in relation to other reported events, such as Bell's palsy, abdominal pain, vertigo, and myalgia. All cases of peripheral swelling were confounded by multiple comorbidities and multiple concomitant medications.

Among serious cases during the reporting period, more events were reported after dose 5 (38 events) than dose 4 (22 events). An additional 79 cases were missing dose information. Events in serious cases occurred most frequently within two days of vaccination, as is the general trend with most doses.

Overview of Fatal Cases with elasomeran/davesomeran)

During the reporting interval, there was one case with a fatal outcome reported among frail recipients of elasomeran/davesomeran, reported spontaneously in the United States and was not medically confirmed. This case ([redacted]) was strongly confounded by comorbidities, including CAD with bypass and diabetes, and is discussed in detail in Section 16.3.6.7.6 [of the PSUR].

Discussion

The general pattern of commonly reported AEs in the frail subpopulation is consistent with expected elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran reactogenicity and comparable to those events observed in the general population and in patients with these underlying conditions,

especially the elderly. This is to be expected, as the elderly comprise 30.2% of the frail subpopulation in the reporting period.

As expected with the time course of reactogenicity events observed in the general population, event clustering in the frail subpopulation was observed in the three-day window after vaccination, irrespective of dose number.

Notably, reports of event term COVID-19 infection were much less prevalent in serious cases in the frail subpopulation (1.3%) compared to the general population (2.0%). This is likely due to the preferential roll out of boosters to this frail subpopulation in many countries. The most frequently reported event terms in serious cases in the frail subpopulation closely match those seen both in the elderly population and in the general population as a whole. Fatal cases in the frail subpopulation in the reporting period (2.0%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, which compromise a little less than a third of the frail subgroup.

Case reports across all available vaccines after doses 3 and above have increased as expected with uptake of booster doses administered in many countries. The total number of cases in doses 3 and above for elasomeran has dropped slightly, which is expected given the emergence of the bivalent boosters, as they are established as the preferred vaccine used for doses after the primary two dose series. With this increase in booster dosing, more events were reported after dose 3 than any other dose in this reporting period. The AE profile observed after booster doses in the frail subpopulation is similar to that seen in the general population, notably as reactogenicity events with similar TTO for dose 3 as after dose 1 and dose 2.

The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in frail individuals with unstable health conditions and comorbidities the benefit-risk profile for elasomeran remains favorable.

The MAH has monitored Use in frail subjects with unstable health conditions and comorbidities in each MSSRs as well as PSURs since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found:

Review of the safety data in frail subjects with unstable health conditions and comorbidities reported in the GSDB indicates that the general pattern of commonly reported AEs in those frail subjects with unstable health conditions and comorbidities is comparable to the general population, rather than as a result of vaccine exposure.

The MAH continues to evaluate Use in frail subjects with unstable health conditions and comorbidities in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies.

Use of elasomeran in frail subjects with unstable health conditions and comorbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines and no longer constitutes missing information in the safety profile of elasomeran.

Rationale for removal:

Extensive use of the elasomeran vaccines (>800 million individuals vaccinated with at least one dose), including in frail subjects with unstable health conditions and comorbidities, has provided extensive safety information in this subpopulation group to support its removal as missing information.

There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of elasomeran with respect to 'Use in frail subjects with unstable health conditions and comorbidities' as long-term safety is being kept as missing information.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in frail subjects with unstable health conditions and comorbidities in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in frail subjects with unstable health conditions and comorbidities as Missing Information from the EU-RMP, and to continue monitoring use in frail subjects with unstable health conditions and comorbidities through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Conclusion

Based on the analysis of all the safety data received during the reporting period and cumulatively, ModernaTx, Inc. considers that events in the frail subpopulation occurring after the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran did not raise any safety issue of concern. ModernaTx, Inc. will continue to monitor events in the frail subpopulation using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH proposed removal of the missing information 'use in frail subjects with unstable health conditions and co-morbidities' from the EU-RMP, which is endorsed (see section 3.1.4.1.5.). Nevertheless, the topic shall remain in the PSUR list of safety concerns and an evaluation of new information on this topic is required with future PSURs.

No new significant safety information was identified.

2.3.3.7. Use in subjects with Autoimmune and Inflammatory Disorders

Source of the New Information

Information presented below includes analyzes performed on cases from the subpopulation with known history of autoimmune and inflammatory disorders (MedHx AI/ID) received by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022.

Background Relevant to the Evaluation

Use of elasomeran in individuals with AI/ID is an area of missing information in the RMP. Because there was limited data from CTs on the use of elasomeran in individuals with AI/ID, the MAH has been closely monitoring the safety profile of elasomeran in this population through routine pharmacovigilance.

Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, countries are recommending a booster dose (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in immunocompromised individuals, especially now with the bivalent vaccines. The third dose of elasomeran recommended for immunocompromised patients is 100 ug dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 ug dose.

In general, public health and professional groups recommend COVID vaccination for patients with AI/ID. These recommendations highlight the likely potential benefits of COVID vaccines in this population with the potential risk of more severe COVID infections, sequelae, and impact on underlying immune-mediated diseases [104-107]. Of note, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine and may be a risk factor for more severe COVID-19 disease [123,124]. Note, those AI/ID cases of patients who are on immunosuppressive therapy included in this section, are also included and overlap with the immunocompromised section of this PBRER (See the Section-Immunocompromised on "Use in Immunocompromised Subjects" and Section-Vaccine Failure "Vaccine Failure").

As it has been described before in previous PBRER, exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID vaccines [125-127]. While decreased immunogenicity for those on immunosuppressive therapies (IST) and the hypothetical risk of disease exacerbation have been recognized by professional and public health organizations, given the risk of the more severe COVID-19 and sequelae, vaccination is generally recommended with monitoring and management of any potential flare or exacerbation after vaccination.

Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran [120,128-130]. No SAEs were reported. Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals with autoimmune/ inflammatory conditions in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in individuals with AI/ID as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals with AI/ID through routine surveillance. elasomeran. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for valid, clinical, and spontaneous case reports for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran in people with a medical history of autoimmune

and/or inflammatory disease (hereafter referred to as "MedHx AI/ID"), received from health-care providers, HAs, consumers, and literature, for the review period (19 Jun 2022–17 Dec 2022) and cumulatively (18 Dec 2020–17 Dec 2022).

Reports from individuals with a MedHx AI/ID were identified from ModernaTx, Inc. GSDB using the Immune-mediated/autoimmune disorders Standard MedDRA Query (SMQ) "Immunemediated/ autoimmune disorders SMQ" PTs identified in past medical history.

Data for this MedHx AI/ID subpopulation was also compared to the general population. The "General Population" (all elasomeran data in the ModernaTx, Inc. GSDB) refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the elasomeran GSDB.

Subsections describe MedHx AI/ID data for all, serious and fatal cases, as well as for adolescents and those who received Dose 3 or more than three doses. Serious events must be interpreted with caution, and many are not events meeting the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases.

To identify cases of potential flares after vaccination among cases with MedHx AI/ID, cases with MedHx AI/ID that also have: 1) events with PT captured in SMQ AI/ID or 2) PTs of "condition aggravated", "disease progression", or "disease exacerbation" were assessed. Medical review of the narratives of these cases revealed three scenarios: 1) flares of pre-existing AI/ID conditions; 2) new onset of an AI/ID condition in the setting of a different pre-existing AI/ID condition (i.e., an individual may have several AI/ID conditions); 3) lastly, coding errors where MedHx PTs are misclassified as AI/ID conditions, or vice versa. ModernaTx, Inc. included an in-depth review of potential flares in PBRER#2, DLP 31 Dec 2021, and in-depth cumulative review of myasthenia gravis during PBRER#3.

Literature Methodology:

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelaosmeran and elasomeran/davesomeranand AI/ID using multiple search strategies to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 1,495 unique literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on cases involving autoimmune or inflammatory disorders please refer to Appendix 11.11.

Overview of MedHx AI/ID Cases Reported for elasomeran:

Cumulatively, there have been 22,478 cases (7,552 serious and 287 fatal) with 104,597 events (26,030 serious) among people with MedHx AI/ID; 12,660 cases were medically confirmed.

During this reporting period, there were 3,048 (1,083 serious, 14 fatal) cases with MedHx AI/ID with 13,299 events (2,931 serious) among people with MedHx AI/ID. Of the 3,048 cases, 600 were medically confirmed. Table 16.73 displays the MedHx AI/ID cases by review period and case seriousness.

Table 16.73 Cases With MedHx AI/ID by Seriousness - elasomeran

Case Seriousness	Prior to Review Period		Review Period		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Non-Serious	13,021	66.5%	1,965	64.5%	14,926	66.4%
Serious	6,563	33.5%	1,083	35.5%	7,552	33.6%

Case Seriousness	Prior to Review Period		Review Period		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Grand total	19,584	100.0%	3,048	100.0%	22,478	100.0%

During the reporting period, as in previous reporting periods, there were more reports involving females 76.8% (2,342; 76.8%) than males (654; 21.5%) with few reports missing gender information (52; 1.7%). The mean age was 51.7 years (SD 14.8), and the median age was 52.0 (range 0.2-93); Table 16.74 presents gender and age group distribution of the cases during the reporting period.

Table 16.74 Gender and Age Distribution of Cases with MedHx AI/ID, Reporting Period - elasomeran

Age Group	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
(0-5 Mths)[1]	0	0	0	0	1	0.0%	1	0.0%
06-11Y[2]	2	0.1%	0	0	0	0	2	0.1%
12-15Y[3]	4	0.1%	3	0.1%	0	0	7	0.2%
16-17Y[3]	5	0.2%	2	0.1%	0	0	7	0.2%
18-24Y	35	1.1%	15	0.5%	0	0	50	1.6%
25-39Y	485	15.9%	121	4.0%	2	0.1%	608	19.9%
40-49Y	508	16.7%	105	3.4%	5	0.2%	618	20.3%
50-64Y	750	24.6%	206	6.8%	8	0.3%	964	31.6%
65-74Y	313	10.3%	104	3.4%	9	0.3%	426	14.0%
75Y+	123	4.0%	68	2.2%	3	0.1%	194	6.4%
Missing	117	3.8%	30	1.0%	24	0.8%	171	5.6%
Grand total	**2,342**	**76.8%**	**654**	**21.5%**	**52**	**1.7%**	**3,048**	**100.0%**

[1] 1 case noted for children 0-5 months pertains to exposure via breastfeeding; please refer to the Subsection on Children <12 years of age.
[2] Please refer to the Subsection on Children <12 years of age.
[3] Please refer to the Subsection on Adolescents 12-17 years of age.

[Note that cumulatively, a total of 2,020 cases (867 serious and 38 fatal) overlaps between the MedHx AI/ID and the immunocompromised/immunosuppressed populations, as many people with AI/ID are taking IST. During the review period, 238 cases (133 serious and 1 fatal) overlapped. (Please also refer to the Section 16.3.5.4 [of the PSUR] on Use in immunocompromised patients)].

During this reporting period, most of the cases were received from the EEA (1,943; 63.7%), followed by the United States (602; 19.8%). The cumulative gender, age and geographic distribution of cases is comparable to that in the reporting period.

Many of the most frequently reported events (pyrexia [4.6%], fatigue [5.0%], headache [4.9%], chills [3.1%], myalgia [3.1%], nausea [2.5%], and arthralgia [2.7%]) in the review period represent expected reactogenicity following elasomeran. The types and distribution of the most frequently reported events during this review period is generally similar to the distribution observed for the cumulative period, and when compared to the general population.

A difference from the previous reporting period, during this review period, more events were reported after Dose 3 (2,389; 18.0%) compared to cumulative reporting for these doses in MedHx AI/ID population; this is likely reflective of the general trend of increased uptake of booster doses. When time

to onset was known, the same pattern observed in the previous reporting period continued with more cases reporting a TTO within less than 7 days after vaccination (6,339; 47.7%), and mostly within 0 to 2 days (5,690; 42.8%) after vaccination, regardless of dose number. Same reporting trend was observed for cumulative reports (0 to 6 days: 62,036; 59.3%; 0 to 2 days: 54,776; 52.4%).

Serious Cases and Events - elasomeran)

Cumulatively, there have been 7,552 serious cases (26,030 serious events) after elasomeran among people with MedHx AI/ID; 4,135 cases were medically confirmed.

During the review period, 1,083 serious cases (2,931 serious events) with MedHx AI/ID (14 cases reported a fatal outcome) were reported. Of the 1,083 serious cases, 303 were medically confirmed. Same reporting pattern was observed for serious cases regarding reported gender, with more cases involving females (775; 71.6%) than males (280;25.9%), there were 28 reports (2.6%) with missing gender information. The mean age was 54.9 years (SD 14.8), the median age was 55.0 years (range, 7.0 to 93.0) and 5.7% (62) cases were missing age information. The gender and age distribution for the cumulative period is similar to the reporting period.

The most frequently reported serious events by cases with MedHx AI/ID during this review period as well as cumulatively, reflect expected reactogenicity events, such as fatigue, headache, pyrexia, myalgia, arthralgia, dyspnoea, nausea, and chills. The types and distributions of the events were generally similar to the most frequently reported serious events cumulatively in cases with MedHx AI/ID as well as in the general population.

Fatal Reports - elasomeran)

During the reporting period, 14 cases (31 events) with MedHx AI/ID had a fatal outcome; 10 fatal cases were medically confirmed. There were no important differences for the cases reporting a fatal outcome regarding gender, with 6 cases (42.9%) involving males, and 7 (50.5%) cases involving females. There was 1 (7.1%) report with missing gender information. The mean age for these reports was 66.2 years (SD: 24.5) and median age was 75.5 years (range 13.0-89.0) and 14.2% (2/14) were missing age data.

During the reporting period, out of the 14 fatal cases reported, there were 9 (64.3%) cases that are considered "frail" persons defined by comorbidities and age. These cases included comorbid conditions such as hypertension, Type 2 DM, COPD, arteriolosclerosis, hyperlipidemia, and chronic kidney disease. The median TTO was 3 days (range 1-181) during the reporting period.

All cases reporting a fatal outcome during the reporting period are heavily confounded by concurrent medical history and according to the reported cause of death, most of them are considered unlikely related to vaccination (Natural causes, Prostate cancer, COVID-19 infection, HV infection and chronic kidney disease stage 3, SLE, etc.). A medical review of all fatal cases in MedHx AI/ID cases received during the review period is presented in Appendix 11.11. Refer to Section 16.3.6.7.6 [of the PSUR] (Elderly), and Section 16.3.5.6 [of the PSUR) (Frail).

Use Among Persons with MedHx AI/ID Who Received a 3rd or Booster Dose of elasomeran

Cumulatively, there have been 2,594 (9,464 events) cases with MedHx of AI/ID after a 3rd Dose or booster dose, with 591 cases medically confirmed. There were 1,273 serious cases (3,928 serious events) with 23 cases reporting a fatal outcome. There were more reports involving females (1,997; 77.0%) than males (558; 21.5%), with 39 reports (1.5%) missing gender information.

During the reporting period, there were 881 (3,140 events) cases with MedHx AI/ID after Dose 3 or a booster with 119 cases medically confirmed. There were 337 (735 serious events) serious cases with 3 fatal reports. Following the same trend observed cumulative, there were more reports involving females (680; 77.2%) than males (191; 21.7%), with 10 reports (1.1%) with missing gender data.

There were no differences of the most frequently reported PTs during the review period, for cases with MedHx AI/ID regardless of the dose number. Table 16.75 presents cumulative distribution of most frequently reported PTs among MedHx AI/ID cases receiving elasomeran (combined data for all doses of elasomeran) versus Dose 3 or booster doses of elasomeran.

Table 16.75 Most Frequently Reported PTs Among MedHx AI/ID Cases Receiving elasomeran Cumulative versus ≥ 3 Doses of elasomeran

elasomeran All doses			elasomeran 3 or more Doses		
PT	# Events	% Events	PT	# Events	% Events
Headache	4,587	4.4	Headache	480	5.1
Fatigue	4,524	4.3	Fatigue	456	4.8
Pyrexia	4,194	4.0	Pyrexia	457	4.8
Chills	2,998	2.9	Chills	301	3.2
Nausea	2,686	2.6	Myalgia	294	3.1
Pain	2,567	2.5	Nausea	272	2.9
Pain in extremity	2,450	2.3	Arthralgia	221	2.3
Myalgia	2,343	2.2	Pain in extremity	212	2.2
Arthralgia	2,242	2.1	Dizziness	204	2.2
Dizziness	1,878	1.8	Vomiting	121	1.3

During the reporting period, TTO of events reported by cases with MedHx AI/ID after Dose 3 or booster was mostly within 2 days (64.0%) after vaccination. The median TTO was 1.0 day (range 0-565). This is comparable to the cumulative data from cases with MedHx AI/ID who received Dose 3 or booster

Serious Cases and Events Among Persons with MedHx AI/ID Who Received Dose 3 or Booster of elasomeran)

Cumulatively, there have been 1,273 (3,928 serious events) serious cases with MedHx of AI/ID who received Dose 3 or a booster dose with 591 cases medically confirmed. During the reporting period, 337 (735 serious events) serious cases with MedHx AI/ID who received Dose 3 or a booster were reported. There were 119 serious cases medically confirmed.

There were no differences in the gender distribution of the serious cases reported after a Dose 3 or booster, when compared with the cumulative reports and non-serious reports, with more reports involving females (680; 77.2%) than males (191; 21.7%) with 10 reports (1.1%) missing gender data. Mean age of these cases was 54.0 years (SD: 13.5), median age of 53.5 years (range 22.0 to 88.0), with 2.8% (5) cases missing age information.

There were no observed differences in the PTs associated with the reported serious events in individuals receiving a 3rd dose or a booster dose, when compared to the rest of the reports received from individuals with MedHx of AI/ID, both during the reporting period or cumulative.

Fatal Events Among Persons with MedHx AI/ID Who Received 3 or more doses - elasomeran

During the review period, 3 cases reported a fatal outcome. All three reports involved males, two cases 83 years of age, and another one 86 years old. All 3 reports are considered unlikely related to the vaccine due to the associated risk factors, comorbidities and clinical course describe in the reported events.

Use Among Children (< 12 Years of Age) With MedHx AI/ID-elasomeran

Cumulatively, 6 cases have been reported in the age group of <12 years old: 1 non-serious case ([redacted] was reported in a child 0-5 months old, and 1 serious case ([redacted]) in a child 6-months to 2 years old, both these cases pertained to exposure via breastfeeding following maternal vaccination; 1 non-serious case ([redacted]) was reported in a child with history of Coeliac disease in the age group of 2-5 years of age; 3 cases were reported in children 6-11 years old with history of Psoriasis ([redacted]), Crohn's disease ([redacted]) and Kawasaki's disease ([redacted]). These include 3 reports received during the reporting period ([redacted], **and** [redacted]). The medical review of the 2 serious cases received during this reporting period ([redacted], [redacted]) in children in the age group of 6-11 years is presented below:

[redacted]: This is a regulatory case concerning a 7-year-old female patient with the concurrent medical conditions of Crohn's disease and hypertension and medical history of knee pain, urinary tract disorder, and skin eruption, who experienced eczema, on the same day after an unspecified dose of elasomeran. The event was described as extensive eczematous rash of both forearms that persisted for 2 months. Concurrent medical condition of Crohn's disease and hypertension in addition to medical history of skin eruption plus the use of concomitant medications (reported as Bisoprolol; Candesartan; Esomeprazole; Loperamide; Loperamide) remains as confounders/co-suspects. This case is considered possible given that there is not enough information regarding the reported medical history of skin eruption and whether or not that is related to the reported extensive rash developed by the patient.

[redacted]**:** This is a regulatory authority case concerning a 7-year-old, female patient with concurrent medical condition of Kawasaki's disease. The patient experienced the event of acute lymphangitis of face the same day of the second dose of elsomeran vaccine administration. The patient developed swelling in the vaccinated region with dizziness, headache, fever, lack of energy, facial numbness, inability to move and chest pain. The patient sought emergency consult and was diagnosed with bilateral lymphadenitis and was subsequently admitted. It was also reported that several lymph nodes in the oral cavity were swollen. The symptoms were largely relieved with an inpatient drip treatment which was unspecified although several lymph nodes in the oral cavity remained swollen. The follow-up reported that the patient's oral condition was recovering, and that patient experienced occasional heart throbbing pain. The outcome of the event was reported as resolving. The concurrent medical condition of Kawasaki's disease remains a confounder for the symptoms of headache, fever, lack of energy, swollen lymph nodes in oral cavity and chest pain. This case is considered possible given that there is important missing information related to the concurrent medical history reported by the patient.

Use Among Adolescent (12-17 years) With MedHx AI/ID - elasomeran

Cumulatively, there have been 57 (120 events) cases reported in children 12 to 17 years of age, with 18 serious (29 serious events) cases and 1 case reporting a fatal outcome; 48 cases were medically confirmed. There were more reports involving females (35; 61.4%) than males (22; 38.6%). The mean age was 15.9 years (SD 1.4), with a median age of 16.0 years (range 12.0 to 17.0); 28.1% (16) of cases were 12-15-year-olds, and 71.9% (41) are 16-17-year-olds. Most of the cases were from the United States (52.6%), followed by the EEA (19.3%).

During the review period, 14 (23 events) cases among adolescents with MedHx AI/ID was reported with 6 serious (7 serious events) cases, and there were no fatal cases during the reporting period; 12 cases were medically confirmed.

Table 16.76 summarizes the distribution of autoimmune conditions in the past medical history in the adolescent population with AI/ID.

Table 16.76 AI/ID Medical Conditions Among MedHx AI/ID 12-17-year-old Subpopulation–elasomeran, Cumulative

Medical History	# Cases
Diabetes mellitus (DM) [Type 1 DM (n=8), and DM/autoimmune disorder (n=2)]	10
Autoimmune disorder	9
Coeliac disease	8
Crohn's disease	4
Rheumatoid arthritis	4
Systemic lupus erythematosus	4
Autoimmune thyroiditis	3
Colitis ulcerative	3
Kawasaki's disease	3
Psoriasis	2
Raynaud's phenomenon	2
Antiphospholipid syndrome	1
Autoimmune thyroiditisFH	1
Autoinflammatory disease	1
Behcet's syndrome	1
Immune system disorder	1
Immune thrombocytopenia	1
Juvenile idiopathic arthritis	1
Myasthenia gravis	1
Polyarthritis	1
Sjogren's syndrome	1

All serious cases reported during the review period were medically reviewed and no unexpected patterns were observed. During the review period, one case, [redacted] of myocarditis/pericarditis in adolescents with MedHx AI/ID was reported; please see Section 16.3.1.2 [of the PSUR] for more information on this case.

Autoimmune and Inflammatory Conditions Aggravated/ Potential Flares

As described in Section 16.3.5.7.3 [of the PSUR] using the applied strategy to identify cases of potential flares after vaccination requires caution in interpretation and medical review of the narrative to identify reports of flares in the MedHx AI/ID subpopulation. Given the nature of spontaneous reporting and insufficient information in some reports, it is sometimes difficult to differentiate expected reactogenicity from a true flare, or to confirm if the reported events are a true flare as often, pre-vaccination disease state/stage, clinical course, diagnostics, treatment and outcome are not reported. Additionally, the number of individuals with potential flares might be an overestimate, because each episode of a flare for an individual might be reported as a separate case (e.g., if an individual reports a flare after Dose 1 and Dose 2, two reports with unique case IDs could be created [one for each episode of a reported flare]).

Cumulatively, 2,437 cases (13,800 events) of potential flares have been reported with 1,779 considered serious cases (6,037 serious events); there were 39 fatal reports. There were 1,321 cases were medically confirmed.

During the reporting period, 420 cases (1,806 events) of potential flares were reported with 306 serious cases (675 serious events), and 3 cases reporting a fatal outcome; there were 155 cases medically

confirmed. There were more reports of flares involving females (293; 69.8%) than males (115; 27.4%), with 12 reports (2.9%) missing gender information. The average age was 55.0 years (SD 14.3) and median age was 55.0 (range 15.0-93.0). The cumulative gender and age distribution was comparable to that in the review period.

During the reporting period there were more reports of flares after dose 3 (206; 11.4%), and after dose 2 (185; 10.2%). When TTO was reported, most of the reports had a TTO within less than 7 days (405; 22.4%), the same trend has been observed cumulative (5,470; 39.6%).

Five of the frequently reported types of potential AI/ID flares (rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, and ulcerative colitis/inflammatory bowel disease) continue to be among the most frequently reported AI/ID conditions cumulatively and were presented in-depth in previous PBRER. Preferred Terms of Autoimmune/Inflammatory Disorder SMQ in reports with past medical history of AI/ID, representing a subset of potential flares are presented in Appendix 11.11.

To date, no cases of potential flares have been reported in children younger than 12 years of age. Cumulatively, 7 cases (7 events) of potential flares have been reported in adolescents 12-17 years of age, with 5 cases considered serious. There have not been any fatal reports cumulatively. During the reporting period there were 2 cases (1 serious) reported, with one of them being serious.

Use in Patients with Autoimmune or Inflammatory Disorders Receiving Booster Dose with elasomeran/imelasomeran

Cumulatively, 146 cases (593 events) have been reported for elasomeran/imelasomeran; there were71 serious cases and 4 that reported a fatal outcome, and 24 cases were medically confirmed; all these reports were received during the reporting period of this PBRER. Same trend was observed for reported gender, with more reports involving females (108; 74.0%) than males (35; 24.0%), there were 3 reports (2.1%) missing gender information. The mean age was 62.7 years (SD 14.7) and median age was 63.5 years (range 23.0-89.0).

The most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among MedHx AI/ID cases receiving elasomeran/imelasomeran represent expected reactogenicity. The types and distribution of the most frequently reported events is comparable to those observed with vaccination with elasomeran in MedHx AI/ID cases. Table 16.77 presents cumulative distribution of most frequently reported PTs in MedHx AI/ID cases by vaccine (elasomeran vs elasomeran/imelasomeran).

Table 16.77 Most Frequently Reported Events by Preferred Term (PT) Among Cases with MedHx AI/ID Receiving elasomeran elasomeran/imelasomeran, Cumulative

elasomeran			elasomeran/imelasomeran		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Headache	4,587	4.4	Headache	46	7.8
Fatigue	4,524	4.3	Fatigue	42	7.1
Pyrexia	4,194	4.0	Pyrexia	30	5.1
Chills	2,998	2.9	Nausea	29	4.9
Nausea	2,686	2.6	Arthralgia	28	4.7
Pain	2,567	2.5	Chills	28	4.7
Pain in extremity	2,450	2.3	Malaise	27	4.6
Myalgia	2,343	2.2	Myalgia	26	4.4
Arthralgia	2,242	2.1	Injection site pain	19	3.2
Dizziness	1,878	1.8	Vomiting	12	2.0

The most frequently reported serious events of cases with MedHx AI/ID receiving elasomeran/imelasomeran were not different from the ones observed for non-serious cases reflecting expected reactogenicity events, such as fatigue, headache, pyrexia, myalgia, arthralgia, nausea, and chills.

Cumulatively, 4 fatal cases were reported for elasomeran/imelasomeran. All cases were considered unlikely related to the vaccine due to the associated comorbidities included in the reports (cancer, kidney disease and peritoneal dialysis, acute hemolytic anemia, SLE; Peritoneal dialysis; Hypertension; Pulmonary hypertension; Sjogren's syndrome, among others).

Use in Patients with Autoimmune or Inflammatory Disorders Receiving Booster Dose with elasomeran/davesomeran

Cumulatively, 58 cases (214 events) have been reported for elasomeran/davesomeran; there were 16 serious cases (28 serious events) and no cases reporting a fatal outcome; there were 9 cases medically confirmed. All these reports were received during the reporting period. Same observed pattern for gender reports was observed for reports after elasomeran/davesomeran, with more cases involving females (42; 72.4%) than males (16; 27.6%). The mean age was 60.9 years (SD 14.5) and median age was 64.0 years (range 25.0-90.0).

The most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among MedHx AI/ID cases receiving elasomeran/davesomeran represent expected reactogenicity. The types and distribution of the most frequently reported events is similar to those observed with elasomeran in MedHx AI/ID cases and the general population receiving elasomeran/davesomeran. Table 16.78 presents the cumulative distribution of most frequently reported PTs in MedHx AI/ID cases by vaccine (elasomeran vs. elasomeran/imelasomeran).

Table 16.78. Most Frequently Reported Events by Preferred Term (PT) Among Cases with MedHx AI/ID Receiving elasomeran or elasomeran/davesomeran, Cumulative

Elasomeran			Elasomeran/davesomeran		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Headache	4,587	4.4	Pyrexia	11	5.1
Fatigue	4,524	4.3	Pain	8	3.7
Pyrexia	4,194	4.0	COVID-19	7	3.3
Chills	2,998	2.9	Headache	7	3.3
Nausea	2,686	2.6	Illness	7	3.3
Pain	2,567	2.5	Myalgia	7	3.3
Pain in extremity	2,450	2.3	Chills	6	2.8
Myalgia	2,343	2.2	Pain in extremity	6	2.8
Arthralgia	2,242	2.1	Vaccination site pain	6	2.8
Dizziness	1,878	1.8	Arthralgia	5	2.3

There have been no MedHx AI/ID cases with fatal outcome reported for elasomeran/davesomeran.

Cumulatively, there were 9 cases (9 events) of which 6 were serious, of potential AI/ID flares in MedHx AI/ID after vaccination with elasomeran/davesomeran.

Literature Findings

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and AI/ID MedHx to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved.

A total of 1,495 literature articles were retrieved using these search criteria. These literature search results were medically/scientifically reviewed and are discussed above, under section Background Relevant to the Evaluation. There was no additional published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran.

Discussion

In the review period for PBRER#4 and cumulatively, the most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among MedHx AI/ID cases receiving elasomeran, elasomeran/imelasomeran and elasomeran/davesomearn represent expected reactogenicity. The types and distribution of the most frequently reported events is comparable to those observed with elasomeran in MedHx AI/ID cases and those receiving elasomeran/imelasomeran or elasomeran/davesomeran.

During this reporting period, Dose 3 and Dose 4/5/6/7 cases constituted 9.5% and 2.1%, respectively of all cases with MedHx AI/ID in the safety database.

Cumulatively, there were 6 reports received for children under 12 years of age and 57 cases of adolescents 12-17 years of age with MedHx AI/ID.

During this reporting period, the 442 potential cases of exacerbation of underlying AI/ID reported after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran may have limited

information and lack a description of the baseline disease status or historic pattern of flares, the clinical course, diagnostics/labs/imaging, treatment, outcome, clear TTO and/or dose number. Those reports also include signs and symptoms of reactogenicity that could mimic signs and symptoms of autoimmune disease (such as fever, myalgia, fatigue, arthralgia, headache), and thus it may be difficult to fully differentiate transient reactogenicity from AI/ID reactivation/flare.

Given the natural waxing and waning course of AI/ID, and that there are no reliable reference data of the background rates of respective flares, the modest number of cases do not represent a safety concern at this time. There have been reports of flares after many vaccines, including various COVID vaccines. Both health-care providers and patients acknowledge the potential risk of flares after any vaccination, yet flares are not specifically described in any vaccine labels. At present, the global consensus is that the benefit of vaccination outweighs the potential risks of flares but should be discussed between patient and HCP.

Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran [120,128-130]. Relevant literature findings during the reporting period provides support to the observed safety and benefit/risk profile of COVID vaccination among individuals with AI/ID. Findings from these articles during this reporting period did not provide new substantive data to impact the benefit-risk profile of the use of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran among persons with MedHx AI/ID. Published studies continue to demonstrate that elasomeran is safe and well tolerated in individuals with MedHx AI/ID. Although, the incidence of flare rates noted in published studies had a wide range for multiple COVID vaccine types and varied AI/ID conditions, the studies consistently showed that flares were transient, typically mild and self-limited. Additionally, the studies that included an unvaccinated arm or captured information on the background flare rates of vaccinated cohort, have not shown a significant difference in the flare rates between vaccinated and unvaccinated individuals or pre and post-vaccination.

Given that each AI/ID has a different immune pathophysiology, makes it difficult to generalize observed flare rates across different AI/ID conditions. Despite the limitations noted above, study findings indicate that the safety profile of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran among individuals with AI/ID is reassuring and disease flares are limited. The published literature continues to support the benefit-risk profile of the use of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran in individuals with autoimmune and inflammatory diseases.

As of the DLP of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in individuals with AI/ID. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. In addition, there have been non-serious, serious and fatal reports of COVID-19 in this subpopulation, perhaps reflective of reduced immunogenicity/effectiveness of the vaccine in this population, the surges of variants and subvariants, waning immunity, and policy and behavior changes. Otherwise, the general pattern of commonly reported AEs in those with a medical history of AI/ID is comparable to the general population.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an

estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of use in individuals with AI/ID, the benefit-risk profile for elasomeran remains favorable. The MAH has monitored use in individuals with AI/ID in each MSSRs as well as PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found:

• Review of the safety data individuals with AI/ID reported in the GSDB indicates that the general pattern of commonly reported AEs in those with a medical history of autoimmune/ inflammatory disorder is comparable to the general population, rather than as a result of vaccine exposure.

• Exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID vaccines. This has been recognized by professional and public health organizations; yet, given the risk of the potential consequences of COVID infection, some are recommending vaccination with monitoring and management of any potential flare or exacerbation occurring after vaccination. In addition, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine, and/or make them more susceptible to infections.

• Use of elasomeran in individuals with AI/ID is embedded in clinical practice and included in the elasomeran SmPC, CCDS and relevant health guidelines.

• The MAH continues to evaluate Use in individuals with AI/ID in reports of elasomeran (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorization safety studies.

Rationale for removal:

• Extended use of the elasomeran vaccines (>800 million individuals vaccinated with at least one dose) has provided extensive safety information including individuals with AI/ID to support the removal of this population as missing information.

• There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to individuals with AI/ID.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals with AI/ID conditions in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of use in individuals with AI/ID as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals with AI/ID through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

Conclusion

Based on the analysis of all the safety data received during the reporting period and cumulatively in the AI/ID subpopulation, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The MAH will continue to monitor AEs in individual with AI/ID using routine surveillance.

Rapporteur assessment comment:

The MAH proposed removal of the missing information 'use in subjects with autoimmune or inflammatory disorders' from the EU-RMP, which is endorsed (see section 2.3.3.7. . Nevertheless, the topic shall remain in the PSUR list of safety concerns and an evaluation of new information on this topic is required with future PSURs.

No new significant safety information was identified.

2.4. Evaluation of Adverse Events of Special Interest (AESI)

2.4.1. Thrombosis with Thrombocytopenia syndrome (TTS)

Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTx, Inc. for the review period, from 19 Jun 2022 to 17 Dec 2022 for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

Thrombosis with Thrombocytopenia syndrome, also known as Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or vaccine-induced immune thrombotic thrombocytopenia (VITT), is a rare and newly identified syndrome which has been reported in people who have received adenoviral vector COVID-19 [141]. This syndrome is characterized by venous or arterial thrombosis, mild to severe thrombocytopenia, and positive PF4-heparin Enzyme-Linked Immunosorbent Assay (ELISA) ('heparin-induced thrombocytopenia [HIT]" ELISA). These clinical and laboratory features are similar to rare cases of HIT-like autoimmune thrombosis with thrombocytopenia, previously described following surgery, certain medications or infections in patients not receiving heparin. The pathogenesis of vaccine-induced thrombotic thrombocytopenia is not known at this time. However, given its clinical presentation and biochemical similarities to heparin-induced thrombocytopenia, which is a prothrombotic and potentially life-threatening condition, a similar immune-mediated response induced by these adenoviral vector vaccines has been postulated as immune complexes with a mixture of antibody specificities similar to HIT was noted in the serum of patients who developed this syndrome [142]. Symptoms on presentation may include intense headache, abdominal pain, back pain, nausea and vomiting, vision changes, change in mental status, shortness of breath, leg pain and swelling, and/or bleeding/petechiae. Patients may complain of severe, recurrent, or persistent symptoms from 4 to 42 days following COVID-19 vaccination, with the peak time period for initial symptoms falling between days 6 to 14 [143]. The MAH has agreed to continue to closely evaluate events of "Thrombosis with Thrombocytopenia related events".

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB for the reporting period of 19 Jun 2022 to 17 Dec 2022 for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The search strategy included using a customized list of MedDRA PTs from the SMQ-Embolic and thrombotic events-narrow, to identify cases with a reported thromboembolic event, which were then cross-checked for any of the following thrombocytopenia related PTs: Acquired amegakaryocytic thrombocytopenia; Megakaryocytes decreased; Platelet count decreased; Platelet maturation arrest; Platelet production decreased; Platelet toxicity; Thrombocytopenia; Megakaryocytes abnormal; Platelet count abnormal; Platelet disorder; Plateletcrit abnormal; Plateletcrit decreased; Immune thrombocytopenia; hemolysis, elevated liver enzymes, and low

platelets syndrome; Thrombotic thrombocytopenic purpura; Thrombocytopenic purpura, Platelet transfusion, Petechiae, Ecchymosis, and Purpura.

All cases identified were reviewed and classified using both the CDC working definition and the Brighton Collaboration interim case definition for TTS.

The CDC classification for possible cases of TTS [18] divides cases into 2 tiers based on the location of thrombosis and severity of symptoms, with Tier 1 being associated with higher morbidity and mortality. Reported cases of possible TTS with insufficient evidence or information to be classified according to either of the case definitions were classified as "unassessable"; and cases with evidence that parameters were not met for either case definition were classified as "Not a TTS case".

The Brighton Collaboration case definition for TTS [144] divides cases into 5 levels:

- Level 1 – Definite Case
- Level 2 – Probable Case
- Level 3 – Possible Case
- Level 4 – Not enough information
- Level 5 – Not a case of TTS

For those cases that are classifiable according to the CDC or Brighton Collaboration definitions, the Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Appendix 11.13 [of the PSUR] includes the reporting period information for all TTS-related case reports according to the Brighton collaboration case definitions for TTS, the CDC working case definition for TTS, and case causality assessments according to the WHO-UMC standardized case causality assessment.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected

See Appendix 11.3 [of the PSUR].

Overview of Cases

For more details on TTS cases please refer to Appendix 11.13 [of the PSUR].

Cumulative Review (cumulative to 17 Dec 2022)

Cumulatively, through 17 Dec 2022, a total of 230 cases (and 224 events) were identified with Thrombosis with Thrombocytopenia related events, of which 224 cases were assessed as serious and 31 cases had a fatal outcome. Of the 230 cases, 194 (84.3%) were medically confirmed. When dose number and TTO was reported, events most frequently were reported after Dose 2 (29.2%) and within 7 to >30 days (96; 38.4%) after vaccination.

There was no major difference observed in cases reported in males (117; 50.9%) compared to females (107; 46.5%); gender information was not reported for 6 cases (2.6%). The mean age was 59.5 years (SD19.0); median age was 63.0 years (min. 15/max. 96); 7 cases were missing age data. Reports most frequently originated from the United States (82; 35.7%), followed by European Economic Area (EEA) (69; 30.0%) and the Asia (50; 21.7%), and were received most frequently from regulatory authorities (184; 80.0%).

Report Period Review (19 Jun 2022 to 17 Dec 2022)

During the reporting period, there were 33 cases (35 events) of Thrombosis with Thrombocytopenia related events, of which 32 cases were serious, and 5 cases had a fatal outcome. During the review period, there were more cases of TTS- related events reported in males (19 cases [57.6%]) than in females (13 cases [39.4%]), with one report with unknown gender (3.0%). The mean age was 60.8 years (SD: 18.5); median age was 67.0 years (min. 18.0/ max. 88.0). Similar to previous report periods, the majority of reports were received from regulatory authorities (16; 48.5%). The majority of case reports during the reporting period continues to occur in individuals aged ≥ 50 years of age (21; 63.6%). During this reporting period there were no cases of TTS-related events reported in individuals <12 years of age (Table 16.88).

Table 16.88. Number and Percentage of Thrombosis with Thrombocytopenia Related Cases by Age group - Review Period 19 Jun 2022 to 17 Dec 2022

Age Group	Prior to Review Period		Review Period		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	2	1.0	0	0	2	0.9
18-24Y	10	5.1	1	3.0	11	4.8
25-39Y	22	11.2	3	9.1	25	10.9
40-49Y	22	11.2	5	15.2	27	11.7
50-64Y	46	23.4	5	15.2	51	22.2
65-74Y	47	23.9	10	30.3	57	24.8
75Y+	44	22.3	6	18.2	50	21.7
Missing	4	2.0	3	9.1	7	3.0
Grand total	**197**	**100.0**	**33**	**100.0**	**230**	**100.0**

During the reporting period most of TTS-related events were reported as occurring after Dose 3 (7; 21.0%), a notable change from the prior review period in which events occurred most frequently after Dose 2 (65.0%). There is no notable temporal pattern in the TTO reported following each of the respective doses. The relatively greater number of reports received following Dose 3 could be attributed to the increasing number of Dose 3 elasomeran administrations during this report period (Table 16.89).

Table 16.89. Number and Percentage of Thrombosis with Thrombocytopenia Related Events by Dose* and Time to Onset - Review Period 19 Jun 2022 to 17 Dec 2022

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total of # Events	Grand total of % of Total Events
		# Events	% of Total Events	# Events	% of Total Events		
Dose 1	Subtotal	51	23.7	4	11.4	55	22.0
	0 days	3	1.4	0	0	3	1.2
	01-02	6	2.8	1	2.9	7	2.8
	03-04	5	2.3	0	0	5	2.0
	05-06	1	0.5	0	0	1	0.4
	07-13	13	6.0	3	8.6	16	6.4
	14-29	17	7.9	0	0	17	6.8
	30+	6	2.8	0	0	6	2.4
Dose 2	Subtotal	72	33.5	1	2.9	73	29.2
	0 days	4	1.9	0	0	4	1.6
	01-02	14	6.5	0	0	14	5.6
	03-04	8	3.7	0	0	8	3.2
	05-06	2	0.9	1	2.9	3	1.2
	07-13	12	5.6	0	0	12	4.8
	14-29	12	5.6	0	0	12	4.8
	30+	20	9.3	0	0	20	8.0
Dose 3	Subtotal	11	5.1	7	20.0	18	7.2
	0 days	1	0.5	1	2.9	2	0.8
	01-02	2	0.9	2	5.7	4	1.6
	07-13	2	0.9	0	0	2	0.8
	14-29	4	1.9	0	0	4	1.6
	30+	2	0.9	4	11.4	6	2.4
Dose 4	Subtotal	0	0	4	11.4	4	1.6

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total of # Events	Grand total of % of Total Events
		# Events	% of Total Events	# Events	% of Total Events		
	0 days	0	0	2	5.7	2	0.8
	01-02	0	0	1	2.9	1	0.4
	14-29	0	0	1	2.9	1	0.4
Unknown	Subtotal	81	37.7	19	54.3	100	40.0
	0 days	5	2.3	0	0	5	2.0
	01-02	8	3.7	0	0	8	3.2
	03-04	2	0.9	0	0	2	0.8
	05-06	6	2.8	0	0	6	2.4
	07-13	3	1.4	3	8.6	6	2.4
	14-29	5	2.3	0	0	5	2.0
	30+	3	1.4	0	0	3	1.2
	Missing	49	22.8	16	45.7	65	26.0
Grand total		**215**	**100.0**	**35**	**100.0**	**250**	**100.0**

During the review period, similar to the cumulative period, the most frequently reported PT were Thrombocytopenia (10; 28.6%), Thrombotic thrombocytopenic purpura (10; 28.6%) and TTS (7; 20.0%). The most frequently reported PTs during the reporting period were in line with those seen in the prior to review period. (Table 16.90).

Table 16.90. Number and Percentage of Reported MedDRA PTs in Cases of Thrombosis with Thrombocytopenia Related Events - Review Period 19 Jun 2022 to 17 Dec 2022

PT	Prior to Review Period		Review Period		Total # Events	% Events
	# Events	% Events	# Events	% Events		
Thrombocytopenia	104	48.4	10	28.6	114	45.6
Thrombotic thrombocytopenic purpura	38	17.7	10	28.6	48	19.2
Thrombosis with thrombocytopenia syndrome	26	12.1	7	20.0	33	13.2
Platelet count decreased	22	10.2	1	2.9	23	9.2
Petechiae	8	3.7	5	14.3	13	5.2
Immune thrombocytopenia	9	4.2	0	0	9	3.6

PT	Prior to Review Period		Review Period		Total # Events	% Events
	# Events	% Events	# Events	% Events		
Purpura	3	1.4	1	2.9	4	1.6
Platelet disorder	3	1.4	0	0	3	1.2
Ecchymosis	1	0.5	0	0	1	0.4
Platelet transfusion	1	0.5	0	0	1	0.4
Thrombocytopenic purpura	0	0	1	2.9	1	0.4

During this reporting period, similar proportions were observed in Not recovered (9; 25.7%) and recovered or recovering (10; 28.6%) categories. Fatal outcomes were reported for 5 cases (5 events; 14.3%) (Table 16.91). Of these 5 cases, there were no specific trends observed, other than most of the cases (3 out of 5 cases) were from ≥70 years of age population. Four (4) out of 5 cases were considered of Brighton Collaboration Level-4 or 5, and 1 case was of Level-1 per Brighton Collaboration definitions of Level of Certainty.

Table 16.91. Summary of Outcomes of Thrombosis with Thrombocytopenia Related Events - Review Period 19 Jun 2022 to 17 Dec 2022

Event Outcome	Prior to Review Period		Review Period		Total # Events	% of Events
	# Events	% Total Events	# Events	% Total Events		
Fatal	32	14.9	5	14.3	37	14.8
Not Recovered/Not Resolved	44	20.5	9	25.7	53	21.2
Recovered/Resolved	35	16.3	3	8.6	38	15.2
Recovered/Resolved with Sequelae	7	3.3	0	0	7	2.8
Recovering/Resolving	28	13.0	7	20.0	35	14.0
Unknown	69	32.1	11	31.4	80	32.0
Grand total	**215**	**100.0**	**35**	**100.0**	**250**	**100.0**

Adolescents aged 12-17 years

Cumulatively there were two cases which were presented in PBRER#3. There were no reports of cases with TTS-related events received by the MAH in adolescents (12-17 years) during the reporting period.

Children aged <12 years

There were no reports of cases with TTS-related events received by the MAH through 17 Dec 2022 of TTS-related events in children <12 years of age.

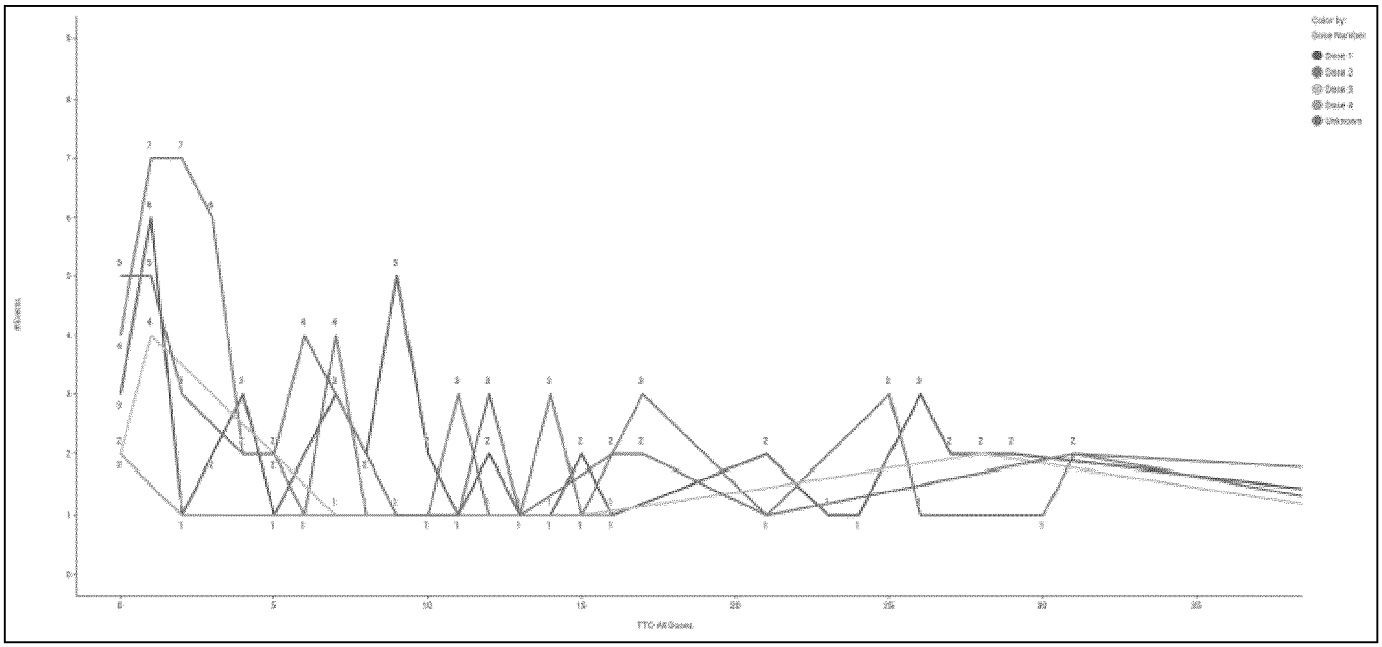
Thrombosis with Thrombocytopenia Syndrome (TTS) Cases After Dose 3 or Booster Dose

Cumulatively, there were 20 cases of thrombosis with thrombocytopenia related events reported following Dose 3 or greater. Of these 10 cases [edit: 10 is expected to by a typo, this number is expected to be 20], 3 were fatal reports, received during the reporting period of this PBRER. Details of these cases, including the fatal report, received during the current reporting period are presented in Appendix 11.13 [of the PSUR].

Health authority request: *The MAH should also address the following issues in the next PSUR: Thrombosis with Thrombocytopenia Syndrome (TTS): The MAH is requested, in the next PSUR, to provide a discussion on the pattern of TTO in TTS, and whether there are differences in TTO according to dose number.*

Response: A cumulative review of all reported cases of TTS-related events (230 cases) by dose number and TTO, did not show any reporting trend or notable temporal pattern in the TTO reported after any dose. As Figure 16-12 shows random peaks are observed for all doses; with most events observed after Dose-1 and Dose-2. This observation may be due to the current trend of more individuals receiving the first two doses than boosters.

Figure 16-12 Time to Onset of Events by Dose Number



Brighton Collaboration/ CDC Working Case Definition/ WHO Causality Assessment

During the reporting period, evaluation of 33 cases identified with thrombosis and thrombocytopenia related events using the Brighton Collaboration case definition for TTS [144] showed that there were One (1) report classified as Level 1–Definitive case, No reports classified as (Level-2 and Level-3) – Possible case, 15 reports classified as Level 4 - Not enough information, and 17 reports classified as Level 5 - Not a case of TTS.

According to the CDC working case definition for TTS, there were 3 reports classified as Tier 1, One (1) report classified as Tier 2 and 6 reports were unassessable due to the lack of information, including platelets levels; and 23 reports were classified as Not a case of TTS based on the report not meeting the case definition or on information available that provided a different clinical explanation for the classification of the events.

According to the WHO causality assessment, there were 5 reports classified as possible based solely on temporal association between the use of the product and the start of the events; however, a causal relationship cannot be excluded due to the lack of supporting information, including medical history, concomitant medications, clinical course, laboratory information, etc. There was 1 report considered conditional, 7 reports were considered as unassessable due to the lack of information, and there were 3 reports that were considered unlikely to be related to the vaccine due to prolonged TTO as well as comorbidities present in some of these patients that provide a more plausible explanation for the

occurrence of the events, and there were 16 events that were not provided a causality assessment as they were not a cases of TTS-related events.

Thrombosis with Thrombocytopenia Syndrome After Receiving Booster Dose with elasomeran/imelasomeran

No reports were received as of 17 Dec 2022 for individual receiving the elasomeran/ imelasomeran booster.

Thrombosis with Thrombocytopenia Syndrome After Receiving Booster Dose with elasomeran/davesomeran

No reports were received as of 17 Dec 2022 for individuals receiving the elasomeran/davesomeran booster.

Discussion

Thrombosis with thrombocytopenia syndrome is a potentially life-threatening condition associated with adenoviral-vectored COVID-19 vaccination.

Cases of cerebral venous sinus thrombosis after vaccination with the Ad26.COV2.S COVID-19 vaccine have previously been described Case patients receiving a COVID-19 vaccine from 14 Dec 2020 through 17 Dec 2022 with thrombocytopenia and thrombosis (excluding isolated ischemic stroke or myocardial infarction) were reported to the VAERS. Reporting rates for TTS were 3.83 per million vaccine doses (Ad26.COV2.S) and 0.00855 per million vaccine doses (mRNA-based COVID-19 vaccines) [145]. Analysis of the data reported during this reporting period does not provide evidence to support a causal association between TTS and elasomeran. Multiple reports lacked laboratory results and imaging test findings, moreover, number of reports were missing level of platelets or results of heparin-PF4 ELISA HIT antibody test. Cumulatively, the reporting rate of TTS for elasomeran is substantially lower than one report per million doses. In addition, in this reporting period most of the reports met neither the CDC nor Brighton definition for TTS, and of those that met the criteria for CDC or Brighton Collaboration definitions, the majority of the cases were considered unlikely related to the vaccine based on the WHO standardize case causality assessment guidance.

Review of the reported TTS-related events by TTO and dose did not show any trending in the occurrence of these events, with a higher number of the events reported after dose 1 and dose, indicating a higher volume of individuals receiving the initial primary series vaccination, but with no evidence of reports happening within any specific risk window.

The MAH will continue to monitor the occurrence of TTS with elasomeran or elasomeran/imelasomeran or elasomeran/davesomeran) and in all populations via routine pharmacovigilance and will be discussed in future reports.

Conclusion

The data provided in this PBRER describe sufficiently the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran cumulatively and during the reporting period. The benefit-risk evaluation remains positive. After careful review of all new safety data received during the reporting period, (19 Jun 2022 to 17 Dec 2022) for the risk of thrombocytopenia and thrombosis, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The risk of thrombocytopenia and thrombosis will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

The MAH has provided detailed data from the latest review period from 19 June 2022 to 17 December 2022 and a cumulative review of *Thrombocytopenia with Thrombosis Syndrome (TTS)* based on data from the global safety database and case reports covering the data period from 18 December 2020 to 17 December 2022. As the recent review period does not change the cumulated overall results significantly, the assessment mainly has its focus on the entire 2-year-period.

Cases were searched by tracking thromboembolic events and cross-checking these for the following preferred terms: "Acquired amegakaryocytic thrombocytopenia; megakaryocytes decreased; platelet count decreased; platelet maturation arrest; platelet production decreased; platelet toxicity; thrombocytopenia; megakaryocytes abnormal; platelet count abnormal; platelet disorder; plateletcrit abnormal; plateletcrit decreased; immune thrombocytopenia; HELLP syndrome [hemolysis (H), elevated liver enzymes (EL), and low platelets (LP)]; thrombotic thrombocytopenic purpura; thrombocytopenic purpura, platelet transfusion, petechiae, ecchymosis, purpura".

The MAH has identified cases according to both the CDC working definition and the Brighton Collaboration interim case definition for TTS, and has performed causality assessment utilizing the WHO-UMC standardized case causality assessment.

Review of the Global Safety Database

Cumulatively, 230 cases (250 events) of TTS and related preferred terms were identified for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. In total, 194 cases (84.3%) were medically confirmed, 224 cases (97.4%) were considered serious and 31 (13.5%) had a fatal outcome.

In the text the MAH has written there was 230 cases, 224 events. Number of events is expected to be larger than number of cases; number of events is 250 according to table 16.89, which seems more adequate. The "224" events is expected to be a typo. The MAH is reminded to proof read text and tables before submitting. If the discrepancy is not due to a typo, the MAH is requested to provide further clarification.

Observed Vs Expected Analysis

The tabulated O/E results include 230 observed cases corresponding to a cumulative reporting rate of 0.44 cases per 100,000 person-years which is less than expected according to the Dutch incidence estimate of 1.61 (RR = 0.27 [0.24, 0.31]) and also less than the expected Spanish estimate of 8.84 (RR = 0.05 [0.04, 0.06]).

Gender and age distribution

Of the 230 cases reported under TTS and TTS-related terms, 117 (51%) were in males, 107 (47%) in females, leaving 6 cases (3%) of unknown gender.

The majority (69%) of cases were reported in patients ≥50 years of age, with a median age of 63.0 years and an age range of 15-96 years of age (age unknown in 7 cases).

TTS in Adolescents (12-17 Years of Age)

Cumulatively, 2 cases of TTS/TTS-related events have been reported for adolescents. These have previously been described in details, and one was by the MAH assessed as BC level 1, CDC Tier 1 and WHO-UMC possible, while the other was BC level 4 and WHO-UMC conditional.

TTS in Children (<12 Years of Age)

There were no reports of TTS-related events for children <12 years of age cumulatively as of 17 December 2022.

Dose number and time to onset

The MAH has provided information on the number and percentage of TTS-related events by dose and time to onset in PSUR table 16.89. Looking at the total number of events by dose, dose 1 accounts for 22.0%, dose 2 for 29.2%, dose 3 for 7.2%, dose 4 for 1.6%, while as many as 40% (100 of 250 events) are of unknown dose number. According to the actual numbers, most cases appear to have occurred following dose 2 (73/250 events), which has now been seen through more review periods.

Despite most events apparently having followed dose 2, it should be kept in mind, that since the majority of events is of unknown dose number this pattern may be distorted. Likewise, there is not a clear indication of time to onset of reported preferred terms.

[Comment regarding wrongly interpreted numbers: The MAH states, that: "During the reporting period most of TTS-related events were reported as occurring after Dose 3 (7; 21.0%), a notable change from the prior review period in which events occurred most frequently after Dose 2 (65.0%) … The relatively greater number of reports received following Dose 3 could be attributed to the increasing number of Dose 3 elasomeran administrations during this report period (Table 16.89)."

This is partly incorrect: according to PSUR table 16.89 there were 7 events = 20% following dose 3 in the current reporting period (19 June 2022-17 December 2022). In the previous reporting period (01 January-18 June 2022) 29.5% (13 events) were reported following dose 3 but only 9.1% (4 events) followed dose 2 (previous PSUR table 16.125). So, for both the current and previous reporting period, the highest frequency is seen with dose 3 and no notable change is seen between review periods. It might be expected that the distribution of events by dose to some extent reflects the rollout of the vaccination program. By now data show that for the entire 2022 most events were reported following 3rd dose, and cumulatively for the complete 2-year-period most cases have been reported following 2nd dose, which possibly indicates a pattern with more events upon re-exposure to vaccine.]

Booster dose with elasomeran/imelasomeran or elasomeran/davesomeran

No reports were received as of 17 December 2022 for individuals receiving the elasomeran/ imelasomeran booster or the elasomeran/davesomeran booster.

Conclusion

The MAH has provided data for the review period and a cumulative review for the 2-year-period 18 Dec 2020 to 17 Dec 2022.

According to the O/E analysis there are fewer TTS and TTS-related events than expected compared to Dutch and Spanish incidence estimates.

For most of the reported TTS-related events following elasomeran, the dose number is unknown. For those of known dose numbers most events were observed after 1st and 2nd dose; this may reflect that more individuals have received the first two doses than boosters. However, more events have been reported following the 2nd dose than the 1st, and whether this is only coincidental or could be related to repeated exposure can be expected to be clarified through continued monitoring and registration of events by dose.

In TTS and TTS-related events reported in association with exposure to elasomeran little or no reports include heparin-PF4 ELISA HIT antibody test results. For TTS, also seen as vaccine-induced immune thrombotic thrombocytopenia (VITT), triggered in persons who have received adenoviral vector COVID-19 vaccines, heparin-PF4 antibodies are a part of the mechanism. The TTS-related events seen following vaccination with elasomeran have affected platelet concentration as a common trait, however, a suspected mechanism for this is not explained.

By now the data do not demonstrate a causal association between elasomeran and TTS and TTS-related events.

The MAH will continue to monitor TTS and TTS-related events using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

2.4.2. Single Organ Cutaneous Vasculitis (SOCV)

Source of the New Information

ModernaTx, Inc. queried the CTs and its GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature cumulative from 18 Dec 2020 to 17 Dec 2022, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

ModernaTx, Inc. was requested by a regulatory authority to continue to provide an overview of SOCV using Brighton Collaboration categorization, and to provide a WHO Causality assessment for each event assessed as Brighton level 1-3.

SOCV refers to vasculitis in arteries or veins of any size in a single organ, the skin, and has no features of systemic involvement. Some patients initially diagnosed with SOCV may develop other disease manifestations, warranting re-evaluation for other systemic vasculitides. Therefore, the MAH adopted the Brighton Collaboration definition, which provides a means of categorizing cases according to level diagnostic certainty, and which refers to small vessel vasculitis of the skin where systemic involvement has been excluded.

SOCV typically presents with a single crop of lesions consisting of palpable purpura (hemorrhagic papules), erythematous papules, urticarial lesions, vesicles, and hemorrhagic vesicles 7–14 days after exposure to a triggering agent. SOCV favors dependent areas, as well as areas affected by trauma or compressed by tight-fitting clothing. The lesions are usually asymptomatic, or associated with burning, pain, or pruritus. Residual post-inflammatory hyperpigmentation may persist for months after the primary process resolves [174]. Skin biopsy is the gold standard method for the diagnosis of cutaneous vasculitis, also allowing differential diagnoses from vasculitis mimics, such as vaso-occlusive conditions and other diseases.

Disease-inducing or promoting factors for SOCV are either post-infectious or drug-induced, but more than half of cases are considered idiopathic. Although non-immunologic factors such as direct infection of endothelial cells can cause vasculitis, most lesions are mediated by immunopathogenic mechanisms. Small vessel vasculitis can also be associated with connective tissue diseases, and it may be a heralding sign of such diseases, particularly systemic lupus erythematosus (SLE).

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB using selected PTs from the MedDRA SMQ Vasculitis (Narrow scope) to include the following PTs: Administration site vasculitis, Cutaneous vasculitis, Hemorrhagic urticaria, Hemorrhagic vasculitis, Injection site vasculitis, Palpable purpura, Purpura, Purpura non-thrombocytopenic, Urticarial vasculitis, Vaccination site vasculitis, Vascular purpura, and Vasculitic rash.

To characterize the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration Single organ cutaneous vasculitis case definition (SOCV) [174]:

- Level 1 (certain)
- Level 2 (probable)
- Level 3 (possible)

• Level 4 (reported SOCV with insufficient evidence to meet the case definition)

• Level 5 (not a case of SOCV)

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case as SOCV. It is not used to ascertain causality. Appendix 11.19 includes detailed summary of Cumulative cases that met Brighton's Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

Health Authority Request from PBRER#3:

Concerning Single Organ Cutaneous Vasculitis (SOCV), the MAH is requested to make an extra effort to provide the information missing to assess causality regarding the 2 cases deemed unassessable, and to update and re-evaluate all cases in the SOCV case listings in the next PSUR. The DLP of PSUR no 4 should be applied, and the MAH is requested to add clear argumentation where the MAH does not agree with the reporter or the description in the case narrative. Also, the MAH is requested to comment on the apparent discrepancy between the total number of literature reports on SOCV (n=47), the number of cases previously listed in PSUR (n=30) and the number of listed cases in the new appendices 1 and 2 (n=12) Appendix 11.22 [this seems to reference to an appendix in the PSUR no 3].

MAH Response:

Cases that are assessed as unassessable are as follows and following are the updated MAH comments:

[redacted]*):*

PSUR #3 MAH Comment: Literature report of a 14-year-old female patient who received elasomeran and on an unknown date, experienced cutaneous vasculitis with biopsy findings of infiltration of lymphocytes into the subcutaneous vessel wall with fibrinoid necrosis. No medical history or concomitant medications were provided. Laboratory evaluation including White blood cells, Rh factor, ESR, C3/C4, ANCA, ANA was normal except for slightly elevated CRP. In light of the missing information that would be beneficial in further characterizing causality, WHO-UMC causality is classified as unassessable.

Updated MAH Evaluation: ModernaTx, Inc. reviewed the full literature case report in detail. The authors describe a 14-year-old female without any previous medical history, who experienced cutaneous arteritis, also known as cutaneous polyarteritis nodosa (PAN), following Dose 2 elasomeran given four weeks after Dose 1. The patient had fever and fatigue the day after Dose 2, which resolved spontaneously the same day. Clinical features of cutaneous vasculitis were identified a week later with no obvious manifestations suggestive of extracutaneous involvement. A skin biopsy revealed infiltration of lymphocytes into the subcutaneous vessel wall with fibrinoid necrosis, compatible with the pathological diagnosis of medium-sized vessel vasculitis. The skin biopsy findings of vasculitis of medium-sized vessels are consistent with the authors' diagnosis of cutaneous PAN, however because PAN is characterized by specific clinical and histological features due to the involvement of medium-size vessels, it is envisioned to be defined separately from SOCV which involves small vessel vasculitis. Based on this exclusionary finding, this case is classified as Brighton Collaboration level 5 and is not a case of SOCV.

[redacted]*:*

PSUR #3 MAH Comment: Case report presented at a scientific meeting of a 49-year-old male patient who experienced erythema and purpura 9 days after receiving dose 1 of an unspecified mRNA vaccine with (presumably from biopsy) "perivascular lymphocytes, neutrophils, nuclear dust, and bleeding images were noted in the tissue at the purpura". No further information such as medical history, concomitant medications and clinical course was provided. In light of the missing information that would be beneficial in further characterizing causality, WHO-UMC causality is classified as unassessable.

Updated MAH Evaluation: The marketing partner originally transmitting the case to ModernaTx, Inc. indicated that follow-up will be performed and ModernaTx, Inc. amends WHO-UMC causality to conditional. While there are clinical features of SOCV, any level of diagnostic certainty cannot be established because the provided information does not exclude involvement of other organs, nor does it specify that the results are from a skin biopsy. Based on the provided information, this case is classified as Brighton Collaboration level 4 (reported SOCV with insufficient evidence to meet the case definition).

Upon receipt of any follow-up information such as the proprietary mRNA vaccine and date administered, event date (or information to determine TTO), biopsy source etc, a follow-up report will be submitted according to applicable reporting requirements.

Health Authority also stated that apparent discrepancy between the total number of literature reports on SOCV (n=47), the number of cases previously listed in PSUR (n=30) and the number of listed cases in the new appendices 1 and 2 (n=12) Appendix 11.19.

Response: The review of the published literature in PubMED retrieved 47 articles which are not necessarily valid case reports, as some of these 47 articles lacked one or more for the four basic elements required (identifiable patient, suspect drug, AE, reporter [if not author]) to create a valid ICSR. Furthermore, articles may contain general information, provide reviews, meta-analyzes or other scientific communications, and are returned in the search results due to the search strategy and keywords. It may also be that a literature article is shared by a regulatory agency as an individual case report which is captured in the safety database as a regulatory case rather than literature case. The apparent discrepancy noted by the health authority is reconciled by considering that PSUR lists the subset of cases that are classified as Brighton Collaboration Levels 1 to 3 for diagnostic certainty for SOCV from the larger set articles retrieved from the literature search. The new Appendices 1 and 2 (n=12) list the Literature Non-Study cases as requested by the health authority. Appendix 11.19.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected Analysis

See Appendix 11.3.

Literature Review:

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and SOCV Events to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 47 literature articles were retrieved using these search criteria for the review period (note that PBRER#3 and PBRER#4 each had 47 literature articles were retrieved which were different in each report). The literature search results were medically/scientifically reviewed. Most of these 47 articles are case reports presenting data on adverse cutaneous reactions or other conditions such as immune-mediated thrombotic thrombocytopenic purpura or thrombocytopenia. Review of these retrieved literature articles describe the occurrence of SOCV with COVID-19 vaccination but none of these provided compelling evidence of a causal association from mRNA vaccines. Overall, a detailed review of the search results found no articles with new and significant safety information.

Overview of Cases

For more details on SOCV cases please refer to Appendix 11.19.

GSDB

Cumulative review (SOCV, Cumulative to 17 Dec 2022)

Cumulatively, a total of 367 cases (and 380 events) were identified for vasculitis of which 197 cases were serious and 1 case had a fatal outcome secondary to systemic complications. There were 267 (72.8%) cases that were medically confirmed. Regulatory authority reports accounted for 82.8% of received reports (304 reports), followed by spontaneous case reports (45;12.3%) and literature reports (18; 4.9%). The largest number of cases originated from the USA (126; 34.3%) followed by France (60; 16.3%) and Germany (26; 7.1%).

There were disproportionately higher cases reported for females (244;66.5%) than for males (113;30.8%). 2.7% of cases had no information on gender. The age group with the highest number of cases was the 50-64 years group (117 cases: 31.9%) (Table 16.123). The median age of reported cases was 57.0 years, ranging from 14.0 years to 94.0 years.

During the reporting period, a total of 41 cases (and 42 events) were identified for vasculitis of which 27 cases were serious and none had a fatal outcome. There were 30 (73.2%) cases that were medically confirmed. Regulatory authority reports accounted for 85.4% of received reports (35 reports), followed by literature reports (6; 14.6%). The largest number of cases originated from France (13; 31.7%) followed by Germany (4; 9.8%) and Japan (4; 9.8%). Overall, the distribution for the reporting period is generally in line with that observed cumulatively.

Table 16.123 Case Distribution by Age Group, Cumulative as of 17 Dec 2022

Age Group All (11)	Prior to Review Period		Review Period		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15Y	1	0.3	0	0	1	0.3
16-17Y	1	0.3	1	2.4	2	0.5
18-24Y	4	1.2	3	7.3	7	1.9
25-39Y	53	16.3	7	17.1	60	16.3
40-49Y	45	13.8	5	12.2	50	13.6
50-64Y	107	32.8	10	24.4	117	31.9
65-74Y	59	18.1	8	19.5	67	18.3
75Y+	43	13.2	7	17.1	50	13.6
Missing	13	4.0	0	0	13	3.5
Grand total	**326**	**100.0**	**41**	**100.0**	**367**	**100.0**

Of the 380 events, 189 were serious and 191 were non-serious. Purpura was the most frequently reported event (242, 63.7%) with the majority of those reports being non-serious, followed by cutaneous vasculitis (87; 22.9%) events (Table 16.124). During the reporting period, Purpura (21; 50.0%) was most frequently reputed PT, similar to the cumulative reports. Overall, this pattern for the reporting period is generally in line with that observed cumulatively.

Table 16.124 Event Distribution by PT, Cumulative as of 17 Dec 2022

PT	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
	# Events	% of Total Events	# Events	% of Total Events		
Purpura	221	65.4	21	50.0	242	63.7
Cutaneous vasculitis	72	21.3	15	35.7	87	22.9
Urticarial vasculitis	16	4.7	3	7.1	19	5.0
Vasculitic rash	14	4.1	1	2.4	15	3.9
Vascular purpura	5	1.5	2	4.8	7	1.8
Palpable purpura	3	0.9	0	0	3	0.8
Vaccination site vasculitis	3	0.9	0	0	3	0.8
Haemorrhagic vasculitis	2	0.6	0	0	2	0.5
Injection site vasculitis	2	0.6	0	0	2	0.5
Grand total	**338**	**100.0**	**42**	**100.0**	**380**	**100.0**

Cumulative event distribution by dose number and time to onset (TTO) are described in Table 16.125. Most of the events were reported after Dose 1 (120; 31.6%), with a TTO within <4 days (55; 14.5%). Dose number and TTO were not reported for 175 events (46.1%). SOCV typically presents 7-14 days after exposure, so the relatively disproportionate number of events reported on post dose days 0-6 is likely driven by cutaneous injection reactions and other events such as purpura.

During the reporting period, event distribution by dose number and time to onset (TTO) are described in Table 16.125. Most of the events were reported after Dose 3 (8; 19.0%). Majority 25 events (59.5%). SOCV typically presents 7-14 days and similar pattern of TTO was observed in cumulative ad reporting period data.

Table 16.125 Event Distribution by Dose and TTO, Cumulative as of 17 Dec 2022

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
		# Events	% of Total Events	# Events	% of Total Events		
Dose 1	**Subtotal**	**115**	**34.0**	**5**	**11.9**	**120**	**31.6**
	0 days	16	4.7	0	0	16	4.2
	01-02	28	8.3	1	2.4	29	7.6
	03-04	10	3.0	0	0	10	2.6
	05-06	7	2.1	0	0	7	1.8
	07-13	33	9.8	3	7.1	36	9.5
	14-29	17	5.0	1	2.4	18	4.7
	30+	4	1.2	0	0	4	1.1
Dose 2	**Subtotal**	**57**	**16.9**	**1**	**2.4**	**58**	**15.3**
	0 days	7	2.1	0	0	7	1.8
	01-02	20	5.9	0	0	20	5.3
	03-04	7	2.1	0	0	7	1.8

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
		# Events	% of Total Events	# Events	% of Total Events		
	05-06	3	0.9	0	0	3	0.8
	07-13	11	3.3	0	0	11	2.9
	14-29	4	1.2	0	0	4	1.1
	30+	5	1.5	1	2.4	6	1.6
Dose 3	**Subtotal**	**16**	**4.7**	**8**	**19.0**	**24**	**6.3**
	0 days	1	0.3	0	0	1	0.3
	01-02	3	0.9	1	2.4	4	1.1
	03-04	3	0.9	0	0	3	0.8
	05-06	1	0.3	2	4.8	3	0.8
	07-13	5	1.5	1	2.4	6	1.6
	14-29	2	0.6	2	4.8	4	1.1
	30+	1	0.3	2	4.8	3	0.8
Dose 4	**Subtotal**	**0**	**0**	**1**	**2.4**	**1**	**0.3**
	14-29	0	0	1	2.4	1	0.3
Dose 5	**Subtotal**	**0**	**0**	**2**	**4.8**	**2**	**0.5**
	03-04	0	0	2	4.8	2	0.5
Unknown	**Subtotal**	**150**	**44.4**	**25**	**59.5**	**175**	**46.1**
	0 days	10	3.0	0	0	10	2.6
	01-02	19	5.6	1	2.4	20	5.3
	03-04	8	2.4	3	7.1	11	2.9
	05-06	3	0.9	0	0	3	0.8
	07-13	13	3.8	0	0	13	3.4
	14-29	7	2.1	2	4.8	9	2.4
	30+	8	2.4	2	4.8	10	2.6
	Event onset prior to first dose reported	2	0.6	0	0	2	0.5
	Missing	80	23.7	17	40.5	97	25.5
Grand total		**338**	**100.0**	**42**	**100.0**	**380**	**100.0**

Cumulatively, a total of 133 events (35.0%) were considered not recovered and 167 (43.9%) events were considered recovered or recovering (Table 16.126). Cumulatively, there has been 1 case with a fatal outcome ([redacted]). Summary of this fatal case is described below, and no fatal cases were reported for the review period.

Table 16.126 Event Distribution by Outcome, Cumulative as of 17 Dec 2022

Event Outcome	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
	# Events	% Of Events	# Events	% Of Events		
Fatal	1	0.3	0	0	1	0.3
Not Recovered/Not Resolved	123	36.4	10	23.8	133	35.0
Recovered/Resolved	77	22.8	11	26.2	88	23.2
Recovered/Resolved with Sequelae	1	0.3	3	7.1	4	1.1
Recovering/Resolving	63	18.6	12	28.6	75	19.7
Unknown	73	21.6	6	14.3	79	20.8
Grand total	**338**	**100.0**	**42**	**100.0**	**380**	**100.0**

Description of the Fatal Cases (Cumulatively as of 17 Dec 2022):

Cumulatively as of 17 Dec 2022, there was one fatal case which was presented in the previous PBRER. During this reporting period (19 Jun 2022 to 17 Dec 2022) there are no fatal reports.

Case Assessment using the Brighton Collaboration Case Definition and WHO-UMC Causality Assessment

Cumulatively, there have been a total of 367 cases (380 events) involving SOCV. All cases were medically reviewed and classified according to the criteria as specified in the SOCV case definition by the Brighton Collaboration [174] and 29 cases were identified as Levels 1 to 3. Note: two (2) cases which were previously assessed as Level-1 and Level-2 were re-assessed and considered as Level-4 and Level-5, hence cumulative counts in Brighton Collaboration Level 1 to 3 were decreased from PBRER#3 to PBRER#4.

For the reporting period, 41 cases including 42 events were received. Of these 41 cases, one was classified as Brighton Collaboration level 1 for SOCV and WHO-UMC causality was assessed as possible due to a plausible temporal relationship.

Cumulatively, 3 cases (4 events) met Brighton Collaboration Level 1 diagnostic certainty, 6 cases (8 events) met the criteria for Level 2, and 20 cases (20 events) for Level 3. All remaining cases either had insufficient evidence to meet the case definition or were determined not to be cases of SOCV. The 29 cases (32 events) that met case definition Levels 1 to 3 are presented in Appendix 11.19. These 29 cases that met Brighton Collaboration case definition for SOCV had a median age of 48 years, with a range from 28 years to 77 years. with. Eight patients were male and 21 were female.

Of the 29 cases meeting Brighton Collaboration level 1-3 for the case definition of SOCV, 28 were assessed as WHO-UMC possible for causality based primarily on temporal association between vaccination and TTO of events; however, a causal relationship cannot be excluded due to the lack of supporting information, including medical history, concomitant medications, clinical course, laboratory information, etc. There was 1 report that was considered unlikely related to vaccine exposure due to prolonged TTO.

Of the 32 events in the 29 cases that were classified as Level 1 to 3, 14 events (13 cases) occurred after Dose 1. Events mostly occurred during the period 7-13 days after vaccination which is when SOCV usually develops, although events are noted to occur earlier, and this may represent some variation in presentation. Table 16.127 presents TTO by Event and Dose for the 32 events in the 29 cases.

Table 16.127 Time to Onset by Event and Dose:

TTO Group in Days	Dose 1	Dose 2	Dose 3	Unknown	Grand Total
<7 Days	3	3		4	10
≥ 7 days and <14	8	1		2	11
≥ 14 days and <30	3		1	1	5
≥ 30 Days			1		1
Missing				5	5
Grand Total	**14**	**4**	**2**	**12**	**32**

In many of cases reported as SOCV, the information provided was inconsistent with the condition, generally due to multiple systemic events involving other organ systems occurring concurrently, or the provided information being insufficient for adequate assessment. In the vast majority of cases, biopsies were not performed, or results were not provided.

Subpopulation Analyzes

SOCV in Children (<12 Years of Age)

Cumulatively, no reports were received in children <12 years of age.

SOCV in Adolescents (12-17 Years of Age)

Cumulatively, three cases of SOCV were received in adolescents 12-17 years of age with one case (MOD-2022-645667) presented below which was received during this interval.

[redacted]: This literature-non-study case, concerns a 16-year-old male patient, with no medical history reported, who received heterologous dose 3 elasomeran vaccination (after Pfizer BNT162B2 primary series) and 3 days later experienced maculo-papular rash with purpuric aspect located on the lower limbs and forearms. Skin biopsy revealed superficial and deep dermal small vessels with lymphocytic perivascular infiltrate, wall aggression and endothelial cell swelling, in absence of thrombosis or fibrinoid necrosis. Patient was diagnosed as cutaneous lymphocytic vasculitis. SARS-CoV-2 test was negative. No further information on risk factors, treatment of the event was available in the report. Outcome of the event was not known at the time of report.

MAH Comment: This is a literature report of a 16-year-old male with no CM, MH provided who experienced cutaneous vasculitis 72 hours after elasomeran and earlier vaccine interchange with Comirnaty x 2. Skin biopsy showed lymphocytic perivascular infiltrate, wall aggression and endothelial cell swelling, in absence of thrombosis or fibrinoid necrosis. This report is classified as Brighton Collaboration level 2 (lacking necrosis) and WHO-UMC causality considered as possible considering plausible TTO with vaccine interchange as confounder.

SOCV in Patients After Bivalent Dose of elasomeran

SOCV After Receiving Booster Dose with elasomeran/imelasomeran)

Cumulatively through 17 Dec 2022, two (2) cases (2 events) of SOCV were reported in recipients of elasomeran/imelasomeran. One case was medically confirmed and there was no case with a fatal outcome. Both cases were reported during this reporting period and classified as Brighton Collaboration level 5. Details of these reports are as follows:

[redacted]: This regulatory authority case concerns a 22-year-old male patient, who had COVID-19 infection 3 weeks prior to vaccination,

received Influenza vaccine the same day as dose 4 elasomeran/imelasomeran vaccine; and one day post-vaccination, experienced the unexpected and non-serious event of purpura. No details of previous doses were provided. A week prior vaccination, a negative SARS-CoV-2 test was performed. Influenza vaccination remains as a confounder.

[redacted]: This regulatory authority case concerns an unknown adult female patient, with no relevant medical history reported, who experienced the unexpected, serious) event of cutaneous vasculitis after a dose (reported as "Dose 3 or more") of Spikevax bivalent vaccine was administered. No further details on onset date of the event, clinical course, diagnostic tests and treatment were reported. At the time of the latest report, the event was resolving.

SOCV After Receiving Booster Dose with elasomeran/davesomeran)

No reports elasomeran/davesomeran were reported as of 17 Dec 2022.

Review of Other Databases

Clinical Trial Data Review:

There are no new data available from the CTs database during this reporting period.

Subpopulation Clinical Trial Data Analyzes

Children ages 6 Months to 11 Years (mRNA-1273-P204 study): As of the last cut-off 21 Feb 2022, there are no cases for the topic of SOCV

Adolescents ages 12-17 Years (mRNA-1273-P203 Study): As of the last cut-off 27 Jan 2022, there are no cases for the topic of SOCV.

Discussion

SOCV refers to vasculitis in arteries or veins of any size in a single organ, the skin, and has no features of systemic involvement. Disease-inducing or promoting factors for SOCV are either postinfectious or drug-induced, but more than half of cases are considered idiopathic. SOCV typically presents with a single crop of lesions consisting of palpable purpura (hemorrhagic papules), erythematous papules, urticarial lesions, vesicles, and hemorrhagic vesicles 7–14 days after exposure to a triggering agent. Skin biopsy is the gold standard method for the diagnosis of cutaneous vasculitis, also allowing differential diagnoses from vasculitis mimics, such as vasoocclusive conditions and other diseases.

Through 17 Dec 2022, 662,871,167 doses of elasomeran were administered and during the same period, 367 cases SOCV were reported after elasomeran administration, yielding a very low reporting rate of 0.49 reports per million doses. The overall observed reporting rate was 0.86 cases per 100,000 person-years vs an expected rate of 6.03 cases per 100,000 person-years, which is significantly lower than expected. In addition, a substantial proportion of reports lack important information such as clinical presentation, TTO, concomitant medications/comorbidities and other pertinent details necessary to perform a proper evaluation. Very importantly, most reports lack documented results of skin biopsy necessary to establish a diagnosis of SOCV.

Based on the analysis of all the safety data available as of 17 Dec 2022, the MAH assessed those cases considered under the AESI of SOCV are temporally associated with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran. However, the information provided is inadequate and uncompelling to establish a causal association between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and SOCV.

Conclusion

After careful review of all new safety data received cumulatively and during the reporting period, the MAH does not consider there is evidence for a causal association between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and SOCV. The benefit-risk profile for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran remains favorable and ModernaTx, Inc. will continue to monitor events of SOCV using routine surveillance.

Rapporteur assessment comment:

In response to the Health Authority Request from PSUR#3 the MAH has 1) reevaluated 2 cases deemed unassessable, 2) updated and re-evaluated all cases in the SOCV case listings and 3) commented on the apparent discrepancy between the total number of literature reports on SOCV from different sources.

1) The 2 cases were reevaluated as "not a case" (alternative diagnosis more likely), and "conditional" (reported SOCV with insufficient evidence to meet the case definition), respectively. This is endorsed.

2) The update with 29 SOCV cases from the reporting period listed in PSUR Appendix 11.19 are acknowledged. All but one of these BC Level 1-3 cases are considered of WHO-UMC "Possible" causality, while one was considered "Unlikely". Endorsed.

3) The MAH explains the apparent discrepancy in the number of cases as a result of different selection criteria for each listing. This is acknowledged.

Furthermore, the MAH presents an update of the cumulative risk evaluation for the AESI SOCV:

O/E analysis (PSUR Appendix 11.3)

Overall, the rate-ratios reported with four different sources including ACCESS (ES and UK) were all below 1. Using the US Arora 2014 data as reference, the age and gender stratified analysis reporting rates did not deviate significantly as reported or considering 50% underreporting. If presuming 25% reporting, the previously reported cumulative risk ratios exceeding 2 in males 25-39 years-of-age in PSUR#3 (using ACCESS, Spain (BIFAP PC) 2019 as reference), were no longer present, while small but significant deviations (RR<1.4) were noted in females aged 25-39 years and 65-74 years in the present analysis. Considering that SOCV is visually recognizable in the skin (indicating biopsy), major underreporting may be less likely than with internal vasculitis manifestations.

In accordance with corePSUR19 guidance (EMA/362988/2021) the MAH is reminded in future reports to justify changes in reference population for O/E analyses. This has not been justified in the present situation.

Literature review

Using and updated search strategy (PSUR Appendix 12.1d), the MAH retrieved 47 publications of interest. However, a medical review of these articles describing the occurrence of SOCV with COVID-19 vaccination did not provide any new or compelling evidence of a causal association with mRNA vaccines. This is endorsed.

However, **the MAH is requested within the current procedure to give full reference to and comment on any new articles (compared to PSUR#3) considered among the 47 publications cumulatively referred to.**

Cases

During the reporting period, a total of 41 cases (and 42 events) were identified for vasculitis of which 27 cases were serious and none had a fatal outcome. There were 30 (73.2%) cases that were medically confirmed. Overall, the distribution for the reporting period is generally in line with that observed cumulatively. In PSUR Appendix 11.19a entitled "Single Organ Cutaneous Vasculitis (SOCV) Cases During

the Reporting Period – Case Evaluations (All) (elasomeran)" the 29 cases (32 events) that met Brighton Collaboration case definition for SOCV Levels 1 to 3 are presented. These 29 cases had a median age of 48 years, with a range from 28 years to 77 years. 8 patients were male and 21 were female. Among events, where the dose number was known (N=20), most (N=14) occurred in relation to dose number 1.

Of the 29 cases meeting Brighton Collaboration level 1-3 for the case definition of SOCV, 28 were assessed as WHO-UMC possible for causality based primarily on temporal association between vaccination and TTO of events; however, a causal relationship cannot be excluded due to the lack of supporting information, including medical history, concomitant medications, clinical course, laboratory information, etc. There was 1 report that was considered unlikely related to vaccine exposure due to prolonged TTO.

No new cases were reported in children. In adolescents, 1 case with BC Level 2 and WHO-UMC Possible causality, was reported during the current period.

Cases of SOCV in patients after Bivalent booster dose of Moderna vaccine targeting SARS-CoV2 was reported in association with elasomeran/imelasomeran (n=2), but not in recipients of elasomeran/davesomeran (n=0). The information provided on the 2 cases did not allow for causality evaluation at this time. **The MAH is requested to make an extra effort to gather further information concerning these two SOCV cases exposed to a Bivalent booster dose of Moderna vaccine targeting SARS-CoV2 and present status and updated information in the next PSUR.**

In conclusion, the PRAC rapporteur agrees with the MAH, that the current evidence is insufficient to establish a causal association between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and SOCV. The MAH should continue to report on SOCV as an AESI.

2.4.3. Guillain-Barre Syndrome (GBS)

New information presented below includes analysis performed on new cases received by MAH from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from the 18 Dec 2020 to 17 Dec 2022.

Background Relevant to the Evaluation

Several reports of Guillain-Barre syndrome (GBS) have been received by the Centers for Disease Control and Prevention (CDC) in the Vaccine Adverse Event Reporting System (VAERS) (CDC-Advisory Committee on Immunization Practices 2021) with the use of adenovirus vectored COVID-19 vaccines.

Guillain-Barre syndrome is an acquired degenerative, demyelinating neurological disorder classically characterized by progressive, symmetrical ascending paralysis. Absent muscle reflexes and loss of sensation are also commonly associated. The etiology remains unclear, but onset has been associated with viral illness, most commonly an upper respiratory infection (URI), next most commonly by gastrointestinal illness. Campylobacter jejuni and Haemophilus influenzae are the most commonly involved bacterial pathogens [146]. Miller Fisher syndrome (MFS) is a rare variant of GBS, observed in only about 1-5% of all cases of GBS in Western countries. In other geographic regions such as Taiwan and Japan, the proportion is higher, 19% and 25%, respectively. Miller Fisher syndrome presents with a clinical finding of ataxia, areflexia, and ophthalmoplegia. One of the main differences between MFS and more common variants of GBS is that the first nerve groups to demyelinate are commonly located in the cranium. This results in difficulties with balance and coordination, ocular muscle movement and vision impairment, and neuronal reflexes. Miller Fisher syndrome is a clinical diagnosis that often goes undiagnosed due to the low prevalence. Miller Fisher syndrome is a clinical diagnosis that can be confirmed serologically with positive anti-ganglioside GQ1b antibodies [147].

Guillain-Barre syndrome is believed to be an immune-mediated disorder resulting from the generation of autoimmune antibodies that cross-react with epitopes on peripheral nerves, leading to nerve damage. Auto-antibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infections. About two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a diarrheal illness or upper respiratory tract infection. The gastrointestinal bacterium Campylobacter jejuni has been found to stimulate cross reactive antibodies that can result in GBS, particularly acute motor axonal neuropathy. Other infectious agents that have been temporally associated with GBS include influenza viruses, Mycoplasma pneumoniae, HIV, Epstein-Barr virus, cytomegalovirus, and the vaccinia virus used in smallpox vaccines. Other exposures that appear to be temporally associated with GBS include surgical procedures and some malignancies, particularly Hodgkin's disease and other lymphomas. Various vaccines have also been temporally associated with GBS [148]. The only vaccines that have demonstrated elevated risk are influenza vaccines. Reviews of reports following use of the swine flu vaccine (1976) suggested a slightly increased risk for GBS (approximately one case per 100,000 vaccine recipients). Since then, increased risks for GBS associated seasonal influenza vaccines wax and wane; when risks are elevated, they are estimated to be approximately 1-2 cases/million doses administered (https://www.cdc.gov/ vaccine safety/concerns/guillain-barresyndrome.html).

A recent review using data from the US VSD suggested that the risk for GBS following receipt of COVID-19 mRNA vaccines in the period 1-21 days following vaccination was no different than the background rate [149].

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulative to 17 Dec 2022 for valid case reports of GBS received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following MedDRA PTs: "Acute motor axonal neuropathy, Acute motor-sensory axonal neuropathy, Bickerstaff's encephalitis, Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Miller Fisher syndrome, and Subacute inflammatory demyelinating polyneuropathy".

Cases were classified into one of five categories, following the Brighton Collaboration case definitions (CD) for GBS, which also includes evaluation for possible MFS. Both GBS and MFS have 3 levels of diagnostic certainty and the lowest, level 3, is limited to clinical findings. Critical for a report of GBS to meet CD level 3, is demonstration of absent or decreased deep tendon reflexes in the same limbs that are weak. Without this, it cannot meet any level of certainty. GBS/MFS overlap syndromes may occur, where there is weakness and features of MFS. In such cases the level of certainty should be based on the GBS criteria, but it can also be described as GBS/MF overlap syndrome [150]:

- Level 1 (Definitive case)
- Level 2 (Probable case)
- Level 3 (Positive case)
- Level 4 is a reported event of GBS/MFS with insufficient evidence to meet level 1, 2 or 3 of the CD
- Level 5 (Not a case)

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Appendix 11.14 includes detailed summary of reporting period cases that met Brighton Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed Vs Expected Analysis

See Appendix 11.3.

Overview of Cases

Cumulative Review (GBS, cumulative to 17 Dec 2022)

Cumulatively, a total of 683 cases of GBS and related PTs were identified for elasomeran. Of the 683 cases, 673 were serious and 10 cases had fatal outcomes. The 683 cases of GBS yielded 713 events, of which 700 were serious. Of the 683 cumulative cases of GBS, 524 cases (76.7 %) were medically confirmed. Most of the cases were received from regulatory agencies (555; 81.3%).

Cumulatively, the 683 cases reported under the GBS-related terms showed that distribution in males (349; 51.1%) was higher than in females (319; 46.7%), and in 15 cases;(2.2%) gender was not known. The majority of events were reported in patients >50 years of age, with a median patient age of 57.0 years (range 13 to 120 years of age) (Table 16.92).

The majority of GBS associated events, 82.3% were captured as PT "Guillain-Barre syndrome" (Table 16.93).

Cumulatively, when dose number and time to onset could be determined, the TTO of GBS events after Dose 1 (173; 24.3%) or Dose 2 (169, 23.7%) was comparable with a drop-off after subsequent vaccinations (Table 16.94).

GBS in Children (<12 Years of Age) (Cumulative as of 17 Dec 2022)

There were no reports of GBS-related events for children < 12 years of age cumulatively through 17 Dec 2022.

GBS in Adolescents (12-17 Years of Age) (Cumulative as of 17 Dec 2022)

Cumulatively, a total of 5 cases of GBS-related PTs were reported for adolescents. All five cases were serious, and none had fatal outcome. Of the 5 cumulative cases, 4 cases were medically confirmed. More cases were reported in females (4 cases; 80%) compared to males (1 case; 20%). All 5 cases were received from regulatory authorities: one case each from Argentina, France, Germany, Japan, and Spain. Of the 5 events, 3 events had not recovered/ not resolved, and 2 events were recovering/resolving.

GBS in Patients After a Third Dose or Booster Dose of elasomeran (Cumulative as of 17 Dec 2022)

Cumulatively 81 cases (80 serious; one fatal case) of GBS-related PTs occurred after Dose 3 or a booster dose of elasomeran was administered. The 81 cases included 82 events (81 serious events). There were 58 medically confirmed reports of GBS in patients receiving a Dose 3 or a booster dose of elasomeran.

Reporting Period 19 Jun 2022 to 17 Dec 2022

During the reporting period, a total of 72 cases of GBS-related PTs were identified for elasomeran. Of the 72 cases, 71 were serious with three cases having a fatal outcome. Of the 72 cases, 50 (69.4%) were medically confirmed.

The event outcomes reported were as follows: 18 (25.0%) events were not recovered/ not resolved, 17 (23.6%) events were recovering/resolving, 13 (18.1%) events recovered/resolved with sequela, 8 (11.1%) events had recovered/resolved, 3 (4.2%) fatal events, and 13 (18.1%) events did not have a reported outcome. The distribution of cases was higher in males (42; 58.3%) compared to that in females (27; 37.5%), and (3; 4.2 %) cases did not specify gender. Most of the reports described patients ≥50 years of age (47; 65.3%) (Table 16.95).

Fatal Case Summary (Review Period 19 Jun 2022 to 17 Dec 2022)

During this reporting period, 3 cases ([redacted], [redacted], [redacted]) with fatal outcomes were received. These reports did not meet Brighton Collaboration Level 1-3 of diagnostic certainty for GBS and are not discussed further here.

Brighton Case Collaboration Case Definition.

Evaluation of the 72 cases received in the reporting period was conducted using the Brighton Collaboration case definition for Guillain-Barre and MFSs.

A review of Level 1-3 cases received during the reporting period was performed. A total of 9 cases meeting Level 1-3 Brighton Collaboration case definition for Guillain-Barre were reported. Three cases met Level 1 case definition of diagnostic certainty, four cases met Level 2 case definition, and two cases met Level 3 case definition.

An analysis of these cases by Brighton Collaboration criteria requires clinical interpretation and judgement. Often, there is a significant level of uncertainty due to missing information. For instance, WHO causality is informed by TTO and temporal relationship, which largely guides the assessment of the reviewer. Dose number and time to onset from vaccine administration were often unavailable. Concomitant medications, comorbid medical conditions and treatment for the event were also infrequently described. Very importantly, key information necessary to apply the Brighton GBS case definition and determine the level of diagnostic certainty such as flaccidity and presence/absence of reflexes, results of cerebrospinal fluid analysis, electrophysiologic studies or other investigations were often not provided. The absence such evidence affects the reviewer's ability to determine the level of diagnostic certainty.

GBS in Children (<12 Years of Age) (Reporting Period-19 Jun 2022 to 17 Dec 2022)

There were no reports of GBS-related events for children < 12 years of age during the reporting period.

GBS in Adolescents (12-17 Years of Age) (Reporting Period - 19 Jun 2022 to 17 Dec 2022)

There were no reports of GBS-related events for Adolescents (12-17 years of age) during the reporting period.

GBS in Patients After a Third Dose or Booster Dose of elasomeran) (Reporting Period-19 Jun 2022 to 17 Dec 2022)

During the review period, there were 26 cases (26 serious; one fatal case) of GBS and GBS-related PTs reported following the administration of Dose 3 and above of elasomeran. Of the 26 cases, 20 cases were medically confirmed.

A total of 5 cases meeting Level 1-3 Brighton Collaboration case definition for Guillain-Barre were reported after Dose 3. One case met Level 1 case definition of diagnostic certainty, two cases met Level 2 case definition, and two cases met Level 3 case definition.

Guillain-Barre Syndrome After Receiving Booster Dose with elasomeran/imelasomeran

During this reporting period MAH received one case ([redacted]) of GBS-related PTs occurring after receiving elasomeran/imelasomeran. The health authority report concerned a 31-year-old female patient with Urinary and respiratory tract infection approximately 10 days prior to vaccination, no concomitant medications reported, who experienced GBS 1-2 days after elasomeran/imelasomeran as dose 3 with no information provided describing vaccine doses 1 and 2. Patient had symptoms consistent with GBS, and CSF revealed protein-cell dissociation. Nerve conduction study was unremarkable.

MAH comment: Based on the clinical presentation and diagnostic evaluation revealing protein-cell dissociation and unremarkable nerve conduction study, this report is classified as Brighton Collaboration

level 2 for GBS and WHO-UMC causality is assessed as possible with recent upper respiratory tract infection noted as possible confounder.

Guillain-Barre Syndrome After Receiving Booster Dose with elasomeran/davesomeran

During this reporting period MAH received one case ([redacted]) of GBS-related PTs occurring after receiving elasomeran/davesomeran. The HCP report concerned a 72-year-old man who experienced GBS 2-3 weeks after receiving elasomeran/davesomeran as dose 5 and the influenza vaccine. The patient reportedly experienced symptoms including severe pain in "both deltoid arms where he got the injections" for days, imbalance that went to his legs and difficulty walking. He was seen in the ED where a lumbar puncture showed protein and confirmed GBS after which the patient was admitted and had plasmapheresis. The pain still persists as shooting/poking discomfort.

MAH comment: The information provided yields insufficient clinical or objective laboratory evidence to meet any level of the case definition for GBS.

Discussion

Out of the 72 cases identified in the reporting period (19 Jun 2022 to 17 Dec 2022), 71 were serious with 9 of those cases evaluated as Level 1-3 according to the Brighton Collaboration case definition discussed above. Cases meeting Brighton Collaboration Level 4 and 5 were generally poorly described and most of those cases did not meet overall criteria for diagnostic certainty because they lacked clinical presentation and laboratory confirmation with evidence of decreased nerve conduction and cytoalbuminologic dissociation. Some cases provided alternative etiologies for the events.

During the reporting period, most cases (including events from Level 4 and Level 5), were consumer reports or reports received from regulatory authorities. These types of reports limit the reviewer's ability to obtain further follow-up information and/or obtain medical confirmation which hinders overall efforts to provide a proper assessment of causality.

There were 2 reports (one each) of patients who received Spikevax bivalent (elasomeran/imelasomeran and elasomeran/davesomeran vaccines, neither of which were informative to furthering the safety understanding of GBS with the bivalent vaccines.

The clinical spectrum of events in this reporting period was similar to that reported in the previous PBRER. Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported GBS, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Conclusion

After careful review of all new safety data received cumulatively and during the reporting period in reports of GBS, the MAH considers there is no evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and GBS, and the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. ModernaTx, Inc. will continue to monitor events of GBS using routine surveillance.

Repporteur assessment comment:

The MAH has provided a cumulative review of Guillain-Barré Syndrome (GBS) based on data from the global safety database and case reports covering the data period from 18 December 2020 to 17 December 2022.

Preferred terms in the queries were 'acute motor axonal neuropathy', 'acute motor-sensory axonal neuropathy', 'Bickerstaff's encephalitis', 'chronic inflammatory demyelinating polyradiculoneuropathy', 'demyelinating polyneuropathy', 'Guillain-Barré syndrome', 'Miller-Fisher syndrome', 'subacute inflammatory demyelinating polyneuropathy'.

The MAH has assessed all cases according to the Brighton Collaboration case definitions for GBS (GBS and MFS) and has furthermore performed causality assessment utilizing the WHO-UMC standardized case causality assessment scale. Most cases did not meet the overall criteria for diagnostic certainty according to the BC case definitions.

Review of the Global Safety Database

Cumulatively, a total of 683 cases (713 events) of GBS and related preferred terms were identified for elasomeran. Of these, 673 cases (98.5%) were considered serious and 10 (1.5%) had fatal outcomes. Of the 683 cumulative cases of GBS, 524 cases (76.7 %) were medically confirmed.

Only two cases have been reported following the bivalent elasomeran-containing COVID-19 vaccines, one case was after elasomeran/imelasomeran, the other after elasomeran/davesomeran.

Age and gender distribution

Of the 683 cases reported under the GBS-related terms, 349 (51.1%) were in males, 319 (46.7%) in females, leaving 15 cases (2.2%) of unreported gender. The majority were reported in patients > 50 years of age, with a median age of 57.0 years and a range from 13 to >100 years of age.

GBS in Children (<12 Years of Age)

Cumulatively, there were no reports of GBS-related events in children < 12 years of age.

GBS in Adolescents (12-17 Years of Age)

No cases in adolescents were reported in the reporting interval. Cumulatively, five cases of GBS and GBS-related preferred terms were reported in adolescents. All were serious, but none were fatal.

Dose number and time to onset

In the majority of cases (40.5%), the dose number was unknown. In cases with the dose number provided, the GBS and related events were reported most frequently after D1 (24.3%), followed by D2 (23.7%), D3 (10.7%) and D4 (0.85).

Irrespective of the dose number, GBS and related events mostly occurred >7 days post-vaccination.

Relevant literature

After the DLP of the current PSUR, an Italian population-based study (Morciano et al.2023*) was published that indicated a possible association between elasomeran and GBS. This study aimed to investigate the association between anti-COVID-19 vaccines and subsequent onset of GBS in the population aged ≥12 years. The study population included persons aged ≥12 years old from five Italian regions. The study period was 27 December 2020 – 30 September 2021. The COVID-19 vaccines investigated were the four different vaccines that were used during the anti-COVID-19 vaccination campaign in the five Italian regions of interest; two mRNA vaccines (mRNA-1273 from Moderna and BN162b2) and two viral vector vaccines (ChAdOx1-S and Ad26.COV2-S). The measured exposure was the 1st and 2nd dose of either one of the vaccines. The exposure risk interval was defined as 0-42 days after vaccination.

During the study period, 27,038,926 doses of anti-COVID-19 vaccines (D1 or D2) were administered to 15,986,009 persons aged ≥12 years of age. The overall vaccination coverage was 67.6% but exceeded

85% in those ≥60 years of age. During the 42-day risk interval, an increased risk of GBS was found for the mRNA-1273 vaccine (both after D1 and D2) and for the ChAdOx1-S vaccine (after D1), but not for the other two vaccines. A subgroup analysis by age defined increased risk of GBS with mRNA-1273 vaccine specifically among those aged ≥60 years after both D1 and D2 (RI=7.71; 95% CI 2.38-24.97). Please refer to the publication, for further details regarding the study, including the subgroup analysis and sensitivity analyses.

Conclusion

The cumulative data drawn from the cases reported to the MAH, including observed vs. expected analysis, does not rise a concern about GBS or any specific related events following vaccination with elasomeran or elasomeran-containing COVID-19 vaccines. The recent Italian study by Morciano et al. indicated an increased risk of GBS following vaccination with mRNA-1273 vaccines. However, there are uncertainties associated with the study, such as the fact that a 42 days risk interval after each of the doses (D1 and D2) was likely overlapping as the interval between vaccinations can be as short as 21-28 days, the difference depending on which vaccine is given.

Epidemiologically, GBS is described with a bimodal age distribution mainly affecting individuals age 15-35 years old and 50-75 years old, although all age groups can be affected. So, although the Italian study found an association between Moderna vaccine and GBS specifically for individuals ≥ 60 years old, this should be seen in light of higher incidence of GBS in the elderly and high vaccination rates in this age group (>85% in the study)

Thus, overall, available evidence does not allow to establish causal association between GBS and vaccination with elasomeran or elasomeran-containing vaccines.

The MAH should continue monitoring of GBS and related events using routine surveillance.

* Morciano C, Spila Alegiani S, Menniti Ippoliti F, Belleudi V, Trifirò G, et al. Post-marketing active surveillance of Guillan Barré Syndrome following vaccination with anti-COVID-19 vaccines in persons aged ≥12 years in Italy: a multi-database self-controlled case series study. medRxiv 2023.01.17.23284585; doi: https://doi.org/10.1101/2023.01.17.23284585.

2.4.4. Multisystem Inflammatory Syndrome (MIS-C and MIS-A)

Source of the New Information

Information presented below includes analysis performed on cases received and entered into the GSDB of ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

Multisystem Inflammatory Syndrome in Children (MIS-C) was first recognized in the UK in Apr 2020, in a fraction of children who develop a life-threatening hyperinflammatory state 4–6 weeks after infection with primary COVID-19 in the pandemic. A similar condition has also been reported as a rare complication of COVID-19 in adults (MIS-A). It is currently unknown if MIS-C/A might follow immunization against SARS-CoV-2, therefore, a need exists to define this potential entity for monitoring as an AE following immunization.

Children who develop MIS-C are generally previously healthy individuals. The primary COVID-19 infection in these patients is almost universally mild or asymptomatic. They typically present to medical attention on day 3–5 after developing a persistent fever associated with gastrointestinal symptoms (pain, vomiting, diarrhea), evidence of mucocutaneous inflammation (rash, conjunctivitis, oromucosal changes),

lymphopenia, and high levels of circulating inflammation (for examples, Elevated CRP, erythrocyte sedimentation rate [ESR], ferritin, or procalcitonin). A subset of MIS-C patients develops severe disease including hypotension/shock and evidence of cardiac involvement including myocarditis, myocardial dysfunction, and coronary artery changes. Immune modulation has been used with best supportive care to treat MIS-C, leading in most cases to prompt resolution of the inflammation. Fatal cases are rare. Given the emerging nature of this disorder, long-term outcomes are unknown, but the overwhelming majority of children appear to return to their pre-morbid baseline with respect to cardiac status.

From early in the pandemic, it was clear that a subset of adult patients experiences a severe hyperinflammatory response during primary SARS-CoV-2 infection. After MIS-C was recognized, a similar presentation in adult patients, MIS-A, was appreciated as a distinct clinical entity. MIS-A has been recognized as a severe illness requiring hospitalization in a person aged >21 years, with laboratory evidence of current or previous (within 12 weeks) SARS-CoV-2 infection, severe extrapulmonary organ dysfunction (including thrombosis), laboratory evidence of severe inflammation, and absence of severe respiratory disease. Patients with MIS-A have been reported up to age 50 years and, compared to MIS-C, are more likely to have underlying health conditions and experience an identifiable antecedent respiratory illness. MIS-A patients otherwise have remarkably overlapped clinical features with MIS-C, although the severity of cardiac dysfunction, the incidence of thrombosis and the mortality of MIS-A may be higher. The prevalence of MIS-C in communities experiencing widespread COVID-19 infections is unclear but has been estimated at 2/100,000 children. MIS-A appears to have an even less clear prevalence [151].

During the reporting period, there was no new information on epidemiology or CD available. The Brighton Collaboration Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) defines MIS-C as < 21 years and MIS-A ≥ 21 years. Based on the presentation and duration of fever, presentation of clinical features, for example, signs of mucocutaneous involvement (erythema, nonexudative conjunctivitis, et al), gastrointestinal involvement (abdominal pain, vomiting, diarrhea, et al), presence of shock/hypotension, and or neurologic involvement (altered mental status, paresthesia, et al); Laboratory evidence of inflammation such as elevated CRP, ESR, ferritin, or procalcitonin; measures of disease activity such as elevated BNP, NT-proBNP, troponin, neutrophilia, lymphopenia, thrombocytopenia, evidence of cardiac involvement by echocardiography or physical stigmata of heart failure, ECG changes consistent with myocarditis or myo-pericarditis; and following COVID-19 infection or vaccination; a MIS-C/A may be classified into one of five levels of diagnostic certainty, refer to the section below.

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for valid case reports of MIS-related events received from HCP, HA, consumers, and literature, worldwide, for the elasomeran, elasomeran/imelaosomeran and elasomeran/davesomeran using the MedDRA PTs of Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, and Systemic inflammatory response syndrome.

Identified cases were evaluated following the Brighton Collaboration Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A): Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data, and were classified into one of five levels of diagnostic certainty:

- Level 1 - Definitive case
- Level 2 - Probable case (Divided into Levels 2a and 2b)
- Level 3 - Possible case (Divided into Levels 3a and 3b)
- Level 4 - Insufficient Evidence

• Level 5 - Not a case of MIS-C/A

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [65].

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on MIS cases please refer to Appendix 11.15.

Observed vs Expected Analysis

See Appendix 11.3.

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and Multisystem Inflammatory Syndrome to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved.

A total of 352 literature articles were retrieved using these search criteria for the review period. The literature search results were medically/scientifically reviewed. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Overview of Cases

Cumulatively, through 17 Dec 2022, a total of 166 cases (167 events) with MIS-related terms have been reported, with 159 serious cases (95.8%) and 143 cases medically confirmed. There were 7 cases (4.2%) with fatal outcomes.

There were 70 cases (42.2%) that involved male patients, 94 cases (56.6%) that involved female patients and 2 (1.2%) cases with unknown genders. The mean patient age was 54.2 years (SD 19.5), with a median age of 58 years (min 12 /max 86); 9 cases were missing age data. Majority of cases were from the United States (62.7%) followed by the EEA (21.1%).

Multisystem Inflammatory Syndrome (Reporting Period – 19 Jun 2022 to 17 Dec 2022)

During the reporting period, a total of 20 cases (20 events) containing MIS-related events were reported, and 14 cases medically confirmed. All cases were serious with 1 case (1 event) with a fatal outcome. There were 7 (35%) cases that involved male patients, 12 cases (60%) involved female patients; and 1 (5%) with unknown gender. The mean patient age was 44.9 years (SD: 18), with a median age of 47 years (min: 19 /max: 69); 1 case was missing age data. There were 5 cases (25%) reported in the 18–24-year-old and 65–74-year-old age group. Other age groups were reported somewhat less frequently (Table 16.96)

Table 16.96 Number and Percentage of Cases Reporting MIS-related Events by Age and Gender-Reporting Period 19 Jun to 17 Dec 2022

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	0	0.0	0	0.0	0	0.0	0	0
18-24Y	2	10.0	3	15.0	0	0.0	5	25.0
25-39Y	1	5.0	1	5.0	0	0.0	2	10.0
40-49Y	3	15.0	0	0.0	0	0.0	3	15.0
50-64Y	2	10.0	2	10.0	0	0.0	4	20.0
65-74Y	4	20.0	1	5.0	0	0.0	5	25.0
75Y+	0	0.0	0	0.0	0	0.0	0	0
Missing	0	0.0	0	0.0	1	5.0	1	5.0
Grand total	**12**	**60.0**	**7**	**35.0**	**1**	**5.0**	**20**	**100**

The two most reported MIS-related events were Multisystem inflammatory syndrome (6; 30%); and Systematic inflammatory response syndrome (5, 25.0%) (Table 16.97)

Table 16.97 Number and Percentage of MIS-related Events by PT-Reporting Period 19 Jun to 17 Dec 2022

PT	# Events	% Total Events
Multisystem inflammatory syndrome	6	30.0
Systemic inflammatory response syndrome	5	25.0
Cytokine storm	3	15.0
Multisystem inflammatory syndrome in adults	3	15.0
Cytokine release syndrome	3	15.0
Grand total	**20**	**100.0**

There were 16 events (80%) with insufficient data to calculate TTO, and 16 events (80%) had missing dose information. There were no events following dose 1, 2 events (10%) following dose 2, and 1 event (5%) following dose 3 and 4. (Table 16.98). The average TTO of the reported events was 5.8 days (SD: 11.9) and the median was 1 day (min: 0/max: 27). All events except one (19; 95%) were reported in less than 7 days after vaccination.

Table 16.98 Number and Percentage of MIS-related Events by Dose Number and Time to Onset (TTO)–Reporting Period 19 Jun to 17 Dec 2022

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	*Subtotal*	*0*	*0*

Dose Number	TTO (Days)	# Events	% Total Events
Dose 2	*Subtotal*	*2*	*10.0*
	01-02	2	10.0
Dose 3	*Subtotal*	*1*	*5.0*
	0 days	1	5.0
Dose 4	*Subtotal*	*1*	*5.0*
	0 days	1	5.0
Unknown	*Subtotal*	*16*	*80.0*
	14-29	*1*	*5.0*
	Missing	15	75.0
Grand total		**20**	**100.0**

Fatal Case Summaries

There was 1 case (1 event) with a fatal outcome received during this reporting period. Case summarized below.

[redacted] **(WWID: US-[redacted]):** This is a Literature non-study case concerning a 23-year-old male patient, with no medical history reported, who experienced Multisystem inflammatory syndrome in adults (MIS-A), Toxic epidermal necrolysis, events of Ventricular fibrillation and Cardiac arrest. Patient presented to the emergency room with fever, cough, shortness of breath, fatigue and painful rashes all over his body. Patient was diagnosed with COVID-19 three weeks prior which resolved after 3 days. He had received 2 doses of elasomeran vaccine 6 months prior. Physical exam revealed macular erythematous rash in his trunk and extremities. Leukocyte count was 4 k/uL, hemoglobin 15.5 g/dL, platelets 99 k/uL, sodium 126 mmol/L, bicarbonate 20mmol/L, blood urea nitrogen 30 mg/dL, creatinine 2.2 mg/dL, lactate 5.1 mmol/L, ferritin >7500 ng/mL, total bilirubin 7.6 mg/dL, AST 298 U/L, ALT 291 U/L, ALP 106 U/L, procalcitonin 14.71 ng/mL, D-dimer 11.98FEUug/mL. Troponin-I peaked at 1359 pg/ml. CT angiography of the chest, venous doppler and echocardiogram were normal. An extensive infectious disease workup was negative. He was suspected to have MIS-A from recent COVID-19. He was started on methylprednisolone 1g/day, intravenous immunoglobulin, anakinra and empiric antibiotics. Over the next 2 days, there was progression of rash with sloughing of skin in his trunk, back and extremities with bullae on his legs, and thigh sparing the face. Skin biopsy revealed Toxic Epidermal Necrolysis. On day 3, patient had a cardiac arrest from ventricular fibrillation, but was successfully resuscitated. Subsequently, he was intubated and required escalating vasopressor support for shock. On day 5, patient developed non-purulent conjunctivitis, and was transferred to a higher center with a burn's unit on day 6. However, despite aggressive supportive measures he succumbed to refractory shock the following day.

Company Assessment: The authors of the article wrote that the patient fit the criteria for MIS outlined by CDC, including fevers, rash with non-purulent conjunctivitis, hypotension and thrombocytopenia, several laboratory criteria, negative infectious workup with a history of recent COVID-19 disease 3 weeks prior. However, the only temperature record was 97.3 F normal, and Blood record showed 116/78 mmHg no hypotension. The clinical presentation seems more to relate to the confirmed Toxic Epidermal Necrolysis (TEN), in which liver injury is common and thrombocytopenia is usually linked to a bad prognosis. Unfortunately, concomitant medications were not reported which will allow to provide more information on the diagnosis of TEN. Shock and system organ failure may well be the primary causes of death in TEN. The case is considered level 5 for MIS-A, due to the alternative etiology of TEN. The WHO causality thus is not applicable for MIS-A.

Multisystem Inflammatory Syndrome (MIS) in Children (<12 years old)–Reporting Period 19 Jun 2022 to 17 Dec 2022

During this reporting period, there were no cases received by the MAH of MIS-related events in children less than 12 years old.

Multisystem Inflammatory Syndrome (MIS) in Children (MIS-C) (Including Adolescents (12 to 17-years-old) and 18 to 20 years old according to case definition)–Reporting Period (19 Jun 2022 to 17 Dec 2022)

There were no cases in the 12-17 adolescent age group. However, during this reporting period, there were 1 case (1 event) reporting MIS-C related events in 18–20-year-olds. The case involved a 19-year-old male whose event outcome is listed as recovered.

Multisystem Inflammatory Syndrome in Patients After a Third Dose or Booster Dose of elasomeran – Reporting Period 19 Jun 2022 to 17 Dec 2022

During the reporting period, there were two cases in female patients, both medically confirmed received by the MAH of MIS-related events occurring on the same day following a 3rd or booster dose of elasomeran.

Brighton Collaboration Case Definition Evaluation/ WHO Causality Assessment

A review of MIS-C/A related cases with diagnostic certainty level 1–3 according to the Brighton Collaboration case definition including WHO causality assessment was performed. The following were the findings from the analysis:

There was 1 report classified as Level 1, 2 report as Level 2b, and no reports as Level 3a or 3b. In 2 of those 3 MIS-C/A related cases with diagnostic certainty level 1–2 according to the Brighton Collaboration case definition, WHO standardized causality assessment, was classified as possible based on temporal association between the use of the product and the start of the events, and a causal relationship cannot be excluded due to the lack of other information.

There was 1 report that was considered unlikely to be related to the vaccine, due to the presence of comorbidities that provided a more plausible explanation for the occurrence of the events and over 9 months after last vaccination.

Multisystem Inflammatory Syndrome After Receiving Booster Dose with elasomeran/imelasomeran

There are no cases of MIS-related events received by the MAH after receiving booster dose with elasomeran/imelasomeran during this reporting period.

Multisystem Inflammatory Syndrome After Receiving Booster Dose with elasomeran/davesomeran

There are no cases of MIS- related events received by the MAH after receiving booster dose with elasomeran/davesomeran during this reporting period.

Discussion

Based on the analysis of all the safety data available reported during this reporting interval, the MAH considers that the majority of cases included under the AESI of MIS-C/A provided insufficient information for medical assessment or were confounded due to the reported events including TEN, COVID-19 infection, cytokine storm related events and others in the period right after vaccination.

Conclusion

A review of the data received during this reporting period showed that there is currently insufficient evidence to suggest a causal relationship between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and MIS-C/A at this point.

Based on the analysis of all the safety data received during the reporting period and cumulatively, the MAH considers that cases included under the AESI of MIS-C/A, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety issue of concern and the information provided is inadequate to provide evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and MIS-C/A. ModernaTx, Inc. will continue to monitor events for MIS-C/A using routine surveillance. A follow-up questionnaire was implemented to obtain additional information for cases reporting MIS-related events. The questionnaire has not increased the reporting of essential details. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has reviewed the AESI MIS-C/A for the reporting period 19/06/2022 to 17/12/2022.

Observed versus expected (O/E) analysis

As recommended, the O/E analysis was based on ACCESS data (here from NL and ES, both 2019). Overall, no significantly increased reporting was observed, neither cumulatively nor in the reporting interval.

An age and gender stratified sub analysis was as previously performed using the 2019 ACCESS database from ES, representing the highest expected rate of 2.03 (vs. SE 0.33) per 100.000, as reference. Very few cases were observed or reported to the ACCESS database in subjects under the age of 18. Thus, no meaningful conclusions regarding MIS-C could be extracted.

In the reporting interval, no overall, gender or age specific significant excess of cases of MIS-A were observed, even if assuming that only 25% of cases were reported.

Cumulatively, and in contrast to the previous PSUR using the same ACCESS reference data but lower exposure, no significant deviations from the expected were noted "as observed" or "assuming 50% reporting". However, assuming only 25% reporting, modest deviations from the expected were found overall in the age groups 50-75+ years (RR's up to 2.64), reflected both among males aged 50-74 years (RR's up to 2.25) and females aged 40-64 years (RR's up to 2.21).

Case reports

Cases were characterized according to the Brighton Collaboration Multisystem Inflammatory Syndrome in Children and Adults and using WHO-UMC standardized case causality assessment.

In the current PSUR (#4) the MAH states, that "Cumulatively, through 17 Dec 2022, a total of 166 cases (167 events) with MIS-related terms have been reported, with 159 serious cases (95.8%) and 143 cases medically confirmed. There were 7 cases (4.2%) with fatal outcomes."

However, in the previous PSUR (#3) it was stated that "Cumulatively, through 18 June 2022, a total of 401 cases (426 events) with MIS-related terms have been reported, with 354 cases medically confirmed. There were 139 cases (32.6%) with fatal outcomes."

The MAH is requested with the next PSUR to explain the numerical incompatibility of the two statements.

Considering the reported cases from the reporting period only, a total of 20 cases (20 events) containing MIS-related events were reported and 14 cases were medically confirmed. All cases were serious with 1

case (1 event) with a fatal outcome. 7 cases (35%) involved male patients, 12 cases (60%) female patients, and 1 case (5%) had unknown gender. The median age of 47 years (min: 19 /max: 69). 15 cases (75%) did not report on dose number, precluding meaningful assessment of any such relation. Cases were scattered over the age range, with no clear tendencies. No cases were reported regarding subjects under the age of 18 years. The median TTO of the reported events was 1 day (min: 0/max: 27). All events except one (19; 95%) were reported in less than 7 days after vaccination.

Fatal case report

One fatal literature case report was submitted in the current reporting period. The case concerned a 23-year-old male with a history of COVID-19 three weeks prior to the event, while the most recent vaccination with elasomeran dated about 6 months earlier. Based on clinical presentation MIS-A was suspected, even though fever was not reported. In spite of aggressive treatment, the condition developed into universal toxic epidermal necrolysis (TEN) and within a week he succumbed to refractory shock. The MAH's assessment, that the case does not qualify as MIS-A, is endorsed.

MIS-C

One cases of MIS-C was reported in a 19-year-old male whose event outcome is listed as recovered. It appears that this case is the same as the literature case published by Kawano et al and discussed in further detail below.

Booster/3rd dose

During the reporting period, there were, according to PSUR Appendix 11.15c/d, two cases in female patients (reported by regulatory authority), both medically confirmed, presenting with MIS-related events occurring on the day of a 3rd or booster dose of elasomeran. The MAH rated both cases Brighton Level 4 (Insufficient Evidence) and WHO-UMC "Unassessable". This is endorsed.

There were no cases of MIS-related events reported after receiving a booster dose with elasomeran/imelasomeran or with elasomeran/davesomeran during this reporting period.

In PSUR Appendix 11.15 g/h further 3 separate (literature) cases receiving elasomeran as a booster dose (according to the heading) are listed, however in the PSUR text they are described under the heading *Case definition and Causality assessment*. Concerning these, there was 1 report classified as Level 1, and 2 reports as Level 2b. According to MAH 2 of these 3 MIS-C/A related cases were classified as possible based on temporal association between the use of the product and the start of the events, and a causal relationship cannot be excluded due to the lack of other information. The third report "was considered unlikely to be related to the vaccine, due to the presence of comorbidities that provided a more plausible explanation for the occurrence of the events and over 9 months after last vaccination."

Concerning the 2 cases rated by the MAH as WHO-UMC causality "Possible" the rapporteur has the following comments:

[redacted], *literature reference Kobayashi et al, ESC Heart Fail, 2022:1-5.*

Citation from the detailed report: "A 51-year-old Japanese woman was admitted to our institution for hypotension, fever, and weakness. Before admission, she had been well without significant past medical history. Three months before admission, Covid-19 was prevalent at her workplace, but she was asymptomatic. A month before admission, she received her first-dose Covid-19 messenger ribonucleic acid (mRNA) vaccine from Moderna (mRNA-1273). On the following day, fever and fatigue appeared. Her fever broke the next day, but fatigue continued for about 2 weeks. She did not undergo SARS-CoV-2 antigen test or real-time polymerase chain reaction (PCR) testing at that time. Four days before admission, she received her second-dose mRNA-1273 vaccine. Again, a high-grade fever and fatigue appeared on the following day. Weakness, diarrhoea, and fainting also appeared on the day of admission,

and she was transferred to our hospital" (and from the abstract) "Elevated inflammatory markers, natriuretic peptide levels and troponin levels, and slightly reduced left ventricular ejection fraction of 50% were noted. We also found the multiple organ damage, including mucocutaneous, gastrointestinal, and neurologic systems. In addition, we revealed the positive results for anti-nucleocapsid SARS-CoV-2 IgG, albeit negative for SARS-CoV-2 polymerase chain reaction testing, suggesting the prior asymptomatic Covid-19 infection. We finally diagnosed her as multisystem inflammatory syndrome after vaccination." The patient recovered fully within 2 months.

Considering the time line, suggesting subclinical COVID-19 about 3 months prior to event and Spikevax vaccination twice with next-day fever and malaise, followed by hospitalization with MIS 4 days after the second vaccination, the rapporteur consider it relatively unlikely, that MIS could be attributed to COVID-19 as opposed to vaccination with elasomeran. Thus, the rapporteur, in accordance with the authors' diagnosis of MIS after vaccination, considers this case WHO-UMC "Probable".

[redacted], *literature reference Kawano H, et al Intern Med 2022:1-8; not found. However, the case was published as Kawano et al. Intern Med 62: 411-417, 2023.*

Authors abstract states: "A 19-year-old Japanese man was hospitalized for cardiogenic shock 28 days after receiving a second dose of the coronavirus disease 2019 (COVID-19) mRNA-1273 vaccine. He had had a high fever for three days with vomiting and abdominal pain before arriving at our hospital. The patient visited a local hospital and was diagnosed with heart failure and acute appendicitis. An endomyocardial biopsy specimen showed myocarditis. Thereafter, Impella CP left ventricular assist device implantation and venoarterial peripheral extracorporeal membranous oxygenation were initiated immediately along with inotropic support and steroid pulse therapy." The authors further conclude that "Given these results, he was finally diagnosed with fulminant myocarditis and acute appendicitis related to the COVID-19 vaccine. In addition, this patient also met the level 1 diagnostic criteria (definitive case) of vaccine-induced MIS-C according to the Brighton Collaboration Network definition."

The MAH argues, that the case is confounded by the concurrent appendicitis, which have not previously been associated with mRNA COVID-19. Thus, a WHO-UMC causality of "Possible" (as opposed to "Probable") is suggested. This is endorsed.

The MAH is requested with the next PSUR to clarify how the case listing criteria differ between Appendix 11.15g: MIS During the Reporting Period BC Criteria Case Evaluations (All) (Booster) (elasomeran), and Appendix 11.15c: MIS During the Reporting Period - Case evaluations (All) (Booster) (elasomeran). Appendix 11.15g includes 3 cases, while appendix 11.15c lists 2 cases.

In the section Subpopulation Analysis of children < 18 years, a MIS-C suspected case is referenced by the MAH ([redacted] (WW Identifier TW-[redacted]). However, this case is not included in the MAH's MIS data. The MAH is requested in the next PSUR to clarify why this case is not included in the MIS data, and the MAH is also requested to provide a detailed assessment of this case within the current procedure, and try to collect additional data if sufficient information is lacking.

In conclusion, considering the totality of the reviewed data, the rapporteur considers that there is insufficient evidence to conclude on a possible causal relation between MIS-C/A and elasomeran at present. However, a new literature case has been re-evaluated by the rapporteur as WHO-UMC "Probable". Going forward, the possibility of further such cases should be actively considered by the MAH.

2.5. Safety topics under monitoring

2.5.1. Arrhythmias

Source of the New Information

New information presented below includes analysis performed on new cases received by MAH cumulatively for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022.

Background Relevant to the Evaluation

The MAH received a health authority request to perform a cumulative review of all cases concerning elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran associated with arrhythmias from all sources, including any relevant articles from literature. Cumulatively, as of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. Cumulatively, as of the end of the reporting period, 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

Cardiac arrhythmia is characterized by irregular rhythm of heartbeat, which could be either too slow (<60 beats/min) or too fast (>100 beats/min) and can happen at any age [131]. Cardiac arrhythmias can be classified according to the site of origin (atria, atrioventricular junction, or ventricles) and whether the response is abnormally fast and early (tachycardia or premature beats), or abnormally slow and delayed (bradycardia or escape beats) [132]. Cardiac arrhythmias are prevalent among humans across all age ranges and may occur in the setting of underlying heart disease as well as in structurally normal hearts. While arrhythmias are widely varied in their clinical presentations, they may possess shared electrophysiologic properties at the cellular level. The 3 main mechanisms responsible for cardiac arrhythmias are automaticity, triggered activity, and re-entry [133]. COVID-19 infection is associated with many different systemic complications.

Among these, cardiovascular system complications are particularly important as these can be associated with significant mortality. There are many different subgroups of cardiovascular complications, including arrhythmias. Arrhythmias are especially important as there is a substantial percentage of patients who have arrhythmia after a COVID-19 infection, and these patients have been noted to have an increased mortality rate [134]. An important aspect with regard to arrhythmias in the context of vaccination is the well-described "immunization stress-related response" (ISRR) that is used to describe the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom. Individual responses to stress vary from person to person and may change according to time or context. According to WHO, ISRR may manifest as acute stress responses, vasovagal reactions or dissociative neurological symptom reactions [135]. Stress can contribute to heart rhythm disorders (arrhythmias) such as atrial fibrillation.

Some studies suggest that stress and mental health issues may cause atrial fibrillation symptoms to worsen. High levels of stress may also be linked to other health problems. An acute stress response is an internal physiological response to a perceived threat in all mammals and is often referred to as a "fight or

flight" response. It may manifest with variable severity of symptoms and may range from mild feelings of worry and "butterflies" in the stomach to sympathetic stimulation: increased heart rate, palpitations, difficulty in breathing or rapid breathing (hyperventilation). It results from activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenocortical axis, which increases blood flow to the brain, heart, lungs and skeletal muscles and reduces the blood flow to less critical body areas.

Relevant Background Literature

The study conducted by Patone et al., is a self-controlled case series study of people aged 16 or older vaccinated for COVID-19 in England between 1 Dec 2020 and 24 Aug 2021 using the English National Immunization Database of COVID-19 vaccination, which includes data on vaccine type, and date of doses for all vaccinated people in England [136]. This information was linked, at individual patient level, to national data for mortality, hospital admissions and SARS- CoV-2 infection data to examine the associations between the first and second dose of ChAdOx1, BNT162b2 or elasomeran vaccines and cardiac AEs including myocarditis, pericarditis or cardiac arrhythmias.

They also investigated the associations between a positive SARS-CoV-2 test (before or after vaccination) as a secondary exposure and the same cardiac AEs. Hospital admission or death due to myocarditis, pericarditis and cardiac arrhythmias were investigated in the 1–28 days following adenovirus (ChAdOx1, n = 20,615,911) or messenger RNA-based (BNT162b2, n =16,993,389; elasomeran, n = 1,006,191) vaccines or a severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) positive test (n = 3,028,867).

Of the 38,615,491 vaccinated individuals included in the study, 385,508 (1.0%) were admitted to hospital with or died with an ICD code related to cardiac arrhythmia at any time in the study period (either before or after vaccination); 86,754 (0.2%) of these occurred in the 1-28 days after any dose of vaccine. Of those who were admitted or died 39,897 (10.3%) had a SARS-CoV-2 positive test, with 29,694 (7.7%) having a positive test before vaccination. There were 7,795 deaths with cardiac arrhythmia recorded as the cause of death (1,108 had a SARS-CoV-2 positive test). There were no deaths associated with cardiac arrythmias and vaccination with elasomeran.

Over the 1–28 days post-vaccination, the authors found:

- A decreased risk of cardiac arrhythmia associated with a first dose of ChAdOx1 (IRR 0.94, 95% CI 0.93, 0.96) and BNT162b2 (IRR 0.89, 95% CI 0.87, 0.90) and following a second dose of ChAdOx1 (IRR 0.95, 95% CI 0.94, 0.96); and BNT162b2 (IRR 0.95, 95% CI 0.93, 0.96)

- No significant increase in the risk of arrythmias for elasomeran first dose (IRR 0.90, 95% CI 0.76, 1.06). (Incidence rate ratios (IRR 95% CI) for single outcomes in pre-defined risk periods immediately before and after exposure to vaccination, adjusted for calendar time from 01 Dec 2020 to 24 Aug 2021).

- An increased risk of cardiac arrhythmia following a second dose of elasomeran (IRR 1.46, 95% CI, 1.08, 1.98), with 24,335 (95% CI 15,547 – 103,369) individuals needed to be exposed to a second dose of elasomeran to cause one excess event.

- An even higher increased risk of cardiac arrythmias for individuals with SARS-CoV-2 positive test (IRR 5.35, 95% CI 5.21, 5.50) with only 416 (95% CI 414 – 419) individuals needed to have a SARS-CoV-2 infection in order to cause one excess event.

Cardiac arrhythmias (n = 385,508) were categorized as atrial fibrillation or flutter (n = 229,248, 59.4%), atrio-ventricular block and related conduction disorders (n = 114,701, 29.7%), ventricular tachycardia (n = 8,211, 2.1%), ventricular fibrillation (n = 2,910, 0.7%) and other, including supraventricular tachycardia (n = 130,485, 33.8%).

According to this categorization, over the 1–28 days postexposure, the authors observed an increased risk of:

- Atrial fibrillation or flutter arrhythmia at 15–21 days following a first dose of elasomeran vaccine (IRR 2.06, 95% CI 1.11, 3.82)
- Ventricular fibrillation at 22–28 days following a second dose of ChAdOx1 vaccine (IRR 1.35, 95% CI 1.05, 1.74)
- Other cardiac arrhythmia at 1–7 days following a second dose of elasomeran vaccine (IRR 2.32, 95% CI 1.49, 3.62).

In those patients with a positive SARS-CoV-2 test there was a higher increased on the risk of all cardiac arrhythmia subgroups in the 1–28 days (IRR 21.35, 95% CI 18.37, 24.80). Important to note that the IRR for elasomeran regarding the occurrence of cardiac arrythmias is very similar after the first dose over 1 to 28 days after vaccination when compared to the other two evaluated vaccines.

Patone et al., [136] acknowledge important limitations of their study. First, their finding cannot determine causal associations. Second, their study relied on hospital admission codes to define the outcome measures, and therefore they do not represent confirmed diagnoses; for example, codes for arrythmia may simply represent "rule out" diagnoses. Third, the elasomeran roll out in the UK occurred toward the end of the study period, and thus the number of immunizations with this vaccine was low. Consequently, the proportion of first doses in the study that involved elasomeran was only 2.6%, and the corresponding proportion for second doses was even lower (1.1%). For elasomeran, the number of first doses was approximately 1.0 million, and second doses were 0.37 million. Thus, in the data analyzed, only 37% of first dose vaccinees received a second dose. For ChAdOx1 and BNT162b2, the corresponding proportions were 96% and 71%. That the number of elasomeran vaccinees was so low raises the possibility that there may have been under- ascertainment of vaccination and that the recording of second doses might have occurred preferentially in association with an AE; this would introduce bias in the results. Illustrative of this dosing disparity, the assessment of risk (IRR) of arrhythmia 1 to 28 days after the second dose of elasomeran (1.46; 95% CI 1.08-1.98) was based on only 48 events, whereas for ChAdOx1 and BNT162b2 there were, respectively, 23,019 and 20,947 events.

Fourth, the authors acknowledge that they are "unclear" about the biologic plausibility of their findings of some reduced risks of arrhythmia and pericarditis linked to vaccination, and they stated that these findings should be interpreted with caution; analogous caution could similarly be applied to their other findings. Fifth, the authors performed numerous statistical comparisons using 95% confidence intervals, not considering multiple testing which, as the authors state "may lead to some erroneous inferences."

Another limitation of the Patone et al [136] study relates to the fact that the elasomeran vaccine was introduced in England on 13 Apr 2021, whereas the vaccination campaign with BNT162b2 began 08 Dec 2020, and the ChAdOx1 vaccination campaign commenced on 04 Jan 2021. On 17 May 2021, the CDC announced cases of myocarditis following mRNA vaccines. In contrast to timing for the other two vaccines, which had been in use for 4 to 5 months, this CDC announcement occurred around the time that the earliest elasomeran vaccinees were receiving their second doses. Thus, in contrast to the other vaccines, nearly the entire dose 2 observation period for elasomeran occurred after the CDC alert, which could potentially bias the findings by heightening awareness of cardiac symptoms and their investigation.

With regards to the outcome arrhythmia, the Patone et al [136] study identified this outcome by collecting 46 different ICD-10 codes, including some that are non-specific such as palpitations (R002), abnormalities of heartbeat (R00), and other and unspecified abnormalities of heartbeat (R008). It is possible that some of these and other ICD-10 codes may have represented "rule out" diagnoses or simply symptoms associated with common vaccine reactogenicity, rather than true ECG-diagnosed arrhythmias.

A large epidemiological study by Dickerman et al., [137] was led by researchers from Harvard University and used data from the US Veterans Affairs Healthcare system to compare the safety of BNT162b2 and elasomeran in a nationwide cohort of US veterans [137]. With regard to arrhythmia, this study's findings do not confirm the findings of Patone et al. In fact, the risk of arrhythmia was higher for BNT162b2 than for elasomeran, as described below.

The Dickerman et al [137] study was designed to emulate target trials. From a base population of 6,226,326 veterans, the investigators identified 3,465,065 who were vaccinated before 21 Sep 2021. Then the investigators excluded veterans with prior documented SARS-CoV-2 infection, with interaction with the health-care system less than or equal to 3 days before vaccination, with no residential address or were in long-term care, with no use of VA health-care system in last year, with no recent body mass index or smoking status data, with incomplete COVID-19 vaccination record.

Then, for study inclusion, the veterans had to be vaccinated in a VA station that administered both elasomeran and BNT162b2 vaccines, with a second dose scheduled 21 days later (BNT162b2) or 28 days later (elasomeran); in contrast with the Patone et al study, 98% of vaccinees received a second dose. Finally, there was careful 1:1 matching for and the ChAdOx1 vaccines. Three of the important study limitations that Montano acknowledged are:

1) there is not conclusive evidence of a causal association; 2) the reported health events are unverified; 3) there may be under- or over-reporting bias.

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively to 17 Dec 2022 for valid case reports of arrhythmia received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following MedDRA PTs: "SMQ Cardiac Arrhythmia (Narrow scope)".

There is no SPEAC or Brighton Collaboration case definition available for arrhythmias, however individual arrhythmias have their own criteria of diagnosis.

The MAH has created the case definition for evaluation of the arrhythmia cases.

Cardiac arrhythmia is characterized by abnormal or irregular rhythm of heartbeat which could be either too slow (<60 beats/min) or too fast (>100 beats/min) and can happen at any age [131].

Cardiac arrhythmias can be classified according to the site of origin (atria, atrioventricular junction, or ventricles) and whether the response is abnormally fast and early (tachycardia or premature beats), or abnormally slow and delayed (bradycardia or escape beats) [132].

Identified cases were classified into four categories as:

1. Confirmed case: has less than 60 beats/min (Bradycardia) or more than 100 beats per min (tachycardia) and ECG identifying irregular heart rhythm

2. Possible Case: Only has information on the irregular rhythm or number of beats per minute (pulse rate, heart rate) and no diagnostic confirmation (no info on ECG)

3. Not a case: Case has normal rhythm

4. Unassessable: Has no information on heart rate or pulse rate or ECG The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Methodology Implemented to Review the Post-marketing Data

The MAH performed the cumulative search as of 17 Dec 2022 in the GSDB, using the MedDRA (v 25.1) SMQ "Cardiac arrhythmias" (Narrow scope), the search retrieved 8,803 cases. These 8,803 cases were screened for the information on ECG, which identified 1,832 cases. These 1,832 cases were further analyzed for Arrhythmia-related information with the following key words (Bradycardia, Heartbeat, Irregular heartbeat, Tachycardia, irregular rhythm, ventricles, Premature beats, and Atrioventricular junction). The review of 1,832 cases with the key terms showed 693 cases. Of these 693 cases, all Tachycardia confirmed cases (475) with no other associated symptom were eliminated (Tachycardia is an increased heart rate for any reason. It can be a usual rise in heart rate caused by exercise or a stress response (sinus tachycardia). Sinus tachycardia is considered a symptom, not a disease) and of the remaining 218 cases (134 serious and 84 non-serious), the serious cases (134) were further reviewed in detail, to identify a true case of Arrhythmia. Details of these reviews are presented below in Post-Authorization Data section.

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and Cardiac arrhythmia to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in PSUR Appendix 12.1d.

A total of 596 literature articles were retrieved using these search criteria. These literature search results were medically/scientifically reviewed, and informative articles are discussed above, under section Background Relevant to the Evaluation. There was no additional published clinical literature that described new and potentially important safety information on the safety profile of elasomeran/imelasomeran and elasomeran/davesomeran).

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed Vs Expected Analysis

See PSUR Appendix 11.3.

PSUR Appendix 11.3 – 1.4.1

1.4.1 Age and gender stratified observed to expected analysis of arrhythmia as of 17 December 2022

		Observed		Expected				
Outcome	Person-years	Cases	Rate	Cases	Rate	As observed: Risk Ratio (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
Arrhythmia								
Reference: UK CPRD 2019[8]								
Interval								
Overall								
Overall	14,371,224	1,447	10.07	68,207	474.61	0.02 (0.02, 0.02)	0.04 (0.04, 0.04)	0.08 (0.08, 0.09)
Overall, by age								
< 2 years	9,697	0	0.00	5	49.32	N/A	N/A	N/A
2-4 years	24,557	0	0.00	12	49.32	N/A	N/A	N/A
5-11 years	533,467	0	0.00	263	49.32	N/A	N/A	N/A
12-17 years	72,544	11	15.16	36	49.32	0.31 (0.16, 0.6)	0.61 (0.36, 1.05)	1.23 (0.79, 1.91)
18-24 years	1,456,403	27	1.85	1,406	96.57	0.02 (0.01, 0.03)	0.04 (0.03, 0.05)	0.08 (0.06, 0.09)
25-39 years	3,222,892	290	9.00	3,112	96.57	0.09 (0.08, 0.11)	0.19 (0.17, 0.2)	0.37 (0.35, 0.4)
40-49 years	2,036,943	315	15.46	3,529	173.24	0.09 (0.08, 0.1)	0.18 (0.16, 0.19)	0.36 (0.33, 0.38)
50-64 years	3,502,470	420	11.99	11,839	338.03	0.04 (0.03, 0.04)	0.07 (0.07, 0.08)	0.14 (0.13, 0.15)
65-74 years	2,075,560	152	7.32	15,561	749.71	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	0.04 (0.04, 0.04)
75+ years	1,436,691	95	6.61	24,263	1688.79	0 (0, 0)	0.01 (0.01, 0.01)	0.02 (0.01, 0.02)
By gender								
Male	6,830,267	621	9.09	64,286	941.19	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	0.04 (0.04, 0.04)
Female	7,540,957	796	10.56	49,895	661.65	0.02 (0.01, 0.02)	0.03 (0.03, 0.03)	0.06 (0.06, 0.07)
Males, by age								
< 2 years	4,634	0	0.00	2	46.08	N/A	N/A	N/A
2-4 years	11,735	0	0.00	5	46.08	N/A	N/A	N/A
5-11 years	259,361	0	0.00	120	46.08	N/A	N/A	N/A
12-17 years	45,492	6	13.19	21	46.08	0.29 (0.12, 0.71)	0.57 (0.28, 1.16)	1.14 (0.64, 2.06)
18-24 years	706,429	15	2.12	508	71.90	0.03 (0.02, 0.05)	0.06 (0.04, 0.09)	0.12 (0.09, 0.15)
25-39 years	1,634,159	121	7.40	1,175	71.90	0.1 (0.09, 0.12)	0.21 (0.18, 0.24)	0.41 (0.37, 0.46)
40-49 years	1,015,494	116	11.42	1,789	176.17	0.06 (0.05, 0.08)	0.13 (0.11, 0.15)	0.26 (0.23, 0.29)
50-64 years	1,718,376	176	10.24	6,866	399.58	0.03 (0.02, 0.03)	0.05 (0.05, 0.06)	0.1 (0.09, 0.11)
65-74 years	949,116	83	8.74	9,028	951.18	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	0.04 (0.03, 0.04)

		Observed		Expected				
Outcome	Person-years	Cases	Rate	Cases	Rate	As observed: Risk Ratio (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
75+ years	485,471	40	8.24	10,139	2088.51	0 (0, 0.01)	0.01 (0.01, 0.01)	0.02 (0.01, 0.02)
Females, by age								
< 2 years	5,063	0	0.00	3	52.74	N/A	N/A	N/A
2-4 years	12,821	0	0.00	7	52.74	N/A	N/A	N/A
5-11 years	274,209	0	0.00	145	52.74	N/A	N/A	N/A
12-17 years	27,310	5	18.31	14	52.74	0.35 (0.13, 0.96)	0.69 (0.31, 1.56)	1.39 (0.71, 2.73)
18-24 years	747,812	10	1.34	915	122.42	0.01 (0.01, 0.02)	0.02 (0.01, 0.03)	0.04 (0.03, 0.06)
25-39 years	1,599,288	168	10.50	1,757	109.84	0.1 (0.08, 0.11)	0.19 (0.17, 0.21)	0.38 (0.35, 0.42)
40-49 years	996,780	196	19.66	1,697	170.22	0.12 (0.1, 0.13)	0.23 (0.21, 0.26)	0.46 (0.42, 0.5)
50-64 years	1,779,979	239	13.43	4,906	275.62	0.05 (0.04, 0.06)	0.1 (0.09, 0.11)	0.19 (0.18, 0.21)
65-74 years	1,110,321	66	5.94	6,166	555.33	0.01 (0.01, 0.01)	0.02 (0.02, 0.03)	0.04 (0.04, 0.05)
75+ years	987,374	49	4.96	13,213	1338.24	0 (0, 0)	0.01 (0.01, 0.01)	0.01 (0.01, 0.02)
Cumulative								
Overall								
Overall	52,482,913	8,886	16.93	249,089	474.61	0.04 (0.03, 0.04)	0.07 (0.07, 0.07)	0.14 (0.14, 0.14)
Overall, by age								
< 2 years	10,638	3	28.20	5	49.32	0.57 (0.14, 2.36)	1.14 (0.35, 3.69)	2.29 (0.82, 6.38)
2-4 years	26,941	0	0.00	13	49.32	N/A	N/A	N/A
5-11 years	585,251	0	0.00	289	49.32	N/A	N/A	N/A
12-17 years	1,119,606	32	2.86	552	49.32	0.06 (0.04, 0.08)	0.12 (0.09, 0.15)	0.23 (0.19, 0.28)
18-24 years	4,561,030	292	6.40	4,405	96.57	0.07 (0.06, 0.07)	0.13 (0.12, 0.14)	0.27 (0.25, 0.28)
25-39 years	10,769,346	1,740	16.16	10,400	96.57	0.17 (0.16, 0.18)	0.33 (0.32, 0.35)	0.67 (0.65, 0.69)
40-49 years	7,344,393	1,468	19.99	12,723	173.24	0.12 (0.11, 0.12)	0.23 (0.22, 0.24)	0.46 (0.45, 0.48)
50-64 years	13,491,082	2,416	17.91	45,604	338.03	0.05 (0.05, 0.06)	0.11 (0.1, 0.11)	0.21 (0.21, 0.22)
65-74 years	8,601,144	1,494	17.37	64,484	749.71	0.02 (0.02, 0.02)	0.05 (0.04, 0.05)	0.09 (0.09, 0.1)
75+ years	5,973,482	1,050	17.58	100,880	1688.79	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	0.04 (0.04, 0.04)
By gender								
Male	24,675,873	3,649	14.79	232,247	941.19	0.02 (0.02, 0.02)	0.03 (0.03, 0.03)	0.06 (0.06, 0.06)
Female	27,807,040	5,104	18.36	183,986	661.65	0.03 (0.03, 0.03)	0.06 (0.05, 0.06)	0.11 (0.11, 0.11)

		Observed		Expected				
Outcome	Person-years	Cases	Rate	Cases	Rate	As observed: Risk Ratio (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
Males, by age								
< 2 years	5,067	2	39.47	2	46.08	0.86 (0.13, 5.66)	1.71 (0.34, 8.61)	3.43 (0.8, 14.72)
2-4 years	12,833	0	0.00	6	46.08	N/A	N/A	N/A
5-11 years	283,633	0	0.00	131	46.08	N/A	N/A	N/A
12-17 years	535,774	18	3.36	247	46.08	0.07 (0.05, 0.12)	0.15 (0.1, 0.21)	0.29 (0.22, 0.38)
18-24 years	2,160,155	134	6.20	1,553	71.90	0.09 (0.07, 0.1)	0.17 (0.15, 0.2)	0.35 (0.31, 0.38)
25-39 years	5,167,748	659	12.75	3,716	71.90	0.18 (0.16, 0.19)	0.35 (0.33, 0.38)	0.71 (0.67, 0.75)
40-49 years	3,500,681	516	14.74	6,167	176.17	0.08 (0.08, 0.09)	0.17 (0.16, 0.18)	0.33 (0.32, 0.35)
50-64 years	6,395,493	1,000	15.64	25,555	399.58	0.04 (0.04, 0.04)	0.08 (0.07, 0.08)	0.16 (0.15, 0.16)
65-74 years	4,004,688	721	18.00	38,092	951.18	0.02 (0.02, 0.02)	0.04 (0.04, 0.04)	0.08 (0.07, 0.08)
75+ years	2,609,800	446	17.09	54,506	2088.51	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	0.03 (0.03, 0.03)
Females, by age								
< 2 years	5,571	1	17.95	3	52.74	0.34 (0.04, 3.29)	0.68 (0.11, 4.1)	1.36 (0.3, 6.14)
2-4 years	14,108	0	0.00	7	52.74	N/A	N/A	N/A
5-11 years	301,720	0	0.00	159	52.74	N/A	N/A	N/A
12-17 years	584,090	14	2.40	308	52.74	0.05 (0.03, 0.08)	0.09 (0.06, 0.13)	0.18 (0.14, 0.24)
18-24 years	2,398,713	150	6.25	2,937	122.42	0.05 (0.04, 0.06)	0.1 (0.09, 0.12)	0.2 (0.19, 0.22)
25-39 years	5,612,153	1,066	18.99	6,164	109.84	0.17 (0.16, 0.18)	0.35 (0.33, 0.36)	0.69 (0.67, 0.72)
40-49 years	3,819,043	943	24.69	6,501	170.22	0.15 (0.14, 0.16)	0.29 (0.28, 0.31)	0.58 (0.56, 0.6)
50-64 years	7,091,474	1,392	19.63	19,546	275.62	0.07 (0.07, 0.08)	0.14 (0.14, 0.15)	0.28 (0.28, 0.29)
65-74 years	4,580,333	762	16.64	25,436	555.33	0.03 (0.03, 0.03)	0.06 (0.06, 0.06)	0.12 (0.12, 0.12)
75+ years	3,399,836	591	17.38	45,498	1338.24	0.01 (0.01, 0.01)	0.03 (0.02, 0.03)	0.05 (0.05, 0.05)

Clinical Trial Data

The topic of arrhythmia was cumulatively reviewed in the clinical trial datasets, within the following studies of P301 study (ages ≥18 years; DLP: 04 May 2021), P203 study (ages 12-17 Years; DLP: 27 Jan 2022) and P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022), for any PT (listed below) included in the SOC cardiac disorders (MedDRA version was 23.0 and 24.0).

P301 Study

The P301 (randomized, stratified, observer-blind, placebo-controlled study) included healthy adults ≥ 18 years of age, at appreciable risk of SARS-CoV-2 infection, with no known history of SARS-CoV-2 infection. There were approximately 30,000 participants randomized in 1:1 ratio to dose groups placebo (n = 15,000) and mRNA-1273 100 µg (n = 15,000) with vaccine schedule of 2 IM doses, 28 days apart. The frequency of arrhythmia events in the clinical trial data showed that the placebo group was comparable to that in the vaccine group as shown in the table below, which is excerpted from the clinical dataset (Table 16.79 and Table 16.80).

Table 16.79 Reported Incidence of Serious Treatment-Emergent Adverse Events of Arrhythmia by Preferred Term Throughout the Entire Duration of mRNA-1273-P301 (Safety Set)

PT	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)
Atrial fibrillation	10 (<0.1)	6 (<0.1)
Atrial flutter	2 (<0.1)	2 (<0.1)
Bradycardia	0	1 (<0.1)
Supraventricular tachycardia	0	1 (<0.1)
Ventricular extrasystoles	0	1 (<0.1)
Arrhythmia	1 (<0.1)	0
Atrioventricular block complete	1 (<0.1)	0
Atrioventricular block second degree	1 (<0.1)	0
Paroxysmal arrhythmia	1 (<0.1)	0
Sinus tachycardia	2 (<0.1)	0

Table 16.80 Subject Incidence of Unsolicited Non-Serious TEAE of Arrhythmias by Preferred Term up to 28 Days After Any Injection Safety Set – mRNA-1273- P301

PT	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)
Tachycardia	9 (<0.1)	15 (<0.1)
Bradycardia	16 (0.1)	13 (<0.1)
Atrial fibrillation	9 (<0.1)	9 (<0.1)
Arrhythmia	10 (<0.1)	6 (<0.1)
Sinus tachycardia	2 (<0.1)	3 (<0.1)
PT	**Placebo (N=15162) n (%)**	**100 µg mRNA-1273 (N=15184) n (%)**
Atrial flutter	1 (<0.1)	0
Atrial tachycardia	1 (<0.1)	0
Ventricular fibrillation	1 (<0.1)	0

P203 Study

The P203 (Phase 2/3, randomized, observer-blind, and placebo-controlled) included healthy adolescents in age group 12 to < 18 years. There were approximately 3,000 participants randomized in 2:1 ratio with a vaccine schedule of 100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart. As shown in Table 16.81

below, the observed incidence of arrhythmia terms was comparable in the long-term follow-up of the placebo and active arms of the clinical study.

Table 16.81 Subject Incidence of Unsolicited TEAE by Preferred Term in Long-term Analysis Safety Set - mRNA-1273-P203

Preferred Term	Placebo-mRNA-1273 (N=1243) n (%)	mRNA-1273 (N=2489) n (%)
Sinus bradycardia	1 (0.1)	8 (0.3)
Tachycardia	0	2 (0.1)
Bundle branch block	0	1 (<0.1)
Postural orthostatic tachycardia syndrome	0	1 (<0.1)
Supraventricular tachycardia	0	1 (<0.1)
Tachyarrhythmia	1 (0.1)	0

P204 Study

The P204 (Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation, and randomized, observer-blind, placebo-controlled expansion) included healthy pediatrics between 6 months to < 12 years. There were approximately 750 to 4500 participants indifferent age groups randomized in 3:1 ratio with a vaccine schedule of 25 ug, 50 ug, 100 µg mRNA-1273 (25 µg only for 6 months to < 2 years age group) or placebo (3:1) 2 IM doses, 28 days apart. The safety data set for this study did not identify any events of arrhythmia.

Post-Authorization Data

Post-Authorization Safety Study Analysis

A Late-Breaking News request was received on 16 Jan 2022 from a health authority to perform a self-control risk interval (SCRI) analysis of arrhythmia for adults as well as the pediatric population from the Post Authorization Safety Studies (PASS) mRNA-1273-P903 and provide the results as part of the cumulative review in the PSUR. Analysis of the data from mRNA-1273-P903 addressing the request from the health authority is presented in Section 16.3.6.1.1.

Overview of Cases for elasomeran (Cumulatively through 17 Dec 2022)

Cumulatively, a total of 8,803 cases (10,044 events) of arrhythmia-related PTs were identified for elasomeran (PSUR Appendix 11.12). Of the 8,803 cases, 6,197 (6,672 serious events) were considered serious with 246 cases (279 events) with a fatal outcome reported. There were 4,193 (47.6%) cases medically confirmed.

Most of the events with reported outcomes were resolved/ resolving (4,080; 40.6%), with 3,738 events (37.2%) reported as not resolved. There were 279 (2.8%) fatal events. There were more reports involving females (5,068; 57.6 %) compared to males (3,604; 40.9 %), and 131 (1.5%) cases did not specify gender. The largest proportion of the reports were in individuals ≥50- 64 years of age (1,686; 27.2%) The median age of reported cases was 56.0 years (min 0.1/ max 121.0 years) with a mean age of 55.0 years (SD: 17.6). For the cumulative listings with 8,803 cases.

Based on the methodology described above in section Methods of Evaluation, of these 8,803 cumulative cases (10,044 events), 218 Cases (319 events) were considered as possible cases of arrhythmia for analysis. Of these 218 cases, there were 134 serious cases (213 events) and 84 non-serious cases (106 events). These 134 serious cases (213 serious events) were further considered for detailed review for

Arrhythmia. These 134 serious cases are described in detail from this point forward in this medical evaluation of Arrhythmia.

Overview of Cases for elasomeran that Qualified for Arrhythmia Review (Cumulatively till 17 Dec 2022)

Cumulatively a total 134 serious cases (213 serious events) with arrhythmia-related PTs were identified for elasomeran. The distribution of the reports was equal in females (66; 49.3%) and males (66; 49.3%), two (1.5%) had unknown gender. Most of the events were in individuals >50 years of age (79;59.0%) (Table 16.82).

Table 16.82. Age and Gender Distribution of Serious cases that Qualified for Arrhythmia Review (Cumulatively through 17 Dec 2022 - elasomeran)

Age Group	Female		Male		Unknown		Grand total # of Cases	Grand Total % Cases
	# Of Cases	% Of Cases	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
18-24Y	2	1.5	6	4.5	0	0	8	6.0
25-39Y	15	11.2	12	9.0	0	0	27	20.1
40-49Y	10	7.5	6	4.5	0	0	16	11.9
50-64Y	20	14.9	16	11.9	0	0	36	26.9
65-74Y	9	6.7	16	11.9	0	0	25	18.7
75Y+	7	5.2	10	7.5	1	0.7	18	13.4
Missing	3	2.2	0	0	1	0.7	4	3.0
Grand total	**66**	**49.3**	**66**	**49.3**	**2**	**1.5**	**134**	**100.0**

The most frequently reported PT for serious cases were Atrial fibrillation (37; 18.5%), arrhythmia (32; 16.0%), and Heart rate irregular (10.0%). The top 10 PTs reported from the 213 serious events of "Arrhythmia" related are presented in Table 16.83.

Table 16.83. Top 10 PTs for the Serious Events that Qualified for Arrhythmia Review Reported following elasomeran (Cumulatively through 17 Dec 2022)

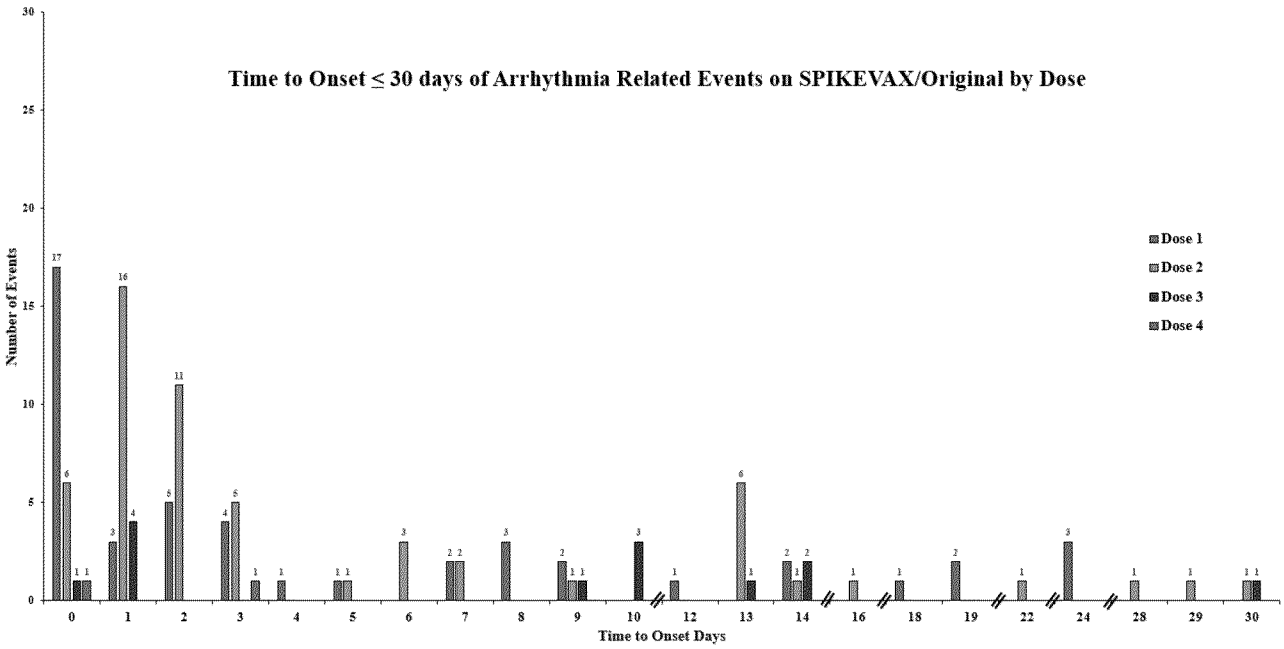
PT	Grand total # of Serious Events	Grand total % of Serious Events
Atrial fibrillation	37	18.5
Arrhythmia	32	16.0
Heart rate irregular	20	10.0
Extrasystoles	17	8.5
Sinus bradycardia	12	6.0
Cardiac flutter	11	5.5
Atrioventricular block	7	3.5
Supraventricular tachycardia	7	3.5
Ventricular extrasystoles	7	3.5
Bundle branch block right	6	3.0

When evaluating serious events of arrhythmia by time to onset (TTO), highest number of events were observed after Dose 2 (81;40.1%), and regardless of dose number, most of the events reported a TTO

≤14 days (89;44.5%). When TTO was known, 124 of 213 events were reported within 30 days, and these are presented in Figure 16-10. Additionally, there were 43 events reported with

TTOs spread out between 31 to 300 days after vaccination. The graphic pattern is generally similar to that of all AEs reported following elasomeran immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination (reactogenicity events, ISRRs events) or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. Currently, with the limited number of reports, the finding is an observation, as there is no clear biological explanation.

Figure 16-10. Number of Serious Events that Qualified for Arrhythmia Review by Dose Number and Time to Onset of elasomeran (Cumulatively through 17 Dec 2022)



Evaluation of the serious arrhythmia-related events showed that many of the reports were in patients with concurrent medical history that can be considered a risk factor/ confounder to the occurrence of arrhythmia. A history of Drug hypersensitivity, Hypertension and Hypersensitivity was reported frequently. It is possible that hypersensitivity or hypertension may contribute to the occurrence of arrhythmias. See Table 16.84.

Table 16.84. Top 10 Medical History* Terms Noted in Reports that Qualified for Arrhythmia Review, by MedDRA PT (Cumulative through 17 Dec 2022) - elasomeran

Medical History	# of Cases	% of Cases
Drug hypersensitivity	89	66.4
Hypertension	24	17.9
Hypersensitivity	19	14.2
Food allergy	11	8.2
Hyperlipidaemia	10	7.5
Cardiac pacemaker insertion	9	6.7
Diabetes mellitus	9	6.7
Osteoarthritis	8	6.0

Asthma	8	6.0
Seasonal allergy	8	6.0

*Include current and past medical history

The incidence of certain clinical arrhythmias varies between men and women. Clinical and experimental observations suggest the existence of true differences in electrophysiologic properties between the sexes [139]. Some of these differences are related to known variations in the frequency of underlying organic heart disease, such as coronary artery disease (CAD) and associated ventricular arrhythmias [140]. Among the 134 serious cases, there were two fatalities reported following elasomeran, details of these cases are summarized below.

1. [redacted] **(WW Identifier: US-[redacted]):** This case involved a 66-year-old man without reported medical history, who was taking two medications (hydrochlorothiazide and lisinopril) for hypertension, as well as albuterol. He experienced syncope at home 19 days after dose 1, Emergency medical services was called, and the patient was hospitalized but was not stabilized. Patient died the day following hospital admission. Patient diagnosed with ST Elevation Myocardial Infarction-myocardial infarction with ST Elevation. ST Elevation Myocardial Infarction is the likely direct cause of the agonal rhythm and bradycardia noted, rather than elasomeran. WHO Causality for arrhythmia: Unlikely.
2. [redacted] **(WW Identifier: US-[redacted]):** This 71-year-old male patient died from acute hypoxemic respiratory failure secondary to COVID-19 pneumonia. The patient's noted arrhythmias likely resulted from multi-organ failure and metabolic derangements due to this fatal infection, rather than from elasomeran. WHO Causality: Unlikely. This case is a duplicate of [redacted].

Arrhythmia in Children (<12 Years of Age) (Cumulatively to 17 Dec 2022) elasomeran

There were no cases of arrhythmia in children <12 years of age.

Arrhythmia in Adolescents (12-17 Years of Age) (Cumulatively to 17 Dec 2022) elasomeran

There were no cases of adolescents identified in the list of 134 cases that were reviewed to identify a true case of Arrhythmia.

Serious Cases Qualified for Arrhythmia Review in Patients After a Third Dose or Booster Dose of elasomeran (Cumulatively to 17 Dec 2022)

The review of the cumulative data as of 17 Dec 2022, identified 134 cases for detailed review, of which, a total of 16 serious cases (22 events [of which 21 serious]), were reported in the GSDB after a booster dose (defined as the third dose or higher) of elasomeran. Of these 16 serious cases, 6 were medically confirmed and 0 fatal cases were reported. There were more reports involving females (11; 68.8%) than males (4; 25.0%) with 1 (6.3 %) report with missing gender information, and the median age was 54.0 years (min 23.0/ max 85.0 years) with a mean age of 54.8 years (SD: 18.0). (Table 16.85)

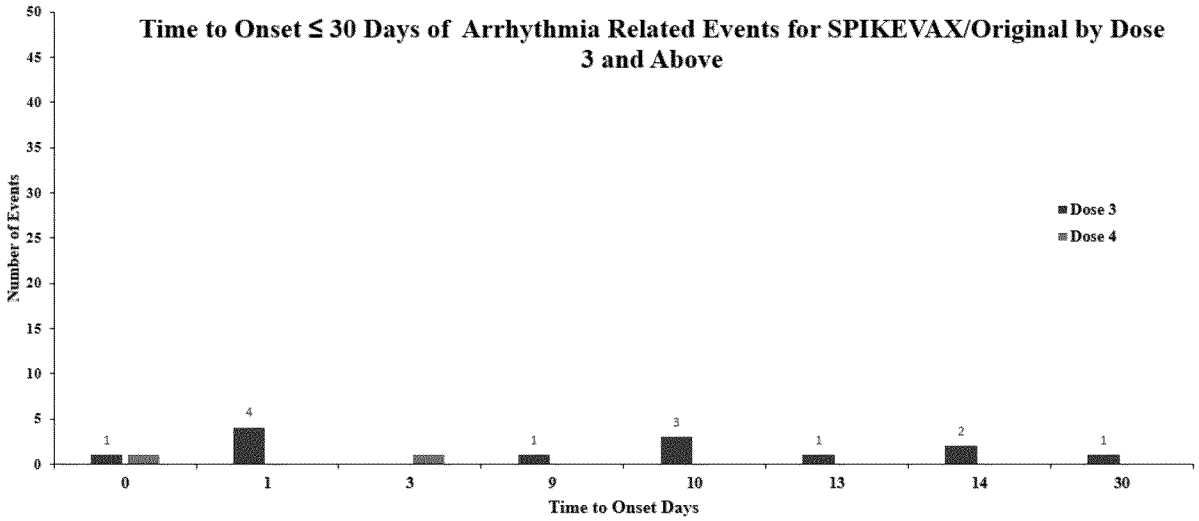
Table 16.85. Age and Gender Distribution Serious Cases Qualified for Arrhythmia Review following booster Dose (Cumulatively through 17 Dec 2022) elasomeran

Age Group	Female		Male		Unknown		Grand total # Of Cases	Grand total % of Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-24Y	0	0	1	6.3	0	0	1	6.3

25-39Y	4	25.0	0	0	0	0	4	25.0
40-49Y	2	12.5	0	0	0	0	2	12.5
50-64Y	2	12.5	1	6.3	0	0	3	18.8
65-74Y	2	12.5	1	6.3	0	0	3	18.8
75Y+	1	6.3	1	6.3	1	6.3	3	18.8
Grand total	**11**	**68.8**	**4**	**25.0**	**1**	**6.3**	**16**	**100.0**

There were 22 events reported on Dose 3 and above; of these 15 events were reported with a TTO of ≤ 30 days. Time to onset and dose for serious events received after dose 3 or more are depicted graphically below (Figure 16-11). Additionally, there were 7 events reported after day 30 until day 129.

Figure 16-11. Number and Percentage of Serious Arrhythmia Cases by Dose Number and Time to Onset after Dose 3 and Booster dose (Cumulatively through 17 Dec 2022)



Fatal Cases After a Third Dose or Booster Dose of elasomeran (Cumulatively through 17 Dec 2022)

Cumulative, no fatal reports were reported in patients receiving dose 3 or above from the list of 134 cases that were reviewed to identify a true case of for Arrhythmia.

Cases that Qualified for Arrhythmia Review After Receiving Booster Dose with elasomeran/imelasomeran) (Cumulatively through 17 Dec 2022)

Cumulatively, there were no reports that qualified for arrhythmia review in patients vaccinated in elasomeran/imelasomeran.

Fatal Cases After Receiving Booster Dose with elasomeran/imelasomeran) (Cumulatively through 17 Dec 2022)

Cumulative, no fatal reports were reported in patients vaccinated in elasomeran/imelasomeran from the list of 134 cases that were reviewed to identify a true case of for Arrhythmia.

Cases that qualified for Arrhythmia After Receiving Booster Dose with elasomeran/davesomeran (Cumulatively till 17 Dec 2022)

Cumulatively, there was one report that qualified for arrhythmia review in patients vaccinated with elasomeran/davesomeran. Details of this case is as follow:

[redacted] (WW Identifier: [redacted]): This spontaneous case reported by a patient, concerns a 74-year-old male with history of Syncope, Right Bundle Branch Block, Obstructive sleep apnea syndrome. He had a prior ECG with atrial fibrillation noted 14.5 months before this reported event. This reported event concerns the unexpected, serious (medically significant) AESI Atrial fibrillation a few hours after receiving the 5th dose of elasomeran/davesomeran as fifth dose in the COVID-19 vaccine series. The patient experienced sudden onset atrial fibrillation post-vaccination notified to him by a device. He was advised by his cardiologist to visit the ED for evaluation. His ECG showed atrial fibrillation, Troponin was 11 ng/L (Unknown-20 ng/L) The patient was started on Eliquis(apixaban) and was eventually discharged. The patient had another episode of atrial fibrillation approximately a month after the initial incident and was scheduled for ancillary procedures the next month. Further details on the clinical course and additional treatment were not provided. The patient's advanced age, medical history of Right bundle branch block and concurrent obesity, hypertension, and high cholesterol may be considered as confounders for this atrial fibrillation; therefore, this this report is assessed as WHO-UMC Causality possible primarily due to temporal association.

Fatal cases After Receiving Booster Dose with elasomeran/davesomeran (Cumulatively till 17 Dec 2022)

There were no fatal reports reported after elasomeran/davesomeran.

Case Evaluation for Cases meeting Arrhythmia's Case Definition

As described in the Post-Authorization Data section, there were 134 serious cases that met the case definition for Arrhythmia. Of these 134 serious cases, seven (7) were classified as unassessable due to lack of information including ECG results; 37 cases were classified as possible cases and 90 cases were classified as confirmed cases. (Table 16.86). Information of those cases is included in PSUR Appendix 11.12.

Table 16.86. Number of cases of Arrythmia According to Case Definition

Classification by Case Definition of Arrhythmia	Number of Cases	% Of cases
Confirmed	90	67.2
Possible	37	27.6
Unassessable	7	5.2
Total	**134**	**100**

According to the WHO causality assessment the 134 serious that were classified as cases of arrhythmia, were assessed as follows: 20 cases were Unassessable, due to the lack of information including medical history, clinical course, among others and 22 case were unlikely. The remaining

(92) cases were assessed as possible, since the time course was consistent, however adequate information to evaluate the underlying cause of the reported events was not generally available. In several cases, there was history of atrial fibrillation or therapy with thyroid hormone replacement, which may have provided alternative explanation for the reported events. In some reports the arrhythmias were reported in the context of myocarditis, which is known to be associated with the product. Details of these cases are included in PSUR Appendix 11.12.

Review of External Databases

- VAERS and EVDAS were reviewed for SMQ Arrhythmia and EVDAS showed disproportionality of ROR for PTs "Agonal rhythm", "Arrhythmia", "Extrasystoles", "Atrial fibrillation" and "Heart rate irregular" (Table 16.87) (PSUR Appendix 11.12).

- VAERS: No Disproportionate Reporting of Arrhythmia-related Events Using EB05 >2 (elasomeran versus All vaccines in adults) in VAERS through 17 Dec 2022 was observed.
- EVDAS: Amongst the PTs of SMQ Arrhythmia, the PTs "Agonal rhythm", "Arrhythmia", "Extrasystoles", "Atrial fibrillation" and "Heart rate irregular" showed disproportionality.

Table 16.87. EVDAS Disproportionality Analysis

MedDRA PTs	ROR (-) All (31 Dec 2021- 31 Dec 2022)
Arrhythmia	2.13
Extrasystoles	2.03
Atrial fibrillation	1.05
Heart rate irregular	1.4

Discussion

Cardiac arrhythmia is a clinically and etiologically heterogenous entity. In the data presented above, no particular type of arrhythmia predominated. Importantly, the pivotal CTs performed in adults, adolescents and children found similar frequency of various arrhythmias in the elasomeran and placebo control arms. Such clinical trial findings provide the most rigorous medical-scientific findings, although they may not detect very rare AEs.

Epidemiological studies, although less rigorous than CTs, may provide useful information; however, their findings should be carefully scrutinized for potential bias, confounding, lack of generalizability and other methodological limitations. Two large epidemiological studies were described above that had different findings with regard to the risk of arrhythmia after elasomeran. The study by Patone et al, [136] with some findings associating elasomeran with arrhythmia described in detail above, had important limitations including: 1) the referral bias acknowledged by the authors; 2) nearly all of the elasomeran second doses were administered after the CDC myocarditis warning that raised awareness of cardiac symptoms; 3) only 37% of elsomeran vaccinees were reported to have received a second dose, raising the possibility that reporting of the second dose was linked to arrhythmia (bias); 4) the assessment of risk (IRR) of arrhythmia 1 to 28 days after the second dose of mRNA-1273 (1.46; 95% CI 1.08-1.98) was based on only 48 events, whereas for ChAdOx1 and BNT162b2 their corresponding risks were based, respectively, on 23,019 and 20,947 events. 5) some arrhythmia events may have represented "rule out" diagnoses or simply vaccine reactogenicity; 6) the "unclear" biological plausibility acknowledged by the authors for some of their cardioprotective findings of vaccination, and the authors' suggestion that these findings should be interpreted with caution likely applies to all their findings.

In contrast to the Patone et al study, the Dickerman et al study [136,137] described above employed a study design to emulate target trials, and their finding did not confirm those of Patone et al. Dickerman et al [136,137] included 433,672 US veterans who were matched 1:1 according to calendar date, age, sex, race, urbanicity of residence, and geographic location; one member of each pair received BNT162b2 and the other elasomeran. The 38-week risk of arrhythmia after vaccination was 277.6 per 10,000 persons for BNT162b2, and 251.4 per 10,000 persons for elasomeran. The risk ratio was 1.1 (95% CI:1.00 to 1.15). The authors concluded: "there were few differences in risk of AEs within 14 days of the first dose of either the BNT162b2 or the elasomeran vaccine and small-magnitude differences within 42 days of the first dose. The 38-week risks of AEs were low in both vaccine groups, although risks were lower for recipients of the elasomeran vaccine than for recipients of the BNT162b2 vaccine". In summary, the two epidemiological studies had divergent findings with respect to arrhythmia, and the Patone et al study had important methodologic limitations; an association of elasomeran with arrhythmia has not been shown epidemiologically.

Medical care and study of arrhythmias require clinical diagnostic testing. The cases in the postmarketing database were screened for the reports that had information on electrocardiogram together with abnormal heart rate, and the cases meeting these criteria were medically reviewed. The medical review showed that most case reports lacked adequately detailed information on the workup to assess the possible etiology of the reported arrhythmia event.

Conclusion

The data provided in this PBRER describe sufficiently the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in the reporting period and cumulatively. The safety profile of the vaccine and the benefit-risk evaluation remain positive.

Based on the analysis of all safety data available as of 17 Dec 2022, the MAH considers that for cases included under the arrhythmia-related PTs, information does not substantiate convincing evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and arrhythmia, and the published epidemiologic studies also do not consistently show an increase in arrhythmia in association with vaccine administration. The MAH will continue to monitor events of arrhythmia using routine surveillance.

Rapporteur assessment comment:

As requested, the MAH has provided an updated cumulative review of all cases concerning elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran associated with arrhythmias from all sources, including any relevant articles from literature. The current PSUR does not compare the potential risk of Arrhythmias associated with the 3 products.

In addition, the MAH was requested to perform a late-breaking SCRI (self-controlled risk interval) analysis of arrhythmia for the adult as well as the paediatric population of the P903 US PASS and provide the results as part of the cumulative review in the PSUR which has been presented in PSUR Appendix 11.12j.

Literature

Among 596 literature articles retrieved by the search strategy only 2 publications were deemed relevant by medical/scientific review. While the Patone study evaluated the potential risk of arrhythmias (and other cardiac risks) associated with the first and second doses of the three vaccines mRNA-1273 (elasomeran), BNT162b2, and ChAdOx1 compared to national UK background rates, the Dickerman study aimed at comparing the risk of several potential ADRs including arrhythmias, head-to-head between 2 mRNA COVID-19 vaccines and in relation to the first vaccine dose only. The Dickerman study does not offer general risk estimates.

Regarding the study by Patone et al, the main findings of interest in the present context concern the risk of arrhythmias at specified time intervals after the *first* and *second* vaccination dose, respectively:

While the study did not show an increased overall risk of arrhythmias after the *first dose* of elasomeran, an increased risk of atrial fibrillation or flutter arrhythmia at 15–21 days following a *first dose* of elasomeran vaccine (IRR 2.06, 95% CI 1.11, 3.82) was found.

At 1-28 days an increased risk of cardiac arrhythmia following a *second dose* of elasomeran (IRR 1.46, 95% CI, 1.08, 1.98), with 24,335 (95% CI 15,547 – 103,369) individuals needed to be exposed to a second dose of elasomeran to cause one excess event. This was in contrast to a significantly decreased risk of cardiac arrhythmias following a second dose of ChAdOx1 and BNT162b2, respectively.

Specifically, an increased risk of "Other cardiac arrhythmia" was observed at 1–7 days following a *second dose* of elasomeran (IRR 2.32, 95% CI 1.49, 3.62).

The MAH considers five areas of confounding that may have influenced results. These are acknowledged as possible, though of uncertain importance and to some extent speculative.

The rapporteur considers that the relatively late roll-out of elasomeran in the UK is the most likely explanation for the lower relative and absolute numbers of second-dose vaccinations with elasomeran. However, in spite of the resulting lower statistical power of the elasomeran statistics, significant increases in the risk of arrhythmias – overall and specified – in particular after the second dose, and not found for the two other vaccines, were calculated. Indeed, the authors regrettably did not adjust for mass significance, however, a such adjustment would not be likely to influence the relative risk profile among the different vaccines.

The study by Dickerman aimed at comparing the head-to-head safety in terms of risk of adverse events of the BNT162b2 and mRNA-1273 vaccines in the national health care databases of the US Department of Veterans Affairs.

The interventions of interest were *first-dose* vaccination with either the BNT162b2 vaccine with a second dose scheduled 21 days later or the mRNA-1273 vaccine with a second dose scheduled 28 days later. This study found only "small-magnitude differences within 42 days of the first dose", including a higher risk of arrhythmia within 42 days using the BNT162b2 vaccine as compared to elasomeran (Risk difference, events per 10,000, 7.5 (1.9, 11.5), Risk Ratio 1.21 (1.05, 1.34)). Importantly, however, and in contrast to the Patone study, the Dickerman study presented no data regarding arrhythmias related merely to the second dose and no (first-dose) data on subsets of arrhythmias.

Thus, it is misleading to conclude in accordance with the MAH that "the two epidemiological studies had divergent findings with respect to arrhythmia" regarding neither the first nor the second dose.

The rapporteur considers that the two studies complement rather than contradict each other. Thus, the findings by Patone *et al* of an increased, although limited, risk of arrhythmias with elasomeran has not been refuted. A supplementary comparative analysis addressing the second dose risk of arrhythmias using the Dickerman data set is recommended.

Methodologies for Literature Search and Data Review

The definitions and the search strategy are described and found acceptable.

O/E analysis (PSUR Appendix 11.3, sections 1.2 and 1.4.1)

No significant deviations from the expected rate of arrhythmias were observed overall or by gender and age, even if assuming a 25% reporting rate.

Clinical trial data (pre- and post-authorization)

As stated by the MAH the frequency of arrhythmia events in the clinical trial data from study P301 showed that the placebo group was comparable to that in the vaccine group, while study P204 (study population of healthy pediatrics aged 6 months to < 12 years) did not identify any cases of arrythmia.

Analysis of the data from **mRNA-1273-P903 PASS study** addressing the request from the health authority is presented in Appendix 11.12j, PSUR page 5078ff (and not in Section 16.3.6.1.1. as referenced). A final study report is planned for June 30, 2023.

Analyses for Arrhythmia were based on all (open or closed) claims provided by HealthVerity truncated by

July 31, 2022, censored for prevalent Arrhythmia in accordance with the ACCESS protocol and also reported by COVID-19 status.

The primary dose-agnostic SCRI analysis was based on a post-dose 1-28-day risk window and a control window of 42 days hereafter (or until a subsequent dose was defining the start a new risk window).

Overall, the proportion of Arrythmia cases among 93,349 *Adult* (i.e. aged ≥ 18 years) Spikevax Recipients was not meaningfully different within the Risk Window (49.3%) as compared to the Control Window (50.7%). The gender and age distributions were similar. A subgroup analysis by age and gender showed "statistically elevated ERR of questionable clinical significance in the 18-29 years age group, especially among women" [largest ERR 1.22 (1.06, 1.4) noted for dose 2 in women aged 18-29] censored for COVID-19 diagnosis. This assessment is endorsed, also considering multiple testing.

Among the 77 Spikevax (dose-agnostic) recipients under the age of 18 years, 43 (55.8%) experienced an Arrhythmia event during the 28-day Risk Window, as compared to 34 (44.2%) in the 42-day Control window, ERR 1.22 (CI 0.78-1.93), thus not statistically significant.

However, in a sub-group paediatric (<18 years) analysis, dose 1 specific data showed a statistically increased ERR of 2.71 (1.2-6.12) which is notable (figure 3 [note title misleading for age]).

Concluding on the present SCRI analysis of the P903 PASS study, no clear signal of Arrhythmia has emerged. However, the statistically increased ERR following dose 1 in the paediatric subgroup should be further considered in the evaluation of the paediatric data from all sources going forward.

Cumulative overview of cases

A total of 8,803 cases (10,044 events) of arrhythmia-related PTs were identified for elasomeran (PSUR Appendix 11.12). Of these cases, 6,197 (6,672 serious events) were considered serious and 246 cases (279 events) had a fatal outcome reported. Based on specified criteria, 218 cases (319 events) were considered as possible cases of arrhythmia for analysis comprising 134 serious cases (213 events) and 84 non-serious cases (106 events). Only the 134 serious cases (213 serious events) were considered for the following detailed review.

The most frequently reported PTs for serious cases were Atrial fibrillation (18.5%), arrhythmia (16.0%), and Heart rate irregular (10.0%). Most events (59%) concerned individuals over 50 years of age. The gender distribution was balanced.

When TTO was known (213 events), the highest number of events were reported after dose 2 and – regardless of dose number – within 30 days (58%) and mainly within 14 days (45%).

As noted by the MAH, it is possible that concurrent medical history, including e.g. frequently co-reported Drug hypersensitivity (66% of cases), Hypertension (18%) and Hypersensitivity (14%) may have contributed as risk factors/confounders to the occurrence of arrhythmia.

The MAH has tabulated the diagnostic validity (by the 4-item sponsor classification referred to above) and WHO-UMC causality evaluations of the 134 serious cases in appendix 11.12c with the corresponding case narratives in Appendix 11.12c, including **111** WHO-UMC "Possible" and **23** "Unassessable" cases. None of the 134 serious cases were evaluated as WHO-UMC "Certain", "Probable", nor "Unlikely". These case counts were manually extracted from Appendix 11.12c by the rapporteur.

However, the MAH states in the PSUR p. 312, apparently referring to the same dataset that "According to the WHO causality assessment the 134 serious that were classified as cases of arrhythmia, were assessed as follows: **20** cases were Unassessable, due to the lack of information including medical history, clinical course, among others and **22** case were unlikely. The remaining (**92**) cases were assessed as possible,

since the time course was consistent, however adequate information to evaluate the underlying cause of the reported events **was not generally available**." This was likewise reflected in MAH's concluding remark, that "**most case reports** lacked adequately detailed information on the workup to assess the possible aetiology of the reported arrhythmia event" (rapporteurs highlighting in bold).

In Appendices 11.12g/h, 162 "uncharacterized" serious cases are listed, comprising 133 WHO-UMC "Possible", 1 "unlikely", and 28 "Unassessable" cases.

The MAH is requested within the current procedure to 1) clarify the definition of an uncharacterized serious case and also clarify the difference in case selection criteria for the tables in Appendix 11.12c (N=134, MAH serious) and 11.12g (N=162, All serious).

The MAH is also requested, within this procedure to

2) explain the differences in case counts attributed to the various WHO-UMC categories in Appendix 11.12c compared to the PSUR text description, and update the Appendices if so indicated.

3) account for the causality evaluation algorithm leading to the WHO-UMC classification "Possible" in an apparently automatic fashion, precluding higher classifications for individual cases, even though "the underlying cause of the reported events was not *generally* available".

4) account for each and all cases that according to the WHO-UMC classification may qualify for higher classification, i.e. "Probable" or "Certain", and update the relevant Appendices accordingly.

The MAH is reminded that the WHO-UMC definition of a *Probable* case states:

* The TTO criterion (Event or laboratory test abnormality, with reasonable time relationship to drug intake) generally use by the MAH

* That the event is "Unlikely to be attributed to disease or other drugs". This in contrast to the "Possible" criterion "Could also be explained by disease or other drugs". When relevant, this distinction should be noted. E.g. a specific allergic state, not related to vaccination, may not be automatically considered a confounder for Arrhythmia in this context.

* Response to withdrawal clinically reasonable. The rapporteur does not consider this criterion useful in the evaluation of vaccination related ADR's.

* Importantly: Rechallenge not required

Fatal cases

Among the 134 serious cases, there were two fatalities reported following elasomeran, both evaluated by the MAH with Unlikely causality according to the WHO-UMC classification, as outlined above. This is endorsed.

Special populations

No cases of Arrhythmias were reported in Children or in Adolescents.

Booster (3+ dose) vaccination

A total of 16 serious cases (including 21 serious events), were reported in the GSDB after a booster dose (defined as the third dose or higher) of elasomeran. No fatal events were reported. The majority of these events (11; 69%) were reported in females and most (15; 94%) with a TTO of less than 30 days.

Vaccine variants

The above analysis was mainly based on the original elasomeran vaccine product. Recently, combined variant vaccines have been marketed (elasomeran/imelasomeran and elasomeran/davesomeran). There have been no fatal cases and no cases that qualified for Arrhythmia Review following elasomeran/imelasomeran. Only one case qualified for Arrhythmia Review following elasomeran/davesomeran was reported and assessed as WHO-UMC Causality possible primarily due to temporal association while a medical history of Arrhythmia and other confounders were noted. Endorsed.

Disproportionality analysis

No disproportionality found in VAERS data.

With EVDAS, the analysis showed modest disproportionality amongst the MedDRA PTs of "Arrhythmia", "Extrasystoles", "Atrial fibrillation" and "Heart rate irregular" with ROR (-) values of 2.13, 2.03, 1.05 and 1.4, respectively.

In conclusion, serious events with Arrhythmia associated with elasomeran in any form are very rarely reported and thus not easily identified in controlled trials. However, there are indications in the literature, among case reports, and in the EVDAS disproportionality analysis, that a causal association between elasomeran and arrythmias cannot be ruled out at this time. However, no such conclusion can be safely drawn based on the present information.

The current status of this issue is to be determined after the MAH's response to the abovementioned requests.

2.5.2. Hearing loss

[only source-background-conclusions are presented below. For full signal evaluation report, please refer to the PSUR]

Source: Cumulative review on hearing loss was requested by the PRAC in the previous PSUSA (EMEA/H/C/PSUSA/00010897/202206).

Background: A health authority requested to perform a cumulative review of all cases concerning elasomeran/imelasomeran and elasomeran/davesomeran associated with the HLT of "Hearing losses" from all sources, including any relevant articles from literature. Cumulatively, as of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran) had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

Sensorineural hearing loss refers to any cause of hearing loss due to pathology of the cochlea, auditory nerve or the central nervous system and is in contrast to conductive hearing loss which is related to obstruction of the ear canal or problems with the cochlear bones [162]. Sudden sensorineural hearing loss is defined as the development of hearing loss of at least 30 dB in three contiguous frequencies over a 72- hour period. The incidence in the United States is estimated to be 27 cases/100,000 population per

year ranging from 11 per 100,000 in people less than 18 years of age to 77 per 100,000 in people over the age of 65 [163]. Etiologies include infections (bacterial and viral), metabolic causes including diabetes and hypothyroidism, hypertension, neoplastic disease, exposure to aminoglycosides and salicylates, vascular causes including cardiovascular bypass and cerebrovascular accident/stroke as well as congenital causes, but a majority of cases are idiopathic [164].

Sensorineural hearing loss has been reported in association with COVID 19 infection. A recent literature review detailed case reports and noted that most cases were associated with other symptoms including tinnitus and vertigo. About one half of the patients reported showed improvement with steroid therapy [165]. Mechanisms of action postulated include direct viral invasion of middle ear cells and vascular injury to the terminal vessels supplying blood to the middle ear [166] [167]. There have been numerous anecdotal case reports in the literature of sensorineural hearing loss after COVID 19 vaccination. These reports include cases associated with mRNA vaccines but also after viral vector vaccines produced by Janssen and Astra Zeneca. Although of interest clinically, these cases do not clearly establish a clear role for vaccination in causing hearing loss.

Conclusions: A cumulative review of the GSDB for reports under the HLT of "Hearing losses" received after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran was conducted, as per request received from a HA. The MAH identified 2,327 cases (2,589 events) for individuals between the ages of 5 to 101 years old. Only one case received during the reporting period of this PBRER, from a literature article had sufficient data to meet Brighton Collaboration case criteria (Level 1). The review of cases identified during the reporting period of this PBRER showed that most of the cases were heavily confounded by known risk factors associated with acute sensorineural hearing loss. There were five cases associated with herpes zoster reactivation.

In general, it is difficult to adequately analyze post-authorization data due to inherent limitations in spontaneous reporting. Evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomernan and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Based on the literature review of the mechanisms of action postulated including direct viral invasion of the middle ear and vascular injury to the terminal vessels of the middle ear and the three epidemiological studies that aimed to assess the relationship between COVID 19 vaccination and hearing loss do not provide convincing evidence to show an association with vaccination; moreover, a pathophysiologic process to explain such an association has not been shown. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Based on the cumulative review of available data as of 17 Dec 2022, the MAH considers there is insufficient evidence to consider Hearing Loss as a safety concern. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities. No changes to the product information are required at this time.

Rapporteur assessment comment:

Following a comment from a MS in the previous PSUSA (EMEA/H/C/PSUSA/00010897/202206), the MAH was requested to present a cumulative review of the HLT 'Hearing losses' including review of post-marketing case reports, cases from clinical trials, literature review, and disproportionality analysis.

In response to the request, the MAH presented the following data:

Clinical trials

No imbalance between the mRNA-1273 arm and the placebo arm was observed for events from the SMQ 'Hearing and vestibular disorders' in the MAH-sponsored clinical trials; mRNA-1273-P301, mRNA-1273-P203 and mRNA-1273-P204.

Post-marketing reports

Cumulatively, the MAH received 2,327 case reports from the HLT 'hearing losses'. The MAH presented the case reports in two separate reports, covering periods from 18 Dec 2020 to 18 Jul 2022 and from 19 Jun 2022 to 17 Dec 2022, respectively. In the future, the MAH is requested to present cumulative data in one report.

Case reports received cumulatively, i.e. from 18 Dec 2020 to 18 July 2022

During this time period, the MAH received 2,116 case reports with 2,372 events from the HLT 'hearing losses'. Of the 2,372 events, 669 events were non-serious and 1,703 events were serious. Hearing loss was reported more frequently in females (57.5%) than in males (40.3%). The age of the concerned subjects ranged from <1 year to 101 years, with the median of 52 years. When TTO was reported, most events occurred after D1 (32.3%) followed by D2 (30.7%) and D3 (6.7%). In 30% of events, TTO was not reported.

During the interval, the MAH received three fatal cases where hearing loss where reported. The cause of death was not associated with hearing loss (Covid-19 infection, respiratory failure, hepatic failure, renal failure).

The MAH did not provide an overview of the events (PTs) reported in the 2,116 cases received from 18 Dec 2020 to 18 July 2022, nor any information about causality assessment of the 2,116 cases (see RSI below).

Case reports received in the reporting interval, i.e. from 19 Jun 2022 to 17 Dec 2022

During this time period, the MAH received 283 case reports with 293 events from the HLT 'hearing losses'. The majority (74.2%) of these cases were serious. Hearing loss was reported more frequently in females (app. 60%) than in males (app. 40%). The age of the concerned individuals ranged from 12 years to 93 years, with the mean of 50.9 years and the median of 52 years.

In the majority of the reports (62.5%), TTO by dose was unknown. When TTO was reported, most events occurred after D3 (14.7%) followed by D2 (13.7%), D1 (6.5%) and D4 (2.7%).

The most commonly reported events (PTs) were hypoacusis (37.9%), deafness (25.3%) and sudden hearing loss (16.0%).

Brighton Collaboration case classification

The MAH stated that they conducted an evaluation of all the interval cases identified under the HLT "hearing losses" using the Brighton Collaboration (BC) case definition for acute sensorineural hearing loss (Carol Liu 2020).

The MAH reported that all but one interval case report were classified as level 4 BC cases (insufficient information). The remaining report, case no.: [redacted] summarised below, fulfilled the definition of BC level 1 (definite case).

Case no.: [redacted] (published in Zoccali et al. (2022)): 67F experienced sudden sensorineural hearing loss (left side) seven days after vaccination with D3 of elasomeran. Her medical history included positive test for coronavirus (one year prior to vaccination with D3 of elasomeran), allergies (unspecified) and periodic use of antihistamines. She had no history of dizziness, vertigo, tetanus or hearing loss. Test results: otoscopy unremarkable (both ears), Weber test lateralized to the right ear, Rinne test positive

(both ears). Audiometry showed profound right sensorineural hearing loss of at least 60 dB in every frequency (250-8000 Hz). No other neurologic deficits were observed. Chest x-ray, blood tests, MRI and MRA were normal. She received dexamethasone and she was recovering.

The MAH assessed this case as WHO-possible and highlighted the medical history of Covid-19 infection as a potential confounder. The assessor classified this case as WHO-probable due to temporal association (TTO =7 days) and lack of other factors that would explain occurrence of the sudden hearing loss. The assessor considers it unlikely that Covid-19 infection one year prior to the vaccination could cause sudden hearing loss.

Hearing loss following vaccination with elasomeran/imelasomeran and elasomeran/davesomeran

During the reporting interval, the MAH received 11 and 5 case reports of events related to hearing loss following vaccination with elasomeran/imelasomeran and elasomeran/davesomeran, respectively. Based on the information provided by the MAH, no major differences were noted in these cases compared to case reports received for elasomeran.

Observed vs expected analysis

The MAH used the US background incidence of 27 cases per 100.000 person-years reported in Alexander et al. (2013) to calculate the expected reporting rates of hearing loss.

Based on the number of cases of hearing loss reported (N=2343) and the total exposure of 52,482,913 person-years (with a risk window of 21 days), the MAH estimated the observed incidence of hearing loss to 4.46 cases per 100.000 years. The O/E rate ratio was thus below one in the overall analysis [0.17 (95% CI: 0.16-0.17)], and in the analyses stratified by age and gender. The sensitivity analysis showed the O/E rate ratios >1 in the age group 12-17 years; with the O/E of 1.72 (95%CI: 0.62-4.79) and 3.45 (95% CI: 1.37-8.68), assuming 50% and 75% underreporting, respectively. However, the observed reporting rate in this age group was calculated based on only 5 case reports.

Disproportionality analysis

The MAH stated that no disproportionate reporting of events related to hearing loss was observed in VAERS.

In EVDAS, there was a signal of disproportionality for the following events (PTs) from the HLT 'Hearing losses': 'deafness', 'deafness neurosensory', 'deafness permanent', 'deafness unilateral', 'hypoacusis' and 'sudden hearing loss'.

Literature

The MAH presented the following three publications:

Formeister 2022: a cross-sectional study of probable cases of SSNHL reported to VAERS during the first 7 months of the US vaccination campaign against COVID-19. In total, 555 reports met the criteria of probable SSNHL, of these 222 reports (40%) concerned recipients of Moderna vaccine. The mean age of the affected individuals was 54 years (range: 15-93 years); the mean TTO was 6 days (range: 0-21 days). The incidence of SSNHL reported within 21 days following vaccination against COVID-19 (vaccines from Moderna, Pfizer and Astra Zeneca) was 0.6 to 28.0 cases of SSNHL per 100. 000 people per year, and it was comparable to the incidence of SSNHL in the general population (11 to 77 cases per 100 000 people per year).

Nieminen 2023: a registry-based retrospective cohort study with 5.5 million Finish residents to assess the risk of SSNHL following COVID-19 vaccination. The incidence of SSNHL occurring during a 55-day post-vaccination risk window was compared with the pre-pandemic incidence of SSNHL in Finland (18.7 per 100.000 person-years). The results suggested no association between SSNHL and COVID-19 vaccination.

For the mRNA-1273 vaccine, the adjusted incidence rate ratios in the age group ≥55 years were 0.7 (95% CI, 0.3-1.5), 0.9 (95% CI, 0.6-1.4), and 1.2 (95% CI, 0.7-2.0) following D1, D2 and D3, respectively. Likewise, no statistically significant increase in the adjusted incidence ratios was observed for three doses of the mRNA-1273 vaccine in individuals aged 0-54 years old.

Yanir 2022: retrospective, population-based cohort study from Israel with the aim to assess a possible association between BNT162b2 vaccine and SSNHL. The observed numbers of SSNHL that occurred within 21 days after each of the first and second vaccine doses were compared with the expected number of cases, estimated from the historic data. The incidence rate of SSNHL was 60.77 (95% CI,48.29-73.26) per 100.000 person-years after D1 and 56.24(95% CI,43.83-68.64) per 100.000 person-years after D2. The corresponding incidence rates of SSNHL in the previous reference years were 41.50 (95%CI, 37.98-45.01) per 100.000 person-years in 2018 and 44.46 (95% CI, 40.85-48.07) per 100 000 person-years in 2019. With the data from 2018 used as reference, the age- and sex-weighted standardized incidence ratios for D1 and D2 were 1.35 (95% CI, 1.09- 1.65) and 1.23 (95% CI, 0.98-1.53), respectively.

Biological mechanism

The MAH stated that "literature review of the mechanisms of action postulated including direct viral invasion of the middle ear and vascular injury to the terminal vessels of the middle ear". However, the MAH did not present any literature that would discuss a possible biological mechanism for the association between hearing loss and Covid-19 vaccines, or did not provide references to such literature.

MAH's conclusion

The MAH stated that available evidence is insufficient to consider hearing loss as a safety concern. Thus, the MAH did not propose and changes to the product information.

Rapporteur's assessment and conclusions

The MAH received cumulatively 2,116 case reports of hearing loss reported with a temporal association to vaccination with elasomeran (and to lower extent bivalent vaccines). In Appendix 11.18 to the PSUR, the MAH presented an overview of the interval cases (including case narratives). However, such an overview was not presented for the cumulative cases and the information provided on the cumulative cases is scarce. For example, it is unknown how many of the 2,116 case reports fulfilled the BC case definition of sudden hearing loss. In addition, the MAH's causality assessment for these reports was not provided. Among the interval cases presented by the MAH, the assessor identified one case report (no.: [redacted] that could be classified as WHO-probable, as per the WHO-UMC causality assessment system.

The observed/expected analyses performed by the MAH showed that the observed reporting rates were not higher than the expected reporting rates, neither in the overall analysis nor in the age-and gender-stratified analysis.

No imbalance between the mRNA-1273 arm and the placebo arm was observed for hearing loss and related events in the MAH-sponsored clinical trials.

A population-based cohort-study from Israel (Yanir 2022), showed a modest increase in the incidence rates of SSNHL following vaccination with Covid-19 (Comirnaty). The age- and sex-weighted standardized incidence ratios for D1 and D2 were 1.35 (95% CI, 1.09- 1.65) and 1.23 (95% CI, 0.98-1.53), respectively. Contrary to these results, Nieminen 2023 did not observe statistically significant differences in the pre- and post-COVID-19 vaccination incidence rates of SSNHL, in the registry-based study in the Finish population.

Overall, the evidence presented by the MAH is not sufficient to establish a causal association between elasomeran and sudden hearing loss. However, given that the MAH did not provide any information on the causality of the cumulative cases and did not state whether any of the 2,116 reports could be

classified as 'index cases', the assessor cannot form an opinion about the strength of the evidence available in the cumulative case reports. **Thus, further information is needed. Within the current PSUSA, the MAH is requested to present in details (including case narratives and MAH's causality assessment) all reports that fulfil level 1-3 BC case definition of sudden hearing loss AND that can be considered as 'index cases'*. If no index cases can be identified by the MAH, it should be clearly stated in the response.**

Final conclusion on the signal will be reached in the updated AR, following review of the additional information submitted by the MAH.

*An index case is defined as a case report that cannot be excluded due to confounding by disease, concomitant medicines, or comorbidities, and has a plausible time to onset and a plausible mechanism of action.

References:

Alexander, T. H. & Harris, J. P. Incidence of Sudden Sensorineural Hearing Loss. Otol Neurotol 34, 1586–1589 (2013).

Carol Liu YC, et al.Sensorineural hearing loss (SNHL) as an adverse event following immunization (AEFI): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2020;38(30):4717-31.

Formeister EJ, et al. Assessment of Sudden Sensorineural Hearing Loss After COVID-19 Vaccination. JAMA Otolaryngol Head Neck Surg 2022;148(4):307-15.

Nieminen TA, et al. Sudden Hearing Loss Following Vaccination Against COVID-19. JAMA Otolaryngol Head Neck Surg 2022.

Weber PC. Sudden sensorineural hearing loss in adults: Evaluation and management. UpToDate. Last updated on 10-May-2022. Accessed on 09-Mar-2023.

Yanir Y, et al. Association Between the BNT162b2 Messenger RNA COVID-19 Vaccine and the Risk of Sudden Sensorineural Hearing Loss. JAMA Otolaryngol Head Neck Surg 2022;148(4):299-306.

Zoccali F, et al. Sudden Sensorineural Hearing Loss after Third Dose Booster of COVID-19 Vaccine Administration. Diagnostics (Basel). 2022; 12(9):2039.

2.5.3. Histiocytolic necrotizing lymphadenitis

[only source-background-conclusions are presented below. For full signal evaluation report, please refer to the PSUR]

Source: Cumulative review on histiocytolic necrotizing lymphadenitis was requested by the PRAC in the previous PSUSA (EMEA/H/C/PSUSA/00010897/202206).

Bakcground: A histologically distinct form of subacute necrotizing lymphadenitis was first described in Japan in 1972 by Kikuchi and independently by Fujimoto and colleagues. Although apparently more common in Asia and Asian people, the disease has been reported in many areas of the world, including Europe, the United States, and Australia [188].

Kikuchi-Fujimoto disease occurs most often in young women (mean age, 30 years; female/male ratio, 4:1). No laboratory study is pathognomonic for this pathology. Laboratory abnormalities associated with KFD include mainly an inflammatory syndrome with moderate granulocytopenia observed in 25-58% of cases. The most common clinical manifestation is cervical adenopathy with or without fever, but some

authors report generalized lymph node enlargement (1.3-22.2%); additional findings may include fever, sore throat, weight loss, sweats, chills, myalgia, arthralgia, splenomegaly, and skin rash [189]. About half of the cases may be associated with painful lymphadenopathy. Leukopenia is reported in 25-50% of the cases and leukocytosis in less than 5% of the cases [190]. Laboratory abnormalities may include leukopenia, an elevated serum transaminase level, and an elevated serum lactate dehydrogenase level. In almost all cases, the course is benign and followed by complete recovery within 1 to 3 months [191]. Recurrence of disease may occur but is infrequent, and fatalities are exceptional.

The diagnosis is confirmed based on histopathological examination of the lymph nodes biopsy and immunohistochemical testing. It shows typically on microscopic examination as a partially preserved architecture with follicular hyperplasia. Three forms have been described in the literature: necrotic form (more than 50% of cases), proliferative form (30%), and xanthogranulomatous form (<20%) [192]. Histological examination, especially seen in sub-Saharan Africa, also helps to exclude the main differential diagnoses such as infectious lymphadenitis (particularly tuberculosis) and lymphomas. Immunohistochemical analysis reveals CD3+ cells as the majority of the cells present in the pathological areas of the lymph node. The cell population is predominantly composed of CD68+ histiocytes, while the lymphocyte population represents 20-50% of the total cell population, mainly CD8+ cytotoxic T-lymphocytes.

These heterogeneous results may be a reflection of the different immunological staging of KFD. KFD has been reported in rare patients infected with the human immunodeficiency virus (HIV). Pathogenesis of the lesion is probably related to an impaired immune function [193]. It has been hypothesized that KFD is predominantly linked to apoptosis mediated by cytolytic lymphocytes. Felgar et al [194] found evidence of apoptosis (DNA fragmentation, using the in situ-end labeling technique, Iressa Survival Evaluation in Lung Cancer) in lymphocytes and histiocytes within and in surrounding areas of necrosis. They found also an increase in CD8+ and TIA1+ lymphocytes, whereas CD56+ cells were present in few numbers. These authors concluded that their findings corroborated a viral (still unknown) or autoimmune (perhaps initiated by a viral infection) pathogenesis in KL.

The etiology of KFD is still unknown. Two main theories have been postulated, but although the clinical and histopathological features point to a viral etiology, this hypothesis has not been proven yet. Generally, the diagnosis is made based on a lymph node excisional biopsy. Its recognition is crucial mainly because this disease can be mistaken for other disorders, including SLE or malignant lymphoma [195]. A KFD-like lesion occurring in a patient with silicone lymphadenopathy suggested that KFD may represent a non-specific autoimmune-like reaction. As mentioned above KFD is thought to either occur as a response to a viral infection or due to an underlying autoimmune disorder [196]. The discovery of histiocytes and CD8-positive cells in KFD-affected lymph nodes supports the viral origin. Numerous studies have attempted to show an association between KFD and different viruses. In a study by Cho et al [197] polymerase chain reaction (PCR) was used to check 50% of lymph node tissues identified with KFD for the presence of human herpesvirus (HHV-6, 7, and 8) but the study could not establish a link between KFD and HHV-6, 7, or 8. Hudnall et al [198] examined 30 lymph nodes affected by KFD and demonstrated that HHV-1, varicella zoster virus, and HHV-8 DNA were not detectable, and HHV-2, CMV, HHV-6, and HHV-7 were occasionally detected. This contrasts with another study by Zhang et al [199] which identified an association between parvovirus B19 and KFD. According to the study by Hudnall et al., it was unlikely that these viruses served as the etiology of KFD.

It has also been demonstrated that autoimmune disorders may play a role in the pathogenesis of KFD. Imamura et al [200] first suggested that KFD might be a lupus-like autoimmune condition triggered by viral infection, given that histologic features of KFD in some cases may be difficult to distinguish from systemic lupus erythematosus (SLE)-associated lymphadenitis. Although at diagnosis KFD is not associated typically with serologic evidence of autoimmune disease, in 2 cases reviewed by Dorfman and

Berry [189], SLE subsequently developed and led to a recommendation that patients with KFD be observed carefully for development of SLE. Several cases of KFD occurring in association with SLE have been described [201]. A study by Sopeña et al [202] detected autoimmune conditions, including SLE, thyroiditis, leukocytoclastic vasculitis, Sjogren's syndrome, Still's disease, and Wegener's granulomatosis, associated with KFD. These findings were also reported in another study by Kucukardali et al [203] who reported 32 cases of KFD associated with SLE. Of these instances, 18 had KFD and SLE at the same time, six developed SLE later, and four had a pre-existing condition that was indicative of SLE. Goldblatt et al [204] discussed three Asian women who had KFD, and none of the three patients had symptoms or signs typical of SLE at the time of their diagnosis and testing for ANA was negative for all three patients however, after receiving a diagnosis of KFD, all three patients experienced symptoms of SLE and a positive ANA test within a 3-14-month window. Although the link between KFD and SLE has been reported, the exact association remains unclear. Thus, KFD pathogenesis may be a consequence of an aberrant T-cells and histiocyte immune response to an immunogenic antigen [205]. A study conducted by Ferreras et al [206] which was based on a search in the Spanish AEs database and the European AEs database (Eudravigilance) looking for any drug and the diagnosis of "HNL" according to MedDRA as of 02 Jun 2022. In the Spanish AEs database, they identified two reports, one related to methotrexate and one to elasomeran. In the Eudrovigilance 14 KFD AEs related to COVID-19 vaccines were identified, including 11 related to Comirnaty vaccination, two after Vaxzervria, and one after elasomeran vaccination.

Cases of KFD associated with COVID-19 infection have also been reported [207]. Taking into account the possible viral origin, it seems logical to think that COVID-19 may also induce the onset of KFD, as do the numerous viruses already described as possible causative agents. It is very uncommon for KFD to occur after vaccination, and only rare cases in the literature of KFD associated with other vaccines can be found, mainly after human papillomavirus vaccine, influenza and Japanese encephalitis virus vaccination. Although the causal relationship between vaccination and KFD is not proven, according to Ferreras et al. the T-lymphocyte-mediated immune response at the lymph node level could contribute to the development of KFD.

There are two hypothesized mechanisms for the development of autoimmune diseases following vaccination, it includes molecular mimicry, wherein vaccines trigger an immune response against self-antigens, and bystander activation, wherein vaccines release self-antigens from host tissues and activate antigen-presenting cells and dormant autoreactive T-helper cells. Following on the autoimmunity hypothesis for KFD, it has been suggested that the cytoplasm of lymphocytes and histiocytes seen in KFD has a tubular reticular structure, similar to that seen in autoimmune diseases, such as SLE. It is also suggested that patients with a genetic component, especially HLA-DPA1 and HLA-DPB1 (more frequent in Asians), develop an immune response that is mainly composed of T-cells, especially cytotoxic T-cells.

Kashiwada et al [191] presents in their article that given that mRNA vaccines induce a rapid and localized infiltration of neutrophils, monocytes, and dendritic cells at the site of administration and in the draining lymph node promptly after vaccination. COVID-19 mRNA vaccine rapidly induces CD8+ T-cells as well as antibody production, contributing to vaccine efficacy, it is possible that the mRNA vaccine-induced a CD8+ T-cell-related immune response in the draining lymph node, resulting in the development of KFD localized to the ipsilateral axillary lymph node. However, a causal relationship between KFD and COVID-19 vaccine has never been proven, and further pathophysiological analysis is warranted, according to the authors.

Conclusions: The etiology of KFD is still unknown. Two main theories have been postulated, but although the clinical and histopathological features point to a viral etiology, this hypothesis has not been proven yet. Generally, the diagnosis is made based on a lymph node excisional biopsy. Its recognition is crucial mainly because this disease can be mistaken for other disorders, including SLE or malignant

lymphoma [195]. A KFD-like lesion occurring in a patient with silicone lymphadenopathy suggested that KFD may represent a non-specific autoimmune-like reaction.

A cumulative review of the safety data in the MAH's GSDB for reports of related HNL events received after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran identified 4 cases (4 events) for individuals between the ages of 45 to 47 years old. There were no reports received for individuals <45 years of age. All cases were considered unlikely related to the vaccine based on the information available which included important confounding factors like associated comorbidities (HIV, Castleman's Disease, SLE), exposure to COVID-19, etc.

Based on the cumulatively estimated total doses of elasomeran administered worldwide (772,908,958 doses) the reporting rate for cases of HNL after administration of elasomeran is 0.0005 cases per million doses administered. In addition, all four reported cases were considered unlikely related to the vaccine.

Evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The cumulative data shows no new safety concerns or change in safety profile of the vaccine and the benefit-risk evaluation remains positive. The MAH considers that at this time there is no need to update the product information or the RMP for elasomeran. The MAH will continue to monitor events of HNL using routine surveillance.

Rapporteur assessment comment:

Background

Kikuchi-Fujimoto Disease (KFD) or histiocytic necrotizing lymphadenitis (HNL) is a rare and benign disorder characterized by subacute necrotizing regional lymphadenopathy. It is usually presented as painful cervical nodes and associated with fever, headache, night sweats, nausea, vomiting and sore throat. Etiology of KFD is still unclear, two theories have been proposed: infections and autoimmune origin (Ferreras 2022).

A signal concerning HNL and COVID-19 vaccination was raised by a MS on 15.07.2022, following identification of one case of HNL related to Spikevax and additional 11 cases related to vaccination with Comirnaty. The signal was not confirmed for Spikevax with the justification that the evidence was insufficient to warrant further analysis (EPITT no.: 19838). The MAH was requested to present a cumulative review of the topic in the current PSUR.

In response to the request, the MAH presented the following data:

Post-marketing case reports

Cumulatively, the MAH identified the following four reports of KFD/HNL in their global safety database:

Case #[redacted]: 47M experienced HNL following D3 of Spikevax (TTO=73 days). Limited information is provided, medical history is missing. Comirnaty is reported as concomitant medication, however, the date of administration is unknown.

The MAH assessed this case as WHO-unlikely, due to a long TTO. The assessor classified this case as WHO-possible. Given that the mechanism is unclear, and the latency for cases of HNL associated with Covid-19 vaccination reported in the literature ranges from 1 day to 3 months (Rodríguez-Ferreras 2022), the temporal relationship of 73 days can still be considered reasonable.

Based on the information provided, it appears that this case was included in the review by Rodríguez-

Ferreras 2022 (see below) and it was one of the case reports that triggered the signal.

Case #[redacted] (Villalba 2022): 45M experienced HNL (cutaneous KFD) two days after vaccination with Spikevax (dose number unknown). Comorbidities included [redacted] infection (Stage A2 on antiretroviral treatment) and Castleman's disease. PCR was positive for EBV. Diagnosis of KFD was based on histopathological examination.

The MAH classified this case as WHO-unlikely due to the confounding by comorbidities (HIV and Castleman's disease) and EBV infection. The assessor considers this case as WHO-possible, due to a close temporal relationship (2 days), although the assessor agrees with the MAH that HNL could also be explained the patient's comorbidities.

Case #[redacted] (Ghang 2022): A previously healthy female in her twenties experienced HNL following vaccination with D1 of Spikevax (TTO=10 days). Co-reported reactions included SLE and aseptic meningitis. She was hospitalized with headache and fever. She had had intermittent fever for 20 days, with hair loss and necrotizing cervical lymphadenitis. It is unclear how the diagnosis of HNL was made. She was treated with prednisolone, naproxen and hydroxychloroquine, and she was recovering.

The MAH assessed this case as WHO-unlikely, due to confounding by comorbidities (SLE and meningitis). The assessor classified the case as WHO-possible, due to close temporal association, although the assessor agrees with the MAH that HNL could also be explained by the patient's comorbidities.

Case #[redacted] (Fadul 2022): 46M presented with cervical lymphadenopathy (KFD) and fever, which was treated with multiple course of antibiotics. The fever started when he was in [redacted], where he had a close contact with a COVID-19 positive person. His COVID-19 antigen test was negative. He had received three doses of Spikevax on an unknown date. He was also negative for CMV, HSV-1, HSV-2, EBV, fungal infection (GMS stain) and mycobacteria (Ziehl-Neelsen stain). Medical history included smoking and drinking. Diagnosis of KFD was based on histopathological evaluation of the affected lymph node. He received analgesics and multivitamins, and was advised to rest. He recovered.

The MAH assessed this case as WHO-unlikely. The assessor classified this case as WHO-unassessable. The publication by Fadul et al. (2022) mentioned that the patient's immunization was up to date, including three doses of Spikevax. However, the dates for the vaccination were not provided.

Literature

The MAH performed focused search in PubMed for elasomeran and KFD, which retrieved 17 publications. The MAH stated that the search did not identify any clinical literature that would describe new and potentially important safety information on the safety profile of elasomeran.

In the future, the MAH is requested to be more specific when presenting results of literature searches. It is unclear how the MAH defines 'potentially important safety information'.

From the background information presented on the topic by the MAH, the assessor identified the following publications concerning the association between HNL/KFD and Covid-19 vaccination:

Rodríguez-Ferreras et al. (2022): review of post-marketing reports of HNL following Covid-19 vaccination submitted to EVDAS and the Spanish AE database (FEDRA). In total, 15 case reports of HNL following COVID-19 vaccination were identified from EVDAS (N=1) and FEDRA (N=14); the vaccines reported were Comirnaty (N=11), Vaxzevria (N=2) and Spikevax (N=2). The age of the patients ranged from 10 to 52 years (median 27 years); eight patients had other immune disease co-reported, including SLE, lymphadenopathy and Kawasaki's disease. When reported, TTO ranged from 1 day to 3 months.

It seems likely that the HNL reports from FEDRA are the case reports that triggered the signal on HNL raised in July 2022.

Kashiwada, et al. (2022): a case report of KFD associated with Covid-19 vaccination in a 27-year-old Japanese female. She noticed swelling of submandibular region a day after D1 (Comirnaty), and a fever and axillary swelling a day after D2 (Comirnaty). Ninety days post-D1, she developed delayed lymphadenopathy diagnosed as KFD. Diagnostic follow-up excluded infections with Covid-19, EBV, CMV, M. tuberculosis and bartonella. She was treated with acetaminophen and NSAIDs, and she recovered.

Data from EudraVigilance

The assessor searched EudraVigilance for cases of 'histiocytic necrotizing lymphadenitis' (PT) associated with Spikevax vaccination, reported through 16-03-2023. No additional reports were identified.

No signal of disproportionality was observed for 'histiocytic necrotizing lymphadenitis' and elasomeran; with N=4 and ROR= 1.68 (95% CI: 0.61-4.60).

MAH's conclusions

The MAH concluded that the evidence from the post-marketing case reports is inadequate to support causality between HNL and elasomeran exposure. The MAH stated that they would continue to monitor events of HNL using routine surveillance.

Rapporteur's conclusions

Data concerning the association between Spikevax and histiocytic necrotizing lymphadenitis consist of four post-marketing case reports, all originating from the literature. Of these, two reports are confounded by the patients' comorbidities (cases #[redacted] and #[redacted]). The remaining two reports contain limited information (case #[redacted]) or the temporal relationship to the vaccination is unclear (case #[redacted]).

The PRAC Rapporteur concludes that the evidence from these four case reports is insufficient to establish a causal association between Spikevax and histiocytic necrotizing lymphadenitis. Therefore, no further actions beyond routine pharmacovigilance are considered warranted at this point.

References:

Fadul A, et al. Kikuchi-Fujimoto Disease: A Rare Cause of Pyrexia of Unknown Origin and Cervical Lymphadenopathy. Cureus. 2022;14(10):e30823.

Ghang B, et al. Autoimmune rheumatic disease after SARS-CoV-2 vaccination. J Med Virol. 2022;94(12):5618-5620.

Kashiwada T, et al. Kikuchi-Fujimoto disease can present as delayed lymphadenopathy after COVID-19 vaccination. Hum Vaccin Immunother 2022;18(5):2071080.

Rodríguez-Ferreras A, et al. Kikuchi-Fujimoto Disease and COVID-19 vaccination: pharmacovigilance approach. Eur Ann Allergy Clin Immunol 2022.

Villalba MAB, et al. Cutaneous Kikuchi-Fujimoto disease (KFD) post COVID-19 vaccination: case report. Virchows Archiv. 2022;481(Suppl 1):S1-S364.

2.5.4. Mechanical urticaria/dermatography

Source of the New Information

The information presented below includes an analysis performed on cases received by ModernaTx, Inc. cumulatively (18 Dec 2020 to 17 Dec 2022) and during the reporting period (19 Jun 2022 to 17 Dec

2022) for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran for cases of mechanical urticaria as per a health authority request.

Background Relevant to the Evaluation

A health authority request was received by the MAH during the reporting period of this PBRER to perform a cumulative review of all cases of elasomeran associated with mechanical urticaria/dermatographism, and should the pattern indicate a co-occurrence of mechanical urticaria and chronic urticaria (CU), also include a review of CU.

• The MAH has previously conducted several comprehensive reviews of safety reports from the GSDB on the topic of urticaria and CU. The MAH determined that the signal of urticaria was considered an identified risk (not important), leading to an update to the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran CCDS.

• On 02 Aug 2022, the MAH updated the elasomeran CCDS *Section 4.8 Undesirable effects, Table 1* by adding "acute and delayed urticaria" as distinct terms to the *Skin and Subcutaneous Tissue Disorders SOC* and removing the reference "includes urticaria" from the *Immune System Disorders SOC* based on the evolving understanding of the types of urticaria reported with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

• The SmPC for elasomeran and Spikevax bivalents was also updated, including under *Section 4.8 Undesirable effects, Table 3. Adverse reactions from elasomeran clinical studies and post-authorization experience in children and individuals 6 months of age and older* in the *Skin and Subcutaneous Tissue Disorders SOC* to include the ADR term "Urticaria", with an uncommon frequency (≥1/1 000 to <1/100), including a footnote indicating: *"Urticaria has been observed with either acute onset (within a few days after vaccination) or delayed onset (up to approximately two weeks after vaccination)"*.

According to the Dermatology Section of the European Academy of Allergology and Clinical Immunology, the EU-founded network of excellence, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization (WAO) developed consensus guidelines for the definition, classification, diagnosis, and management of urticaria.

Urticaria is defined as a condition characterized by the development of wheals (hives), angioedema, or both [152]. Urticaria is a common dermatologic condition, typified by "intensely pruritic, well-circumscribed, raised wheals ranging from several millimeters to several centimeters or larger in size". Urticaria can occur with or without angioedema, which is defined as a painful, localized, warm, nonpitting oedema of the subcutaneous or interstitial tissue. The intensity of the pruritus can cause significant discomfort and impairment of daily functioning and disrupt normal sleep.

The current guidelines classified urticaria based on the clinical manifestation of urticaria which are broad, and patients may exhibit two or more subtypes at one time [153]. In this classification, the term CU is strictly reserved for spontaneous appearance of wheals, but this does not mean that the physical subtypes of urticaria are not chronic; in these cases, symptoms are not chronic but only visible when physical stimuli are present [154].

Urticaria subtypes-classification

Type	Subtype	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema <6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema >6 weeks
Physical urticaria	Cold contact urticaria	Elicited by cold objects, air, fluids, or wind
	Delayed pressure urticaria	Elicited by vertical pressure, wheals arising after 3-12 h
	Heat contact urticaria	Elicited by localized heat exposure
	Solar urticaria	Elicited by UV and/or visible light
	Dermographic urticaria (urticaria factitia)	Elicited by mechanical shearing forces, wheals arising after 1-5 min
	Vibratory urticaria/angioedema	Elicited by vibration, for example, jackhammer
Other types of urticaria	Aquagenic urticaria	Elicited by water
	Cholinergic urticaria	Elicited by increase in core body temperature, for example, exercise
	Contact urticaria	Elicited by contact with triggering substance
	Exercise-induced anaphylaxis/urticaria	Elicited by physical exercise

Source: Classification of urticaria2. Zuberbier T. Classification of Urticaria. Indian J Dermatol. 2013;58(3):208–10.

Chronic urticaria is defined by "the presence of recurrent urticaria, angioedema, or both, for a period of more than 6 weeks" whereas acute urticaria has a duration of ≤ 6 weeks [155]. Urticaria has a lifetime prevalence of about 20%, whereas CU has a lifetime prevalence of approximately 0.5% to 5%. The estimated point prevalence of CU is 0.1 to less than 1% globally [152]. Acute urticaria is typically benign and self-limited and resolves with avoidance of triggers. Chronic urticaria is often spontaneous (formerly termed "idiopathic", with no identifiable triggers), only 15% have clear inducible urticaria (where triggers are known and consistent), and many people have episodes of both induced and spontaneous flares. Chronic spontaneous urticaria is an episodic and self-limited disorder in most patients, and for 80% of patients CU resolves within a year, however, >10% may have a duration 5 years or longer. Chronic urticaria is twice as frequent in females compared to males, and most often occurs over the age of 20, and can be triggered or flared by non-steroidal inflammatory drugs [152]. A proportion of patients diagnosed with CU have physical urticaria, also referred to as chronic inducible urticaria, which is urticaria incited by a physical stimulus, such as mechanical (friction, vibration, pressure) urticaria, thermal (heat or cold) urticaria, solar urticaria, and symptomatic dermatographism [156]. Dermographism is the most common form of physical or chronic inducible urticaria. It is also called dermatographia and dermographic urticaria [157]. Mechanical urticaria is the most common of the inducible urticarias and is present in 20 to 30 percent of adults with CU and also occurs in children, although there are fewer reports regarding this population [158].

Etiology

Urticaria is believed to be caused by "immunoglobulin E- and non–immunoglobulin E-mediated release of histamine and other inflammatory mediators from mast cells and basophils" [159] [159] [159]. This may be due to immune activation in response to certain viral, bacterial, or parasitic infections; IgE-mediated allergic reactions; direct mast cell activation; NSAIDs (pseudo-allergic or allergic reactions); or physical factors such as cold exposure or exposure to sunlight [160][160][160]. Although urticaria has always been considered a mast cell-driven disease, it is now known that it involves dysregulation of both mast cell and basophils with their subsequent activation and degranulation as well as the participation of other cells, e.g., eosinophils, T and B lymphocytes, epithelial, and endothelial cells. Up to 80-90% of cases of CU are idiopathic [159][159][159]. The pathogenesis of chronic spontaneous urticaria has not been established and potential hypotheses include autoimmunity mediated by functional auto-antibodies directed against IgE or the high-affinity IgE receptor, cellular defect theories and serum or plasma factors that directly or indirectly activate mast cells or basophils.

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively (18 Dec 2020 – 17 Dec 2022) and for the reporting period (19 Jun 2022 – 17 Dec 2022), for valid case reports received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The search strategy used to identify cases of mechanical urticaria included the MedDRA PT "Mechanical urticaria". Within the retrieved cases, those that included medical history PT "Urticaria chronic" or PT "Urticaria" were further evaluated by medical review for co-occurrence of mechanical urticaria and CU.

There are no recognized Case Definition for mechanical urticaria and reports where PT "Mechanical urticaria" was captured were evaluated based on the WHO-UMC system for causality assessment.

Literature Search Methodology:

The MAH performed a focused search of PubMed for elasomeran and mechanical urticaria to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 363 literature articles were retrieved using these search criteria. The literature search strategy was broad, capturing mainly published literature regarding COVID-19 vaccine-induced and COVID-19 infection-induced cutaneous manifestations. Of these 161 articles, there were no published clinical literature specific to vaccination induced mechanical urticaria that conclusively describe mechanism of action or new and potentially important safety information regarding the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases with Exposure to elasomeran

Cumulatively, through 17 Dec 2022, a total of 466 cases of mechanical urticaria were reported (including 395 non-serious events of mechanical urticaria and 76 serious events of mechanical urticaria) in individuals who received elasomeran. Of the 466 cumulative cases, 184 (39.5%) were medically confirmed and no case reported a fatal outcome.

Regions with the greatest number of cases were EEA (172 cases, 36.9%) Switzerland (155 cases, 33.3%), United States (101 cases, 21.7%) and the UK (30 cases, 6.4%)

During this PBRER interval, a total of 71 cases of mechanical urticaria were reported (including 61 non-serious events of mechanical urticaria and 10 serious events of mechanical urticaria) in individuals who received elasomeran. Of the 71 interval cases, 31 (43.7%) were medically confirmed and no case reported a fatal outcome.

Regions with the greatest number of cases were EEA (49 cases, 69.0%), Switzerland (8 cases, 11.3%), United States (7 cases, 9.9%), and the UK (3 cases, 4.2%).

Event Time to Onset by Dose

Cumulatively, when dose and TTO were reported, the majority (246, 52.2%) of mechanical urticaria events were reported after Dose 3 of elasomeran. Of those 246 events, 186 (75.6%) events had a delayed TTO ranging from 7 to 13 days post-vaccination. This pattern is similar to what has been observed in previous evaluations of urticaria.

During the reporting period, a similar pattern was observed for events of mechanical urticaria. Of the 71 events of mechanical urticaria reported during the reporting period, 35 (49.3%) events were reported

after Dose 3 of elasomeran). Of those 35 events, 26 (74.3%) events had a delayed TTO ranging from 7 to 13 days post-vaccination.

This is notable given the relatively fewer number of individuals who have received a third dose of the vaccine compared to Dose 1 and 2. Please see Figure 16-13 and Table 16.99 for a comparison of mechanical urticaria events by dose and TTO for the prior reporting period and current reporting period.

Figure 16-13. Percentage of Mechanical Urticaria Events by TTO and Dose Number, Prior Reporting Period vs. Reporting Period – elasomeran

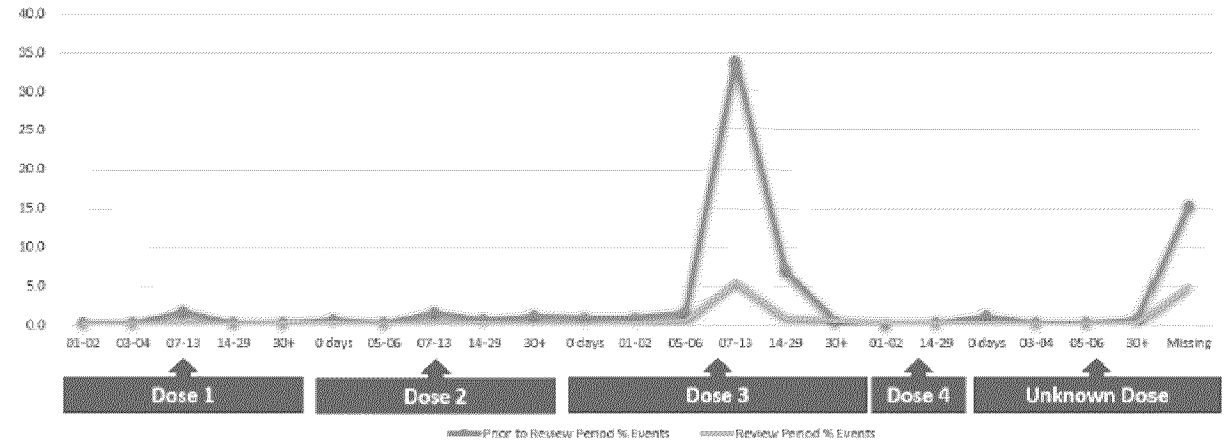


Table 16.99 Latency of Mechanical Urticaria Events by TTO and Dose Number-elasomeran, Cumulative

Dose Number	TTO (Days)	Prior to Review Period		Review Period[1]		# Events	% Events
		# Events	% Events	# Events	% Events		
Dose 1	Subtotal	14	3.0	2	0.4	16	3.4
	0 days	2	0.4	0	0	2	0.4
	01-02	1	0.2	0	0	1	0.2
	03-04	1	0.2	0	0	1	0.2
	07-13	8	1.7	1	0.2	9	1.9
	14-29	1	0.2	0	0	1	0.2
	30+	1	0.2	1	0.2	2	0.4
Dose 2	Subtotal	21	4.5	3	0.6	24	5.1
	0 days	3	0.6	1	0.2	4	0.8
	01-02	2	0.4	0	0	2	0.4
	05-06	1	0.2	0	0	1	0.2
	07-13	7	1.5	1	0.2	8	1.7
	14-29	3	0.6	1	0.2	4	0.8
	30+	5	1.1	0	0	5	1.1

Dose Number	TTO (Days)	Prior to Review Period		Review Period[1]		# Events	% Events
		# Events	% Events	# Events	% Events		
Dose 3	Subtotal	211	44.8	35	7.4	246	52.2
	0 days	4	0.8	0	0	4	0.8
	01-02	4	0.8	1	0.2	5	1.1
	03-04	1	0.2	0	0	1	0.2
	05-06	7	1.5	2	0.4	9	1.9
	07-13	160	34.0	26	5.5	186	39.5
	14-29	33	7.0	4	0.8	37	7.9
	30+	2	0.4	2	0.4	4	0.8
Dose 4	Subtotal	1	0.2	2	0.4	3	0.6
	01-02	0	0	1	0.2	1	0.2
	14-29	1	0.2	1	0.2	2	0.4
Unknown	Subtotal	153	32.5	29	6.2	182	38.6
	0 days	5	1.1	1	0.2	6	1.3
	01-02	5	1.1	0	0	5	1.1
	03-04	1	0.2	0	0	1	0.2
	05-06	1	0.2	0	0	1	0.2
	07-13	54	11.5	4	0.8	58	12.3
	14-29	12	2.5	0	0	12	2.5
	30+	3	0.6	1	0.2	4	0.8
	Missing	72	15.8	23	4.9	95	20.2
Grand total		**400**	**84.9**	**71**	**15.1**	**471**	**100.0**

[1]Please note: Events reported during the reporting period should be interpreted with caution. The majority of individuals reporting events during the reporting period received their primary series of vaccinations prior to the reporting period. The majority of events reported during this reporting period were among individuals receiving 3 or more doses of elasomeran.

Demographics

Cumulatively, there were more cases reported in females (248; 53.2%) compared to males (211; 45.3%) with 7 (1.5%) reports that did not report gender. Patient age ranged from 13 years-old to 77 years-old, with a mean age 36.6 years-old and a median age of 35.0 years-old. Of the 466 cases, 389 (83.5%) cases were reported in individuals 18-49-years of age while the majority (253, 54.3%) of cases were reported in individuals 25-39 -years of age.

During the reporting period, fewer cases were reported, and no conclusions can be drawn with regards to gender imbalance with 32 reports involving females, 37 reports involving males, and 2 reports which did not report gender. Patient age ranged from 17 years-old to 74 years-old, with a mean age of 33.2 years-old, and a median age of 32.0 years-old. Of the 71 cases, 64 (90.1%) cases were reported in individuals 18-49-years of age while the majority (49, 69.0%) of cases were reported in individuals 25-39-years of age. For a summary of cases by age group, gender, and review period please see Table 16.100 in the PSUR.

Critical Review and Analysis of Cases

WHO-UMC causality assessment was performed for the 71 cases reported during the review period. There were 23 cases with WHO-UMC causality classified as "Unassessable" primarily due to missing event or

vaccination dates where TTO could not be determined. There were 10 cases with WHO-UMC causality assessment classified as "Unlikely" due to an implausible, extended TTO of greater than two weeks (up to >1 year), as well as alternate etiologies (such as concomitant medications, history of urticaria, or other conditions predisposing to hypersensitivity reactions). There were 38 cases with a WHO-UMC causality assessment classified as "Possible" due to a plausible temporal relationship between the administration of elasomeran and the reported event of mechanical urticaria and/or the lack of significant alternate etiology for the event. Of the 38 cases assessed as possibly related to elasomeran, six cases had a TTO of 0-6 days post-vaccination and 32 cases had a time to onset of 7-13 days post-vaccination.

The 71 cases were reviewed for medical history to characterize risk factors for the development of mechanical urticaria. The most frequently captured medical history PTs during this interval > 2 cases included "Seasonal allergy" (5 cases), "Drug hypersensitivity" (4 cases), and "Allergy to animal" (3 cases) suggesting that patients with a history of allergic or hypersensitivity conditions who are already predisposed to urticarial reactions may be more susceptible to developing mechanical urticaria.

Further review was performed to identify cases that included a medical history of PT "Urticaria chronic" or PT "Urticaria" for consideration of co-occurrence of both mechanical urticaria and CU. One case ([redacted] was identified from the prior reporting period (none from this reporting period) that included urticaria as a historical condition (in addition to multiple allergies to metals, animals, and mites), however there was no evidence that this was CU.

Seven cases reporting events of CU as a co-occurrence with mechanical urticaria were identified in the review period. Six of the seven cases reported non-serious events of mechanical urticaria. One case reported a serious event of mechanical urticaria and is summarized below:

[redacted]: A health authority report concerning a 24-year-old female who experienced multiple events including mechanical urticaria and CU (reported as medically significant, but no evidence of hospitalization) following Dose 3 of elasomeran. The patient's medical history reported as negative for eczema, positive for multiple pets (presumably in household), prior right axillary "lymphoid tissue operation", and no reactions reported from two previous elasomeran doses. Within a month of receiving Dose 3, the patient started azithromycin for an unspecified indication and experienced rash pruritic, eczema, oropharyngeal pain, tonsillitis (timing of events and azithromycin not known). Two months after Dose 3, the patient experienced mechanical urticaria and 3 months after Dose 3 the patient experienced urticaria which was reported to progress to CU after one more month. Laboratory workup was unremarkable (including negative IgE to azithromycin) except for borderline antinuclear antibodies. At the time of the report, the event outcomes for mechanical urticaria were reported as "unknown" and for CU was reported as "ongoing".

MAH Comment: Despite the extended TTO, WHO-UMC causality is assessed as "Possible" considering the unremarkable diagnostic workup. Mechanical urticaria preceded CU and the progression of the events is consistent with CU.

In three reports [[redacted]; [redacted]); and [redacted], WHO-UMC causality is considered "Possible" based on the temporal association between elasomeran and the events of mechanical urticaria and CU. However, important information necessary for adequate evaluation such as medical history, concomitant medications, evolution of the two events, and diagnostic workup was not provided. No conclusions could be drawn with regards to mechanical urticaria and the co-occurrence of CU.

[redacted]: This regulatory case concerns a 37-year-old male patient with no medical history reported, who experienced the unexpected serious (medically significant) event of "Chronic spontaneous urticaria" and the non-serious event of "Mechanical urticaria" (Dermographism) 22

days after receiving Dose 2 of elasomeran. Diagnostic evaluation described human leukocyte antigen (HLA)-B27 assay as "positive" approximately 4 months after the most recent vaccination.

MAH Comment: Based on the TTO of 22 days and HLA-B27 positivity suggesting rheumatoid disease, WHO-UMC causality is considered "Unlikely". No conclusions can be drawn with regards to mechanical urticaria and the co-occurrence of CU.

Two reports **[and** were lacking important information necessary for adequate evaluation including event dates, medical history, concomitant medications, clinical course, and diagnostic workup. WHO-UMC causality is considered "Unassessable". No conclusions can be drawn with regards to mechanical urticaria and the co-occurrence of CU.

Subpopulation Analysis of Mechanical Urticaria Cases Among Children <17 Years of Age

During the reporting period, there was one non-serious case reported involving an adolescent patient. Case is a health authority report concerning a 17-year-old male who experienced the non-serious event of "Mechanical urticaria" 7 days after receiving Dose 2 of elasomeran. At the time of the report, the event outcome was reported as "not resolved". No other information was provided such as medical history, concomitant medications, clinical course, and diagnostic evaluation which are necessary for proper evaluation. According to the WHO causality assessment this case is considered "Possible" given the temporal association.

Mechanical Urticaria Cases Among Individuals Receiving Three or More Doses of elasomeran

During the reporting period, there were 37 cases (5 serious, none with fatal outcome) that were reported in individuals receiving three or more doses of elasomeran. Of the 37 cases, seventeen (46%) were medically confirmed. There was no significant difference in regard to gender in this subpopulation with 17 cases (45.9%) cases reported in males compared to 19 cases (51.4%) reported in females and one case (2.7%) which did not report gender. Patient ages ranged from 23 years to 66 years with a mean age of 34.3 years and a median age of 32.0 years. The majority of events (35, 94.6%) occurred after Dose 3 with only 2 events reported after Dose 4 (these numbers should be interpreted with caution given the fewer number of patients receiving subsequent doses). When TTO was reported, the majority (70.3%) of events occurred in the post-vaccination window of days seven to thirteen with a median TTO of 10.0 days.

Mechanical Urticaria After Receiving Booster Dose with elasomeran/imelasomeran

During this reporting period, there were two non-serious reports (1 medically confirmed) of mechanical urticaria reported in individuals who received elasomeran/imelasomeran. Both cases are summarized below.

Case concerned a 35-year-old pregnant patient (gravida 2, para 1), with relevant medical history of hypersensitivity and coeliac disease, who experienced the non-serious event of "Mechanical urticaria" (reported as dermatographia and full body skin itchiness) 13 days after Dose 4 of elasomeran/imelasomeran. Pregnancy outcome was still pending, although first trimester screenings were reported as normal. According to the WHO causality assessment this case is considered "Unlikely" given the patient's history of hypersensitivity and that hormonal changes during pregnancy can trigger urticaria.

Case concerned a 47-year-old female who experienced the non-serious events of "Mechanical urticaria" (reported hives with redness and itching all over on the body, scalp, and face; spreads with scratching) and "Pruritus" 13 days after receiving Dose 4 of elasomeran/imelasomeran. No additional information was provided such as medical history, concomitant medications, clinical course,

and diagnostic evaluation which are necessary for proper evaluation. According to the WHO causality assessment this case is considered "Possible" given the temporal association.

Mechanical Urticaria After Receiving Booster Dose with elasomeran/davesomeran

No cases of mechanical urticaria have been reported in individuals who received a booster dose with elasomeran/davesomeran.

Discussion

Cumulatively, there are a total of 466 cases of mechanical urticaria. Seventy-one of those cases were received during this reporting period. The cases describe events of mechanical urticaria that were mainly non-serious and often had little to no information reported regarding clinical course. No fatal cases of mechanical urticaria have been reported.

The occurrence of mechanical urticaria in reports during this PBRER interval mirrored the pattern observed prior to this interval; especially with regard to reports of urticaria in general. Mechanical urticaria occurred in a bimodal distribution during elasomeran post-vaccination window of days 0-6 and then again in the post-vaccination window of days 7-13, more often after Dose 3. The most common medical history reported in cases of mechanical urticaria described allergic or hypersensitivity conditions which would be expected to predispose patients to developing urticarial events. Furthermore, there was no evidence that suggests a co-occurrence of mechanical urticaria and CU in association with elasomeran administration. Overall, there was no appreciable change in the pattern of occurrence of mechanical urticaria noted in the reports received thus far.

Urticaria is recognized as a common dermatologic condition and inducible urticarias are considered subtypes of CU. Mechanical urticaria is the most common of the inducible urticarias and is present in 20 to 30 percent of adults with CU and also occurs in children, although there are fewer reports regarding this population [158]. Simple dermographism is thought to occur in approximately 2 to 5 percent of the general population.

Core labeling of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, as well as the SmPC, adequately describe urticaria observed to occur acutely following elasomeran vaccination including the delayed window of 7-13 days after vaccination, consistent with the findings in this review.

Conclusion

Based on the analysis of all the safety data received during the cumulative and reporting periods, ModernaTx, Inc. considers that the pattern of events of mechanical urticaria continues to present following the bimodal distribution previously described for urticaria events in general. The reports of mechanical urticaria are rare and no different than reports of urticaria, with no co-occurrence identified with CU in association with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The current CCDS (v15.0) is considered to adequately reflect the understanding of urticaria with respect to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

ModernaTx, Inc. concludes that no further action is warranted at this time and will continue to monitor events of mechanical urticaria using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

As requested in the previous PSUSA procedure, the MAH has provided an analysis on mechanical urticaria/dermatographism. The MAH was also requested to provide a review of chronic urticaria (CU), if the pattern indicated a co-occurrence of mechanical urticaria and CU.

In the Spikevax SmPC, "urticaria" is listed in 4.8 with a frequency Uncommon, and it is specified in a footnote that urticaria has been observed with either acute onset (within a few days after vaccination) or

delayed onset (up to approximately two weeks after vaccination). Mechanical urticaria or dermographism is not listed, nor is chronic urticaria.

Co-occurrence of mechanical urticaria/dermatographism and CU is not uncommon. In fact, the MAH highlights this in their background section, stating that "*a proportion of patients diagnosed with CU have physical urticaria*", and that "*mechanical urticaria is present in 20 to 30 percent of adults with CU*". Dermographism is often an incidental finding in other skin conditions, such as atopic dermatitis, chronic spontaneous urticaria, and other inducible urticarias. https://www.uptodate.com/contents/physical-inducible-forms-of-urticaria?search=mechanical%20urticaria&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Literature review:

The literature review provided is inadequate. It is stated that 363 literature articles were retrieved. Without mentioning any filtering criteria, the MAH continues by describing 161 articles. **This discrepancy should be clarified within this procedure (RSI).**

Further, there is no description of the findings from the literature review, the MAH is solely stating that "*there were no published clinical literature specific to vaccination induced mechanical urticaria that conclusively describe mechanism of action or new and potentially important safety information regarding the safety profile of elasomeran* […]".

When performing a quick search on Spikevax and mechanical urticaria/dermatographism, several case reports regarding mechanical urticaria/dermatographism and Spikevax could be identified by the assessor, several of which with co-occurring CU.

Published case reports concerning dermatographism after Spikevax retrieved by the assessor (*not a complete list*):

DOI:10.7759/cureus.26566 – publ. 05 July, 2022: "COVID-19 Vaccine Booster-Induced Dermatographism" this case concerns a patient who developed persistent severe dermatographism after receiving a booster shot of the Moderna vaccine

DOI: 10.3934/Allergy.2022003 – publ. 17 Feb 2022: "Migratory dermatographic urticaria following COVID-19 vaccine booster in young adult male". Symptoms started one week after booster dose of Moderna vaccine.

DOI: 10.1002/emp2.12709 – publ. April 2022: "Woman with pruritic rash and dermatographism". No apparent allergic exposures. Moderna COVID-19 vaccine booster administered 10 days prior. Symptoms continued despite medical treatment, and the patient was later diagnosed with CSU.

DOI: https://doi.org/10.1016/j.jdcr.2022.05.012 - publ. July 2022: "Chronic spontaneous urticaria after COVID-19 primary vaccine series and boosters". 2 cases of CSU following Moderna booster. In both cases, there were no significant medical history. Urticaria and dermatographism started 11 and 12 days after booster and continued for >6 weeks.

DOI: 10.1002/clt2.12206 – publ 12 Nov 2022: "Delayed onset urticaria and symptomatic dermographism following COVID - 19 booster vaccination: A case series". In this publication, 16 patients were included, of which 12 were vaccinated with Spikevax (all 3rd dose). Thirteen patients had no previous medical history of urticaria and developed inducible urticaria post vaccination and seven of these patients also had coexisting spontaneous urticaria. All patients developed symptoms within one day to three weeks following vaccination with a median time of 14 days. No other plausible cause than the vaccinations were found, despite a thorough medical history and routine blood tests following international EAACI/GA2LEN/EUROGuiDerm/APAAACI guideline.

Of note, these published case reports concern booster administrations (3rd dose) and also co-occurrence of mechanical urticaria and chronic urticaria. Also, a recently published abstract was also identified concerning the same subject:

https://doi.org/10.1016/j.jaci.2022.12.521 - abstract to be presented during scientific sessions at the 2023 AAAAI Annual Meeting. "Delayed Onset of Symptomatic Dermatographism following COVID-19 mRNA Booster": 13 patients with dermatographism following COVID-19 mRNA boosters, most had received mRNA vaccine boosters one to two weeks prior to symptom onset, 85% received Moderna. Seven patients had persistent symptoms 4-7 months later.

The MAH is, within this procedure, requested to provide the literature review again and to be clear in how many case reports concerning Spikvax and mechanical urticaria or dermatographism that were identified in the literature review (RSI).

Case review:

In total, the MAH has identified 466 cases with a reported event of mechanical urticaria, of which 76 were reported as serious. 71 cases were reported during the reviewing period.

A notable TTO pattern was observed by the MAH; the majority of events have been reported after dose 3, and mostly with a TTO from 7-13 after vaccination. This is in line with the findings of urticaria, which is known to occur with either acute onset or with a delayed onset up to two weeks after vaccination.

The MAH has only performed a case review of the 71 cases from the reporting period. It is unclear why the MAH has not analyzed the remaining 395 cases.

Of the 71 cases from the reporting interval, 38 were considered WHO Possible. 84% (n=32) of these had a TTO of 7-13 days.

The most frequently captured medical history among the 71 patients from the reporting interval included allergic conditions. However, as allergic conditions are prevalent in the population; unless a particular pattern has been observed, this finding cannot be used for arguing that these patients have been predisposed for an urticarial reaction. The analysis could preferably be done on all cases, instead of the group of 71 cases from the reporting period.

In 7 cases from the reporting period (10%), mechanical urticaria and CU were co-reported events. No information is presented regarding the co-occurrence of mechanical urticaria and chronic urticaria among the remaining 395 cases, hence, the above estimate of 10% is uncertain.

The MAH claims that "there was no evidence that suggests a co-occurrence of mechanical urticaria and CU in association with elasomeran" – this conclusion is not endorsed. It is apparent that cases with co-occurring mechanical urticaria and chronic urticaria have been reported, and also published as literature case reports. However, as the MAH has not presented data on the cumulative case, conclusions cannot be drawn based upon the findings from the 71 case reports from the interval period.

The MAH is requested, within this procedure, to provide an overview of the co-occurrence of mechanical urticaria/dermatographism and chronic urticaria for all cases with reported mechanical urticaria/dermatographism. The MAH should discuss potential underreporting as cases reported as "urticaria" with a prolonged course of >6 weeks, may not have been updated as chronic urticaria in the reporting system (RSI).

Disproportionality:

This has not been provided by the MAH. The following has been retrieved by the assessor (mechanical

urticaria and Spikevax):

In Vigilyze, there is a signal of disproportionate reporting, with 1350 observed cases vs 75 expected (IC025: 4.1). In Eudravigilance, the ROR rose in the first quarter of 2022, (concurrent with the booster administrations), and the ROR(-) at present is also disproportionate at 7.85.

Conclusion:

The MAH has provided an evaluation and presentation of mechanical urticaria. The presentation has several limitations. The literature review is inadequate and requires clarifications, and the case review only includes cases from the reporting interval and not cumulatively. The MAH states that there is no co-occurrence of mechanical urticaria and CU; a conclusion which is not endorsed, as it is not possible to draw conclusions based on the data presented by the MAH. The MAH has been requested to re-perform the analysis on the co-occurrence of mechanical urticaria and chronic urticaria within this procedure.

From the presentation, it is however clear that the occurrence of mechanical urticaria follows the same TTO pattern as the acute urticaria (listed in 4.8), with the majority having a TTO from 7-13 days after vaccination. Of note, the vast majority of events were reported after Dose 3.

The MAH is asked to clarify upon several issues within this procedure before a conclusion can be made.

Of note, an additional publication has been identified concerning CSU (reporting period for the next PSUR with DLP 17.06.2023) by Duperrex et al: "Incidence of Chronic Spontaneous Urticaria Following Receipt of the COVID-19 Vaccine Booster in Switzerland" doi:10.1001/jamanetworkopen.2022.54298

The MAH is requested to comment upon the publication by Duperrex et al (doi:10.1001/jamanetworkopen.2022.54298) in the next PSUR. (RSI)

2.5.5. Overdose

Source of the New Information

ModernaTx, Inc. queried the GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

Assessing harm due to administration of an extra dose of a vaccine is not well understood. Among all the VAERs reports received from 2007-2018, more than three-fourths of the reports of an excess dose of vaccine did not describe an AE. Among reports where an AE was reported, most of the common events included expected conditions such as pyrexia, injection site erythema, pain, and headache. Although most of the reports were of other vaccines (e.g., trivalent inactivated influenza, varicella, hepatitis A, and measles, mumps, rubella, varicella, the percentage of the AEs among these vaccine reports were comparable to all reports submitted to VAERS during the same period [175]. A case report of excess administration (or overdose) in a woman in Italy, who accidentally received six doses of the Pfizer-BioNTech COVID-19 vaccine all at once, without experiencing any serious side-effects has been published [176]. Although these data have been mainly anecdotal, overdose appears to be rare with limited harm/effects.

[Please refer to the PSUR for sections on methodology and results]

Discussion

Cumulatively, 923 overdose cases (3,102 events; 242 serious events) have been reported of which 77 cases were serious, 8 with a fatal outcome, and 645 cases were medically confirmed.

During the reporting interval, 110 Overdose cases (346 events; 8 serious events) were reported. Of these, 6 cases were serious, and 92 cases were medically confirmed. No cases reported a fatal outcome. Four of the 6 serious cases reported in the reporting interval were considered of interest. However, all 4 cases contained confounding factors and were clinically dissimilar. Temporal association was the primary association that made elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran considered possibly related to these events. Due to the small number of cases in the pediatric population, no trends were identified.

Conclusion

Cumulatively and based on the analysis of all the safety data received during the reporting interval of this PBRER, ModernaTx, Inc. considers that Overdose cases reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, did not raise any safety concerns, and the information provided does not support or is inadequate to provide evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and reported Overdose and Overdose-associated events. The cumulative and reporting interval data do not represent a new safety issue of concern. ModernaTx, Inc. will continue to monitor events for Overdose and Overdose-associated events using routine surveillance.

Overall, based on the analysis of all the Overdose safety data in this reporting interval, there is no change in the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. No significant information was identified that impacts elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran benefit-risk balance. Therefore, the benefit-risk evaluation of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains positive.

Rapporteur assessment comment:

Cumulatively, the MAH identified 923 cases of overdose, of which 77 cases were serious and 8 had a fatal outcome. In the cases reporting adverse events of harm, the most frequently reported events (PTs) were 'pyrexia' (129 events), 'headache' (87 events) and 'chills' (75 events).

During the reporting interval, the MAH received 110 cases of overdose, including 6 serious cases. None had a fatal outcome. Overdose following vaccination with elasomeran/imelasomeran and elasomeran/davesomeran was reported in one and 15 patients, respectively. As observed in the previous interval, cases of overdose were most frequently reported following D3. When reported, the most common adverse events of harm were 'pyrexia', 'headache', 'malaise', 'chills' and 'fatigue'. The median age of the concerned patients was 54.5 years (range 0-96 years). Review of the interval cases of overdose reported in children and adolescents did not identify any unusual patterns.

Overall, no new and significant safety information was identified from the interval cases of overdose. It appears that the adverse events of harm, if co-reported, were consistent with the known safety profile of Spikevax.

Endorsed.

2.5.6. Off-label use

Source of the New Information

Off-label Use data presented below includes valid case reports of medication errors involving elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran received from HCPs, HAs, consumers and literature, for the reporting period of 19 Jun 2022 through 17 Dec 2022.

Background Relevant to the Evaluation

ModernaTx, Inc. performs routinely monitors cases of Off-label use of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in patient populations, dosage or dosage form for which it is not currently authorized.

Off-label use is defined as, "Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization. Examples include the intentional use of a product in situations other than the ones described in the authorized product information, such as a different indication in terms of medical condition, a different group of patients (e.g., a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorization in the country where the product is used." (EMA GVP Annex 1 – Definitions [Rev 4]).

[Please refer to the PSUR for sections on methodology and results]

Discussion

During the reporting period, the total number of off-label use cases was significantly lower than last review period (60 vs 212) as well as the number of medically confirmed cases (37 vs 114). The reported serious cases were also lower compared with the last review period (32 vs 64). Same as the last review period, "off-label use" was the most frequent reported term. Only isolated non serious case of off-label use were received from both bivalent booster during the review period. No fatal cases were reported during this review period. The reported AEs representing harm reported and cases of Off-label use were in line with expectation for reactogenicity following elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. There was no pattern of Offlabel use observed that changes the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Conclusion

Based on the analysis of all the safety data received during this reporting period of this PBRER, ModernaTx, Inc. considers that Off-label use cases, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, did not raise any new safety concerns, and the information provided does not support or is inadequate to provide evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and reported Off-label use/ Off-label associated events. The reporting period data do not present a new safety issue of concern. ModernaTx, Inc. will continue to monitor Off-label use cases and associated events using routine surveillance.

Overall, based on all the information presented in this analysis, ModernaTx, Inc. considers that there is no change to the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The benefit-risk evaluation of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains positive.

Rapporteur assessment comment:

The MAH presented an overview of interval off-label cases. The MAH identified 60 off-label cases, of which

32 cases were serious and none had a fatal outcome. This is lower than the number of off-label cases reported in the previous interval (n=212). The most frequently reported events related to off-label use (PTs) were 'off-label use' (92.1%), followed by 'intentional product use issue' (6.3%) and 'intentional dose omission (1.6%). The median age of the concerned individuals was 44.0 years (range 0- 81 years). Review of interval off-label cases reported in children and adolescents did not identify any unusual patterns.

Three of the interval off-label cases concerned bivalent vaccines, i.e. elasomeran/imelasomeran and elasomeran/davesomeran.

The MAH concluded that 1) the adverse events of harm reported in the interval off-label cases were in line with the expected safety profile of elasomeran and the bivalent vaccines, 2) no new safety concerns were identified based on the review of the interval off-label cases.

Endorsed.

2.5.7. Lack of Efficacy/ Vaccine Failure

Source of the New Information

ModernaTx, Inc. queried the GSDB for the reporting period for valid, spontaneous case reports of lack of efficacy/vaccination failure received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

Lack of efficacy/vaccine failure is defined as COVID-19 infection occurring 14 days or more after the second dose of elasomeran. In order to better characterize the effect of the booster dose on vaccine failure, ModernaTx, Inc. has further broken down its definition of lack of efficacy into primary series vaccine failure (breakthrough infection 14 days or more after 2nd dose of primary vaccination) and booster dose vaccine failure (breakthrough infection 14 days or more after booster dose of vaccine. Recently emerged severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) Omicron sublineages, including the BA.2-derived BA.2.75.2 and the BA.5-derived BQ.1.1 and XBB.1, have accumulated additional spike mutations that may affect vaccine effectiveness [180]. In a CDC Morbidity and Mortality Weekly Report study, relative benefits of a bivalent booster compared with monovalent vaccine doses alone increased with time since receipt of last monovalent dose [181]. The article discusses more rapid waning of efficacy overtime since receipt of monovalent during the Omicron-predominant period Omicron BA.4/BA.5 lineages.

Results from this study show that bivalent boosters provide protection against symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages; and restore protection observed to wane after monovalent vaccine receipt, as demonstrated by increased rVE with longer time, since the most recent monovalent dose. BA.5 bivalent booster elicited a high neutralizing titer against elasomeran/davesomeran measured at 14–32 days after boost; however, the BA.5 bivalent booster did not produce robust neutralization against the newly emerged BA.2.75.2, BQ.1.1 or XBB.1.

ModernaTx, Inc. continues to monitor breakthrough infections and lack of efficacy/vaccine failure cases, and the impact of booster doses. Based on the MAH data supporting their authorizations, the bivalent COVID-19 vaccines are expected to provide increased protection against the currently circulating omicron variant.

[Please refer to the PSUR for sections on methodology and results]

Discussion

Research suggests the protection offered by COVID-19 vaccines might wane over time, prompting consideration of booster vaccinations. Vaccine failure reports represent 2.3% of all cases in this reporting period (80,461 cases). Likely due to recent approvals, relatively fewer cases have been reported for elasomeran/imelasomeran and elasomeran/davesomeran.

In this PBRER period, the reported gender distribution was approximately 56.9% males and 41.8% females with the median age reported was 42.3. There were 7 cases (0.6%) in the primary vaccine series and none of the secondary vaccine series cases were in children under ⩽ 17 years; and 64 (5.1%) of the primary vaccine series and 170(28.4%) of the secondary series cases were in the elderly (⩾65 years). 64.1% of cases of vaccine failure were serious.

The median TTO for cases of vaccine failure after the primary vaccine series was 155 days and that for the secondary series cases was 88 days.

In this PBRER period, the primary vaccine series and booster series combined, most of the cases were from Austria (45.5%), followed Japan (16.5%), Spain (6.5%), Australia (6.4%), Sweden (6.3%), Italy (4.9%) and the United States (2.4%). Cases from all other countries were responsible for <2% of the cases reported in the reporting period per country.

Additionally, all of the .214 cases and 70% of the .222 cases were in the elderly age group for bivalents. No specific safety patterns or concerns for these differences could be established. The elderly, the frail and those with immunosuppressive conditions are more prone to vaccine failure due to multifactorial reasons including host immune response and preponderance of comorbid conditions. Immunosenescence is known to be associated with decreased immune response and is more common in the elderly. Though older age is also a known risk factor for severe COVID disease, it is also an independent risk factor for death from comorbid conditions or natural causes. Fatalities attributed to vaccine failure may therefore be an overrepresentation, especially in the elderly.

The institution of 3rd dose boosters has become more widespread in different countries, with percentage of vaccine failure cases reported after dose 3 representing 89.9% of all vaccine failure cases in this reporting period. Current data is still limited from spontaneous reporting with 715 case reports in the reporting period >= 14 days after 3rd dose (booster vaccine failure).

In all 4 fatal cases reported during this reporting period, the patients reported significant comorbidities that either may have interfered with the mounting of an adequate immune response to vaccine or in other ways contributed to fatality. No new safety patterns or concerns were identified following a review of these data.

No published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran were identified during the reporting period of this PBRER.

Although there may be occasional breakthrough cases, based on reports received it is reassuring that many such cases are rare and generally mild (not commonly resulting in hospitalization).

Conclusion

After careful review of all new safety data received during the reporting period and cumulatively for vaccine failure, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The safety topic of vaccine failure will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

Cumulatively, the MAH received 12,370 cases of vaccine failure. During this reporting period, there were 1,857 cases of vaccine failure; 1,258 cases in persons who completed the primary vaccination series and 599 cases in those who also received a booster dose. The mean age of the concerned patients was 42.3 years (failure after primary series) and 53.7 years (failure after booster dose).

Five of the interval vaccination failure cases were fatal; all concerned elderly persons (age >65y) with comorbidities including hypertension, diabetes, alcoholism, chronic renal failure and ischaemic heart disease.

Vaccination failure after administration of bivalent vaccines was reported in 6 patients who received elasomeran/imelasomeran and in 10 patients who received elasomeran/davesomeran, respectively.

The MAH mentioned one publication relevant to the topic that became available during the reporting interval. The study by Link-Gelles, et al. (2022) reported on the effectiveness of the bivalent booster doses. In the future PSUR, the MAH is reminded to present new published studies on efficacy and effectiveness of their mono- and bivalent vaccines in section 17.2 of the PSUR ('Newly indetified information on efficacy and effectiveness').

No information concerning lack of efficacy/vaccination failure was identified from the data presented by the MAH that would warrant further actions.

Endorsed.

Link-Gelles R., et al. Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection - Increasing Community Access to Testing Program, United States, September-November 2022. MMWR Morb Mortal Wkly Rep. 2022;71(48):1526-1530.

2.5.8. Subpopulation Analysis: Elderly 65 years and above

Source of the New Information

Information presented below includes analysis performed on worldwide reports received by ModernaTx, Inc. cumulatively (18 Dec 2020–17 Dec 2022) and for the PBRER#4 reporting period (19 Jun 2022 to 17 Dec 2022) for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Background Relevant to the Evaluation

The impact of COVID-19 on older populations is well documented. The elderly is highly vulnerable to severe COVID-19 infection. This subpopulation is at most risk due to comorbidities and age-related complex conditions. During this reporting period, based on concerns of waning immunity, viral mutation and different VOCs (Delta, subvariants of Omicron [BQ.1.1, BQ.1, BA,5, XBB), characterized by unclear transmissibility and possible immune escape, some countries authorized bivalent, variant containing vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) The biological rationale for the bivalent booster doses of both Moderna COVID-19 mRNA vaccines is increased immune response directed against SARS-CoV-2, including the Omicron variants, in those who have completed a primary series and previous booster.

The impact of immunosenescence (the decline of immunity with age) on the safety of COVID-19 vaccines in the elderly is not well documented. Lack of consistency has been observed in both quantitative and qualitative aspects of immune system responses in the elderly which impact the safety and efficacy of vaccines in this subpopulation [182]. Advancing age has been associated with a reduction in naive T-cells which are needed to respond to a vaccine. Due to a significant decrease in CD8 T-cells in older age, the ratio of CD4:CD8 cells becomes much higher. [183] also reported that aging causes a loss of T-cell receptor diversity in both CD8 and CD4 cells and a general reduction in T-cell survival. Qualitative

changes include the production of short-lived effector T-cells over memory cells, resulting in "an impaired response of T follicular helper cells to vaccination." [184] reported consistent B-cell numbers with age but observed the production of fewer functional antibodies due to a reduced expression of select proteins in old age. Based on the above variability in immune response in the elderly, Soiza et al hypothesized that the risk of serious AEs mediated by overactivation of the immune system may be lower [182] and the benefits outweigh the risks.

[Please refer to the PSUR for sections on methodology and results]

Discussion

Review of the data received during this review period showed that the most frequently reported AEs in the elderly were representative of expected reactogenicity for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and other vaccines, and remarkably, fewer AEs were reported in the elderly compared to the general population. The early data for the bivalents and safety in the elderly are reassuring. Similar age-related reactogenicity had also been reported for the Flu vaccines in the elderly. The high number of reported cases in the elderly from the United States, the UK, and Germany, may be associated with a recent COVID-19 vaccination campaign for elasomeran/imelasomeran and elasomeran/davesomeran Cases reporting COVID-19 still ranked prominently among serious cases in the elderly, including a cluster of cases from Austria which all reported COVID-19 and vaccination failure, but contained little other information for assessment. A majority of the other serious cases of COVID-19 in this reporting period contained insufficient information to ascertain symptomatology or severity of infection.

When reported, more events were reported after the booster dose compared to the primary elasomeran series. This is expected since most of the elderly would be expected to have received their primary elasomeran vaccination series in previous reporting periods.

Although more cases after elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran continue to be reported, there is no observed pattern of event terms or TTO differing from that seen after the primary series of vaccine doses in the elderly. A reduction in the number of cases with fatal outcome was noted during this review period, compared to the prior period. These fatal cases were strongly confounded by comorbid conditions and advanced age and were not suggestive of any safety concerns.

Also reported in the elderly were product administration (accidental underdose) and labelling issues. These may be related to a misunderstanding of the posology of the newly available elasomeran/davesomeran.

Conclusion

After careful review of all new safety data received during the reporting period and cumulatively in the elderly subpopulation, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in the elderly population remains favorable. The risk profile in the elderly will continue to be monitored using routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

The MAH performed PubMed search for relevant publications concerning vaccination of elderly individuals with elasomeran and the MAH's bivalent vaccines. The MAH identified 73 abstracts, of which one (Liz et al.) was presented.

Liz et al. performed a systematic review and metanalysis of 32 RCTs investigating safety and efficacy of Covid-19 vaccines in adults aged ≥55 years. According to the MAH, the authors concluded that COVID-19 vaccines had acceptable safety and efficacy in this age group. The MAH did not provide reference to this

publication.

Cumulatively, the MAH received 133,331 cases concerning individuals ≥65 years, of which 10,686 cases (incl. 3400 booster cases) were reported in the current interval. Of these, 2993 cases were serious; the most frequently reported serious events (PTs) were fatigue (3.4%), COVID-19 (2.7%), headache (2.7%), pyrexia (2.4%) and dizziness (2.1%).

Of the interval elderly cases, 191 cases were reported with a fatal outcome. The top four reported events (PTs) in these cases were death (7.7%), COVID-19 (3.4%), cardiac arrest (2.5%) and pneumonia (2.5%). The MAH stated that the 191 fatal cases concerned patients that had multiple comorbidities with strong confounders including respiratory/cardiovascular diseases, diabetes, COVID-19 infection, and malignancy.

During the reporting period, 999 cases with elasomeran/imelasomeran and 710 cases with elasomeran/davesomeran were reported in the elderly 65 years and older.

Based on the information presented by the MAH, no new and significant information was identified concerning safety and efficacy of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in the elderly. No further actions are thus considered warranted.

Endorsed.

2.5.9. Subpopulation Analysis: Children < 18 Years (incl adolescent and young children)

Source of the New Information

Information presented below includes analysis performed on cases received by the MAH from 19 Jun 2022 to 17 Dec 2022 for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022, and for the PBRER reporting period (19 Jun 2022 to 17 Dec 2022).

Background Relevant to the Evaluation

In addition to approval in adults over 18 years, elasomeran has received approval under EUA (or similar international public health measures) for age groups 6 months to 17 years as of 17 Jun 2022. Prior to this date and during the reporting period, elasomeran received approval under EUA (or similar international public health measures) for age groups 6 years to 11 years. As is the case for all drugs and vaccines, it is of high importance to keep the safety profile of this pediatric subgroup under close monitoring.

In the context of subpopulation analyzes, ModernaTx, Inc., continues to evaluate topics of interest such as myocarditis and pericarditis identified as being of higher risk in children. This topic is discussed in detail in a Section 16.3.1.2 of this PBRER report.

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB for the PBRER reporting period (19 Jun 2022 to 17 Dec 2022) for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran using the search criteria "Age groups <18 years", "Age group 0 to 5 months", "Age group 6 months to 5 years", "Age group 6 to 11 years" and "Age group 12 to 17 years." This age group collectively is referred to as the pediatric group.

A review of pediatric cases associated with elasomeran elasomeran/imelasomeran and elasomeran/davesomeran was performed by age group for neonates, infants, children, and adolescents. Data are presented and analyzed for the age groups and for children taking more than two doses (e.g.,

elasomeran as the primary series and/or booster, elasomeran/imelasomeran booster, or elasomeran/davesomeran booster. If no designation is provided, then data are associated with elasomeran

Pediatric cases are summarized cumulatively and for the reporting period where appropriate.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Appendix 11.26 [of the PSUR] contains details about the serious cases involving children.

Cumulative Overview of Cases in Children <18 Years of Age

Cumulatively, there were 10,080 cases (1,224 serious and 37 fatal cases) with 21,597 events 2,920 serious events) reported in children <18 years of age. Of these total cases, 8,153 cases were medically confirmed. When gender was known more cases were reported in females (51.7%; 5,213 cases) compared to males (42.8%; 4,315), with small proportion of cases (5.5%; 552 cases) having no gender reported. The mean age was 13.8 years (SD: 4.6) and median age was 16.0 years (min: -1.0/max: 17.0). Majority of these cases were received from regulatory authorities (73.5%;7,404 cases), with highest number of cases reported in United States (50.0%; 5,041 cases), EEA (22.6%; 2,282 cases), Asia (11.4%;1,153 cases) followed by Latin America (7.0%; 708 cases) and Australia (5.7%; 570 cases).

A cumulative overview of the Top 10 MedDRA PTs by event counts in children < 18 years of age is presented below in Table 16.163. The most frequently reported MedDRA PTs in children < 18 years of age were Product administered to patient of inappropriate age followed by Pyrexia and Headache. It should be noted that PT 'No AE' (4.9%; 1,050 events cumulatively) is not included in order to maintain the most informative display of AEs.

Table 16.163 Cumulative Summary of Top 10 MedDRA Preferred Terms (PTs) by Event count for Children < 18 Years of Age by Frequency

PT	Total Events (N)	Total Events (%)
Product administered to patient of inappropriate age	4,632	21.4
Pyrexia	1,435	6.6
Headache	933	4.3
Fatigue	452	2.1
Nausea	377	1.7
Vaccination site pain	376	1.7
Pain	359	1.7
Vomiting	347	1.6
Myalgia	339	1.6
Chest Pain	336	1.6

MedDRA – Medical Dictionary for Regulatory Affairs, PT- Preferred Term.

Cumulative Overview of Cases in Children < 18 Years of age After a Third Dose or Booster Dose of elasomeran

Cumulatively as of 17 Dec 2022, there were 230 cases (of which 26 were serious and one was fatal) with total of 460 events (82 Serious events) reported in children <18 years of age that received booster dose with elasomeran. Of these total 230 cases, 177 cases were medically confirmed. When gender was known, more cases were reported for females (54.3%;125) compared to males (40.0%; 92 cases), with

small proportion of case (5.7%; 13 cases) having no gender reported. The mean age was 11.3 years (SD: 5.5) and median age was 13.0 (min:0.0/ max:17.0).

Overview of Cases for the Reporting Period (19 Jun 2022 to 17 Dec 2022) for Children < 18 Years of Age:

During the reporting period, a total of 2,535 cases (including 426 serious, 12 fatal cases) with total of 6,784 events (887 serious events) were reported, in children <18 years of age. Of these total, 2,182 cases were medically confirmed. When gender was known, slightly more cases were reported in females (48.7; 1,234) compared to males (44.5; 1,127), with small proportion of cases (6.9%;174 cases), having no gender reported. The mean age was 11.0 (SD: 5.6) with a median age of 13.0 (min: 0.0 / max: 17.0). The majority of these cases were received from regulatory authorities (69.2%; 1,753 cases) with highest number of cases reported in Latin America (22.7%; 576 cases), Australia (22.0%; 558 cases), United States (20.5%;519 cases) followed by Asia (17.0%; 432 cases) and EEA (14.5%;367 cases).

Cases were most frequently reported in 12 to17-year-old (60.9%;1,543 cases) followed by 2 to 5-year-old (16.9%; 429 cases) children. The distribution of case reports by age is provided in Table 16.164.

Table 16.164. Distribution of Case Reports by Age group During Reporting Period (19 Jun 2022 to 17 Dec 2022)

Age Group	Review Period	
	# Cases	% of Cases
Months	40	1.6
6 months < 2 Years	170	6.7
02-05	429	16.9
06-11	353	13.9
12-15	753	29.7
16-17	790	31.2
Grand total	**2,535**	**100.0**

During reporting period, the most frequently reported events were 'Pyrexia', 'Expired product administered' and 'Headache'. The events were generally reactogenicity and associated systemic events. Product use related PTs are noted, however these very rarely also had AEs concurrently reported.

There were 170 reports that included an event of Product administered to patient of inappropriate age (170 events, 2.5% in reporting period vs 4,632 events 21.4% cumulative). Of these 170 reports, 169 were non-serious reports and 87 reports included PT No AE. PTs such as Vaccination error, Expired product administered, and Product storage error were otherwise most frequently reported, often together. The remaining events (<=7 each) generally described reactogenticity and did not demonstrate any unusual pattern. There was only one serious report [redacted] which concerned a 15-year-old male with no medical history provided who experienced Hallucination (medically significant) approximately 1.5 months after elasomeran administered as third dose after primary vaccination (non-serious Product administered to patient of inappropriate age) completed with Pfizer vaccine. The patient also experienced coronavirus infection, with fever rising to 39.2°C and hallucinations. No further information was provided.

The 10 most frequently reported MedDRA PTs following elasomeran administration are provided in Table 16.165. It should be noted that PT 'No AE (7.5%; 506 events during reporting period) is not included in order to maintain the most informative display of AEs.

Table 16.165 Top 10 MedDRA PTs by event counts in Children Under 18 years During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Pyrexia	421	6.2
Expired product administered	270	4.0
Headache	254	3.7
Product storage error	242	3.6
Chest Pain	173	2.6
Medication error	173	2.6
Product administered to patient of inappropriate age	170	2.5
Fatigue	169	2.5
Nausea	153	2.3
Myalgia	149	2.2

During Reporting period, when dose number and TTO could be determined, events were most often reported within the first two days of vaccination (Table 16.166).

Table 16.166 TTO by Dose in Children Under 18 years During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 1	**Subtotal**	**1,556**	**22.9**
	0 days	878	12.9
	01-02	319	4.7
	03-04	54	0.8
	05-06	36	0.5
	07-13	104	1.5

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
	14-29	60	0.9
	30+	105	1.5
Dose 2	**Subtotal**	**1,342**	**19.8**
	0 days	636	9.4
	01-02	422	6.2
	03-04	68	1.0
	05-06	25	0.4
	07-13	42	0.6
	14-29	45	0.7
	30+	104	1.5
Dose 3	**Subtotal**	**203**	**3.0**
	0 days	97	1.4
	01-02	76	1.1
	03-04	1	0.0
	05-06	2	0.0
	07-13	8	0.1
	14-29	19	0.3
	30+	0	0.0
Dose 4	**Subtotal**	**50**	**0.7**
	0 days	29	0.4
	01-02	11	0.2
	03-04	2	0.0
	05-06	1	0.0
	14-29	2	0.0
	30+	5	0.1
Dose 5	**Subtotal**	**1**	**0.0**
	0 days	1	0.0
Unknown	**Subtotal**	**3,632**	**53.5**
	0 days	343	5.1
	01-02	94	1.4
	03-04	15	0.2
	05-06	14	0.2
	07-13	34	0.5
	14-29	24	0.4

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
	30+	54	0.8
	Event onset prior to first dose reported	5	0.1
	Missing	3,049	44.9
Grand total		**6,784**	**100.0**

Adverse Event Outcomes in Children < 18 Years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

The most frequently reported event outcomes in Children < 18 Years of age during reporting period was 'unknown', in (38.3%; 2,598 events), followed by 'Not recovered/Not resolved' in (26.6%; 1,805 events) and 'Recovered/Resolved' in (23.5%; 1,596 events) (Table 16.167).

Table 16.167 Adverse Event Outcomes in Children < 18 years of Age During the Reporting Period (19 June 2022 to 17 Dec 2022)

Event Outcome	Review Period	
	# Events	% of Total Events
Fatal	24	0.4
Not Recovered/Not Resolved	1,805	26.6
Recovered/Resolved	1,596	23.5
Recovered/Resolved with Sequelae	34	0.5
Recovering/Resolving	727	10.7
Unknown	2,598	38.3
Grand total	**6,784**	**100.0**

Details of Reports in the Age group 0-5 months During the Reporting period (19 Jun 2022 to 17 Dec 2022).

During this reporting period, the MAH received 40 cases (11 Serious and no fatal cases) with total of 115 events (including 27 serious events) in children 5 months of age or younger who have been vaccinated with elasomeran. Exposure to elasomeran by other means (eg, maternal exposure/lactation) is described in Section 16.3.5.1 and Section 16.3.5.2 [of the PSUR].

When gender was known, more cases were reported in females (42.5% ;17 cases) compared to males (35.0%;14 cases), with 9 cases (22.5%) having no gender reported. The mean age was 0.1 years (SD: 0.2) with a median age of 0.1 year (min: 0.0 / max: 0.4). The majority of these cases were received from regulatory authorities (77.5%; 31 cases).

Table 16.168 presents the Top 10 frequently reported events (by PT) for reporting period. It should be noted that PT 'No AE' (3.5%; 4 events) is not included in order to maintain the most informative display of AEs. The three reports with event Product administered to patient of inappropriate age involved different 5-month-old patients who received elasomeran with no resulting AE.

Table 16.168 Top 10 MedDRA PTs by event counts in Children 0-5 months of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT*	# Events	% of Total Events
Pyrexia	8	7.0
Exposure via breast milk	7	6.1
Headache	5	4.3
Chills	4	3.5
Foetal exposure during pregnancy	3	2.6
Product administered to patient of inappropriate age	3	2.6
Medication error	3	2.6
Fatigue	2	1.7
Diarrhoea	2	1.7
Malaise*	2	1.7

* The PTs of Abdominal pain, Rash, Dizziness, Constipation, Faeces discoloured, Lymphadenopathy, Restlessness, Atrial septal defect, Bradycardia neonatal, inflammation, COVID-19 immunization and Wrong product administered, each were also reported twice (1.7%; 2 events each) during Reporting period.

Of the 11 serious cases (30 events) received during this period, 8 involved fetal exposure during pregnancy and are discussed in Section 16.3.5.1 [of the PSUR]. The remaining three cases most likely involved adult patients whose ages were miscaptured because based on the clinical circumstances, the patients are most likely adults (eg, histories of caffeine/alcohol consumption, appendectomy; AE of headache which a 2 day-old would not be able to communicate).

Details of Reports in the Age group 6 months to 5 years of Age During the Reporting period (19 Jun 2022 to 17 Dec 2022).

During this reporting period, the MAH received 599 cases (44 Serious and no fatal cases) with total of 1,585 events (including 95 serious events) in children 6 months to 5 years of age who have been vaccinated with elasomeran. Of the total cases, 532 cases were medically confirmed. When gender was known slightly more cases were reported in females (47.9%; 287 cases) compared to males (42.6%; 255 cases), with small proportion of cases (9.5%; 57 cases) having no gender reported. The mean age was 2.6 years (SD :1.3) with median age of 3.0 years (min:0.5/max: 5.2). The majority of these cases were spontaneous reports (76.0%; 455 cases).

Table 16.169 presents the Top 10 frequently reported events (by PT) for the reporting period. There were 32 non-serious reports (111 total events) that included an event of Product administered to patient of inappropriate age, and of the 32 reports, 26 included PT No AE. PTs Expired product administered, and Product storage error were the next most frequently reported PTs (19 each) and were reported together in 19 cases received from Israel. These were 19 of the 28 reports where PT No AE was reported. The remaining events were reported <=2 each and did not demonstrate any unusual pattern.

It should be noted that PT 'No AE' (22.5%; 357 events) is not included in order to maintain the most informative display of AEs.

Table 16.169 Top 10 MedDRA PTs by event counts in Children 6 months to 5 years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Expired product administered	234	14.8
Product storage error	223	14.1
Product temperature excursion issue	81	5.1
Poor quality product administered	79	5.0
Pyrexia	62	3.9
Medication error	59	3.7
Inappropriate schedule of product administration	55	3.5
Product administered to patient of inappropriate age	32	2.0
COVID-19 Immunization	20	1.3
Rash	16	1.0

The serious reports received during this period generally described events known to occur with elasomeran such as pyrexia, rash, vomiting or those commonly occurring in this population such as diarrhoea. Most serious events were reported once and did not demonstrate any pattern of concern. In some cases, such as [redacted] describing a 6-month-old male who experienced apnea within 24 hours of receiving elasomeran, ankyloglossia provided a plausible and more likely etiology for the event.

There were 10 reports describing serious events of seizure-type activity, and of these, 2 reported patients with a history of seizure disorders, 3 described TTO of 1-2 days post-vaccination but lacked information such as medical history, concomitant medications and clinical management necessary for proper assessment, one report [redacted] described febrile convulsion in a 17 year-old female 6 weeks post-vaccination, and one report [redacted] described a seizure in a 2 year-old male after exposure via breast milk. Three other reports are presented below.

[redacted]**:** This is a regulatory case concerning a 1-year-old male patient with no reported medical history, who was hospitalized due to febrile convulsion. The patient had fever followed by convulsion on the night after receiving the first dose of elasomeran vaccine. The patient presented with cyanosis of limbs and face, both eyes slanted to the right and stiffness of limbs at the hospital. Clinical course, diagnostic tests and treatment details were not provided in the case. The event was resolving at the time of the report.

MAH Comment: Based on the temporal relationship, a causal association is possible, however febrile seizures are common in this age group.

[redacted]**):** This spontaneous case concerns a 4-year-old male patient, born prematurely at 24 weeks, who experienced febrile convulsion pyrexia, pain in extremity and vaccination site pain. Febrile convulsion occurred 1 day after vaccination when the patient was observed with unusual breathing with shaking and voided during the episode. The event recurred when he woke up from a nap. His head was hitting the wall, with eyes rolled back and stiffness which lasted for 5-12 mins. He started foaming at the mouth, unresponsive, barely moving and had voided during the episode. Emergency services was called and transported to hospital. Patient symptoms were consistent with complex febrile seizures vs lowered seizure threshold secondary to fever following covid vaccination. He is back to neurological baseline with normal parameters. He's been admitted for observation. On an unknown date Body temperature reported as 38.6.

MAH Comment: Based on the temporal relationship, a causal association is possible, however premature birth is a risk factor and febrile seizures are common in this age group.

[redacted]: This regulatory authority case concerns a 3.9-year-old male patient, with no medical history reported, with febrile convulsion, seizure and pyrexia less than 24 hours after receiving the second dose of elasomeran. Patient developed fever at night and the febrifuge was given firstly. after the second time of fever, the child developed convulsion with a whey-face, was transferred to the hospital, and has discharged.

WHO-UMC Causality: Based on the temporal relationship, a causal association is possible, however febrile seizures are common in this age group.

Other noteworthy serious cases are presented below.

[redacted]**(WW Identifier** [redacted]**):** This is a report of anaphylaxis in a 9-month-old female. Refer to Section 16.3.1.1 [of the PSUR] for additional details.

[redacted] **(WW Identifier:** [redacted]**):** This spontaneous case concerns a 4-year-old male with no medical history reported, who experienced meningitis within one week of elasomeran vaccination. Lumbar tap done on an unknown date showed active inflammation with negative bacterial culture and viral screening. No further information on risk factors, detailed clinical course, investigations, treatment of the events was available in the report.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation.

[redacted]**(WW Identifier** [redacted]**:** This Regulatory authority case concerns 3 years old female child, with recent respiratory infection, who experienced unexpected immune thrombocytopenia 7 days after first dose of elasomeran vaccine. The patient had associated hematomas and petechiae, and response to IVIg was reported. Leukemia and Thrombotic Thrombocytopenic Purpura (TTP) were ruled out.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation.

[redacted]**(WW Identifier** [redacted]**:** This is a regulatory authority case of product administered to patient of inappropriate age for a 4-year-old female with no medical history reported who experienced vomiting and dizziness requiring hospitalization 11 days after receiving the second dose of the elasomeran vaccine. It was reported that 8 days after vaccination, the patient started to show decreased mobility and 3 days later she experienced vomiting and dizziness. The patient was taken to the hospital and was subsequently admitted for a total of 5 days. CT of the brain showed 'mild brain swelling' and lumbar puncture showed increased pressure (anterior pressure of 27 cm H2O and posterior pressure of 8 cm H2O). Various examinations (unspecified) were conducted; however, the cause of increased brain pressure could not be identified. No further details were provided.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** This is a regulatory authority case concerning a 4-year-old, male patient with no reported medical history who experienced rhinorrhoea, oropharyngeal pain, pyrexia and abdominal pain approximately 4 days after Dose 2 elasomeran. An echocardiogram was performed resulted in suspected Kawasaki like disease, myocardial ischemia, suspected "MIS-C". Due to high fever, high white blood cell count and high C-reactive protein patient was admitted to hospital and treated with antipyretics, aspirin and intravenous immunoglobulin.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** This regulatory authority case concerns a 4-year-old male patient, with no reported medical history, who experienced acute disseminated encephalomyelitis and confusional state approximately 24 days after receiving a dose of elasomeran (reported as booster dose). Hospitalization details including clinical course, diagnostic evaluation, concomitant medications, and treatment given was not reported. The outcome was reported as not recovered.

MAH Comment: Acute Disseminated Encephalomyelitis typically occurs after a viral or bacterial infection the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation. Furthermore, given the extended TTO, this case is considered unlikely related.

Details of Reports in the Age group 6 to 11 Years of Age During the Reporting period (19 Jun 2022 to 17 Dec 2022).

During the reporting period, the MAH received 353 cases (86 serious cases and 2 fatal cases) with total of 728 events (157 serious events) for 6 to11-year-old children who have been vaccinated with elasomeran. Of the total cases, 339 cases were medically confirmed. When gender was known, the number of cases reported in females (48.7%; 172 cases) were slightly higher compared to males (45.9%; 162 cases), with a small proportion of cases (5.4%, 19 cases) having no gender reported. The mean patient age was 8.7 years (SD: 1.8) with median age of 9.0 years (min: 6.0/max: 11.0). The majority of these cases were received from regulatory authorities (75.9%;268 cases).

Table 16.170 presents the Top 10 frequently reported events (by PT) for reporting period. There were 25 non-serious report that included an event of Product administered to patient of inappropriate age, and of the 25 reports, 12 were from the Australia Health Authority and also included Vaccination error, the next most frequently reported term in these 25 cases. Only one of the TGA reports also included an additional event: Injection site reaction. Overall, the majority of the 25 reports did not describe an AE and no unusual pattern was identified. It should be noted that PT 'No AE' (9.1%; 66 events) is not included in order to maintain the most informative display of AEs.

Table 16.170 Top 10 MedDRA PTs by event counts in Children 6 to 11 years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Pyrexia	74	10.2
Medication Error	61	8.4
Chest Pain	31	4.3
Product administered to patient of inappropriate age	25	3.4
Wrong product administered	24	3.3
Rash	21	2.9
Expired product administered	20	2.7
Vomiting	18	2.5
Headache	17	2.3
Vaccination error	17	2.3

Serious and Fatal cases in Children 6-11 Years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022

During the reporting period MAH received 86 serious cases (including two fatal cases) with 178 events (157 serious events) in this age group.

Two Fatal cases are summarized below. ([redacted], [redacted]) are summarized below:

[redacted] **(WW Identifier** [redacted]**):** This regulatory case concerns a 10-year-old male patient with a prior history of fainting requiring hospitalization, who suddenly died and was diagnosed with a cardiorespiratory arrest. The event occurred approximately 7 days after the third dose of elasomeran. Information regarding clinical evaluation, diagnostic tests, treatment provided, or autopsy reports has not been disclosed.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation., including autopsy results. The prior fainting spell requiring hospitalization suggests a pre-existing serious condition may be contributory. Causality is assessed as conditional.

[redacted] **(WW Identifier** [redacted]**):** This regulatory authority case concerns a 10-year-old male patient, with no medical history reported, who died 5 days after receiving a booster dose of elasomeran. Death was reported as the only event and cause of death was unknown at the time of the report. It was not stated if an autopsy was performed. No further relevant clinical information was available.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation., including autopsy results. Causality is assessed as conditional.

The serious reports received during this period generally described events known to occur with elasomeran such as nausea, vomiting, rash or those commonly occurring in this population. Most serious events were reported once and did not demonstrate any pattern of concern.

During this reporting period, there were 10 cases of myocarditis and 1 case of pericarditis. Refer to Section 16.3.1.2 [of the PSUR]. Cases of chest pain and chest discomfort were reviewed to identify potential cases of myocarditis, myopericarditis, or pericarditis where these more clinically significant events were not reported. There were no cases of chest pain or chest discomfort which yielded evidence of increased troponin, electrocardiogram, echocardiogram, or MRI abnormalities that would help establish a level of diagnostic certainty for myocarditis, myopericarditis, or pericarditis.

Other noteworthy serious cases are presented below.

[redacted] **(WW Identifier** [redacted]**:** This is a regulatory case concerning a 10-year-old female patient with no reported medical history who experienced immune thrombocytopenia approximately two weeks dose 1 elasomeran. The patient developed bleeding and bruising with a platelet count 7000/mm3. Two weeks later was she was hospitalized with a platelet count of 5000/mm3 and received treatment with IVIg 1g/kg/day for two days with improvement in platelet count two days later to 47000/mm3 and was discharged home. One week later the platelet count was 21000/mm3 and she was treated with prednisolone. After a week, the platelet count was 226000/mm3 and the prednisolone dose was reduced.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**:** This is a regulatory case concerning an 11-year-old male patient with no reported medical history, who experienced livedo reticularis which occurred approximately 2 months after receiving the 1st dose of COVID-19 vaccine elasomeran. The patient had a suspected allergy to the excipient Tris contained in the elasomeran vaccine, leading to livedo annularis in arms and legs (generalized reticular pattern). Lymphocyte Transformation Test for Tris was positive; IgE was 1280. Fluocinolone 0.025%+ Neomycin 0.35%, (Fradiomycin) ointment was given as treatment. Outcome was reported as resolving.

MAH Comment: Based on the temporal association and laboratory evaluation, a causal association is possible.

[redacted] **(WW Identifier** [redacted]**):** This regulatory authority case concerns a 9-year-old, female patient with no medical history reported who experienced febrile convulsion, pain, induration and pyrexia 1 day after dose 3 elasomeran vaccine. No information was available regarding the first and second vaccine doses. It was reported that the patient experienced local reaction, seizure, and fever. The diagnosis was febrile seizure.

MAH Comment: Febrile seizures occur commonly in children. Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** Regulatory authority report of a 9-year-old female patient with no medical history reported who cerebrovascular accident 33 days after elasomeran vaccine. It was also reported that the patient "had not received previous dose and another vaccine. Patient received booster dose." The patient had dizziness, right hemiparesis, dysarthria and fall without loss of consciousness or sphincter control. No further information on clinical course, investigations and treatment received was available in the report. Outcome of the event was reported as resolved. The benefit-risk relationship of elasomeran vaccine is not affected by this report.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation. Furthermore, it is unclear which vaccinations she received thus the case is unassessable.

[redacted] **(WW Identifier** [redacted]**):** This regulatory case concerns a 9-year-old, female patient with no reported medical history, who experienced seizure and confusional state the same day of dose 3 elasomeran. Details of concomitant medications, medical history, clinical course, and treatment were not provided. The events have resolved at the time of the report.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** This is a regulatory authority case concerning a 6-year-old female patient with no reported medical history who experienced epileptic seizure the same day of dose 3 elasomeran vaccine administration. It was reported that the patient experienced a convulsion with loss of consciousness. At the time of the report the patient was hospitalized. No further clinical information was available.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

Details of Reports in the Age group 12 to 17 years of Age During the Reporting period (19 Jun 2022 to 17 Dec 2022).

There were 1,543 cases (including 285 serious and 10 fatal cases) with total of 4,356 events (608 serious events) reported in the children of 12–17-year age group, representing 60.9% of cases in children (<18 years) in this reporting period. Of the total cases, 1,297 were medically confirmed. When gender was known, more cases were reported in females (49.1%; 758 cases) compared to males (45.1%; 696 cases), with small proportion of cases (5.8%; 89 cases) having no gender reported. The mean patient age was 15.0 years (SD:1.8), with a median age of 16.0 years (min:12.0/max:17.0). The majority of these cases were received from regulatory authorities (85.0%; 1,311 cases) and in particular, 112 of 113 non-serious events of inflammation were from cases from the Argentina health authority.

There were 110 non-serious reports that included an event of Product administered to patient of inappropriate age. There was only one serious report [redacted], presented here again for completeness, which concerned a 15-year-old male with no medical history provided who experienced Hallucination (medically significant) approximately 1.5 months after elasomeran administered as third dose after primary vaccination (non-serious Product administered to patient of inappropriate age) completed with Pfizer vaccine. The patient also experienced coronavirus infection, with fever rising to 39.2°C and hallucinations. No further information was provided. PT: No AE was included in 51 of the remaining 109 non-serious cases. Of the total 110 reports, 41 from the Australia Health Authority also included Vaccination error, the next most frequently reported term. Overall, the majority of the 110 reports did not describe an AE and no unusual pattern was identified in those that did. The 3 most frequently reported PTs in this age group were 'Pyrexia', and 'Headache' and 'Fatigue' which are consistent with expected events following vaccinations including elasomeran (Table 16.171).

Table 16.171 Top 10 MedDRA PTs by event counts in Children 12 to 17 years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Pyrexia	277	6.4
Headache	227	5.2
Fatigue	146	3.4
Nausea	139	3.2
Chest pain	139	3.2
Myalgia	132	3.0
Vomiting	114	2.6
Inflammation	113	2.6
Product administered to patient of inappropriate age	110	2.5
Dizziness	108	2.5

Serious and Fatal Cases in Children 12-17 Years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

During the reporting period, MAH received 285 Serious cases (10 fatal cases) with 1,037 events (608 serious events) in this age group.

The ten fatal received cases in this reporting period are summarized below:

[redacted] **(WW Identifier AR-[redacted]):** This regulatory authority case of a 13-year-old female, with history of premature birth, Sjogren's syndrome, rheumatoid factor 512 IU/ml 6 months prior to vaccination, family history of arterial hypertension, who experienced

subarachnoid hemorrhage, intraventricular hemorrhage and fatal cerebral hemorrhage with symptoms first occurring 2 days after first dose of elasomeran. CT informed showed massive ventricular hemorrhage on the right side with dilation of the atrium and temporal horn, slight deviation to the left, of the middle line and hemorrhage of the fourth ventricle. The patient underwent surgery 12 days later for evacuation of a hematoma and hemodynamic decompression. The patient died approximately two weeks after vaccination. The reported cause of death were intraventricular haemorrhage and subarachnoid hemorrhage, cerebral haemorrhage. It is unknown if an autopsy was performed

MAH Comment: The patient has multiple underlying conditions including premature birth, Sjogren's disease/rheumatic disorder and family history of hypertension that could predispose to the reported intracranial events and causality is assessed as unlikely.

[redacted] **(WW Identifier AU-**[redacted]**):** is consumer report from Australia of a 14-year-old female patient, with no medical history reported, who experienced the fatal event of immunization reaction. The event occurred on an unknown date after receiving a dose of elasomeran vaccine. Treatment information was not provided. The reported cause of death was death from an adverse vaccination reaction; however, it is unknown if an autopsy was performed. The event was considered related to the product per the reporter's assessment. No further information was provided.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier AU-**[redacted]**):** is an HCP report from the Australia health authority of a 14-year-old female patient with no reported medical history, who experienced the fatal events of brain injury with brain herniation, cardiac arrest, multiple organ dysfunction syndrome, headache, dizziness, nausea and pyrexia after receiving a dose of elasomeran on an unknown date. It is not known if an autopsy was performed. No further information was provided.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier SE-**[redacted]**:** is a consumer report from the Sweden health authority of a 13-year-old male patient, with history of heart surgery at 3 days old, "heart valve operation", thymectomy and liver transplantation, who experienced fatal endocarditis, sepsis and immunodeficiency with death occurring approximately 4 months after the second dose of elasomeran vaccine. The reported cause of death was liver transplantation. It is unknown if an autopsy was performed. No further information was provided.

MAH Comment: There is an extended TTO of about four months and the patient's extensive cardiac and surgical history compounded by likely immunodeficiency from thymectomy provide plausible alternate etiologies for the events, and causality is assessed as unlikely.

[redacted] **(WW Identifier AU-**[redacted]**):** A 15-year-old patient of unknown gender experienced a fatal event of "AE" following immunization' following vaccination with elasomeran and Comirnaty. No further information was provided including vaccination/event dates, medical history, concomitant medications, clinical course or whether autopsy was performed.

MAH Comment: The report is lacking important information for proper assessment including treatment/event dates, details of medical history, concomitant medications, clinical course and diagnostic evaluation, and thus is unassessable.

[redacted] **(WW Identifier AU-**[redacted]**):** A 14-year-old female patient experienced a fatal event of immunization reaction following vaccination with elasomeran. No further information was provided including vaccination/event dates, medical history, concomitant medications, clinical course or whether autopsy was performed.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier PH-PH**[redacted]**:** A 16-year-old female patient experienced diarrhoea and vomiting 5 months after the 2nd dose of the elasomeran with an outcome of death on an unspecified date. No other information was provided such as medical history, concomitant medications, clinical course, treatment, or autopsy results, if performed.

MAH Comment: Minimal information is provided, however given the extended TTO of 5 months, a causal association is unlikely.

[redacted] **(WW Identifier PH-PH**[redacted]**:** A 15-year-old male patient experienced dyspnoea and COVID-19 on unknown dates after receiving a dose of elasomeran vaccine. The reported cause of death was reported as difficulty of breathing and COVID-19, however, it is unknown if autopsy was performed. No other information was provided such as medical history, concomitant medications, or clinical course.

MAH Comment: The report is lacking important information for proper assessment including treatment/event dates, details of medical history, concomitant medications, clinical course, and diagnostic evaluation. Given that COVID-19 is attributed as cause of death, a causal association with elasomeran is unlikely.

[redacted] **(WW Identifier IT-**[redacted]**)** is a consumer report concerning a 16-year-old male with no medical history reported, who reportedly got sick and died (PT Illness) after an unspecified dose of elasomeran vaccine. It was reported that after the ModernaTx, Inc. vaccine, the patient began to get sick. Death occurred on an unknown date. The reported cause of death was Illness. The exact course of event of illness (began to get sick) which led to the fatal outcome was not disclosed. It is unknown if an autopsy was performed. No further clinical information including medical history, concomitant medications and vaccination dates was provided.

MAH Comment: The report is lacking important information for proper assessment including description of the AE, treatment/event dates, details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier: SE-**[redacted]**):** is a consumer report concerning a 13-year-old male patient with prior cardiac surgery 3 days after birth and liver transplant at 6 months of age who experienced serious events of sepsis, hepatic failure, renal failure, cardiac arrest, cerebrovascular accident, brain injury and endocarditis on an unknown date after 2 doses elasomeran and subsequently died from endocarditis nearly 4 months after Dose 2 and 5 months after Dose 1. Death occurred on hospital day 67 after supportive care was discontinued. Causes of death were reported also as endocarditis and sepsis.

MAH Comment: The minimal information provided suggests that the patient experienced complications due to endocarditis which is known to occur in children with a history of prior cardiac surgery. WHO-UMC causality is assessed as unlikely

The serious reports received during this period generally described events known to occur with elasomeran such as pyrexia, myalgia, vomiting and headache. Most serious events were reported once

and did not demonstrate any pattern of concern.

There were 80 events of syncope (78 serious) of which 50 serious events of syncope containing minimal information were from the Australia health authority, 8 serious events of syncope containing minimal information were from the Argentina health authority, and 11 serious events of syncope from a literature report containing minimal case level information.

During this reporting period, there were 41 cases of myocarditis and 22 cases of pericarditis and 8 myopericarditis cases. Refer to Section 16.3.1.2 [of the PSUR]. Cases of chest pain and chest discomfort were reviewed to identify potential cases of myocarditis, myopericarditis, or pericarditis where these more clinically significant events were not reported. Most cases of chest pain or chest discomfort yielded no evidence of increased troponin, electrocardiogram, echocardiogram, or MRI abnormalities that would help establish a level of diagnostic certainty for myocarditis, myopericarditis, or pericarditis. One noteworthy report is presented below

[redacted] **(WW Identifier** [redacted]**:** This is a health authority report from an HCP which describes a 12-year-old male patient who experienced chest tightness (PT: Chest pain) and was hospitalized 4 days after dose 2 elasomeran and 74 days after dose 1 elasomeran. No medical history or concomitant medications were reported. The patient had normal fibrin D-dimer and elevated troponin (129.9 ng/dL) on day 3 and elevated CRP and cardiac enzyme "at Leptomeningeal disease" on day 4. After admission, the symptoms subsided spontaneously. Follow-up troponin-I and ECG showed no ischemic change with improved "lab data". Echocardiography revealed good cardiac function. The patient was subsequently discharged.

MAH Comment: Based on the clinical presentation and plausible temporal association, WHOUMC causality is assessed as possible with further information such as medical history and concomitant medications necessary to exclude disease or other drugs and attribute a more compelling causal association.

Other noteworthy serious cases are presented below.

[redacted] **(WW Identifier:** [redacted]**:** is a regulatory authority report with follow-up on a 13-year-old female with no medical history or concomitant medications reported, who experienced thrombocytopenia, neutropenia, COVID-19, gingival bleeding, iron deficiency, haematoma, serum ferritin decreased, epistaxis, fatigue, platelet morphology abnormal and HMB 1 month and 19 days after vaccination with Dose 2 of elasomeran and requiring hospitalization. The outcome of the events was reported as unknown.

MAH Comment: Important data needed for proper evaluation are missing including full medical history, detailed diagnostic evaluation, and clinical course. Evaluation is confounded by concurrent COVID-19. The case is unassessable.

[redacted]**(WW Identifier** [redacted]**):** This was received from a health authority describing a 17-year-old-female with no reported medical history or concomitant medications who received elasomeran Dose 2 and approximately 9 months later experienced endocarditis. No treatment information was provided.

MAH Comment: While minimal information is provided, the extended TTO of 9 months following vaccination makes a causal association unlikely.

[redacted] **(WW Identifier:** [redacted]**:** is a regulatory authority report concerning a 16-year-old female with medical history of factor V Leiden heterozygote and concomitant use of drospirenone, who experienced the serious (reported as medically significant) events of HMB, menstruation irregular and dysmenorrhoea almost two months after dose 2 elasomeran.

MAH Comment: Minimal information is provided, however the history of factor V Leiden heterozygote and concomitant drospirenone offer more likely alternate etiologies for the events which are considered unlikely related.

Reports in Children < 18 years Who Received Booster with elasomeran/imelasomeran During Reporting period (19 Jun 2022 to 17 Dec 2022)

During the reporting period, 27 cases (22 medically confirmed, 2 serious, and no fatal cases) with 63 events (4 serious events) were reported in Children < 18 years of age who received elasomeran/imelasomeran. When gender was known, more cases were reported in males (48.1%;13 cases) compared to females (37.0%;10) with small proportion of cases (14.8%;4) having no gender reported. The mean patient age was 12.3 years (SD: 5.7) with median age of 15.0 years (min :0.0 /max :17.0). The majority of these cases were reported in children 12-17-years of age (77.8%; 21 cases).

Of the 27 cases, 25 were non-serious and involved product use issues with no AE reported, or describe events known to occur with elasomeran such as fever, pain and malaise. One of the 25 non-serious cases and one serious case likely involved adult patients whose age was miscaptured.

The other serious case [redacted] is a regulatory authority report concerning a 16-yearold male with no reported medical history, who experienced the medically significant event of dizziness, tension headache, and palpitations within one day of elasomeran with no indication of hospitalization. Given the plausible TTO, a causal association is possible with the events likely representing reactogenicity.

Reports in Children <18 years Who Received Booster with elasomeran/davesomeran During Reporting period (19 Jun 2022 to 17 Dec 2022)

During this reporting period, 65 Cases (of which 57 were medically confirmed, 3 serious and no fatal cases) with 160 events (5 serious events) were reported in children <18 years of age who received elasomeran/davesomeran. When gender was known slightly more cases were reported in males (38.5%; 25 cases) compared to females (33.8%; 22 cases), and (27.7% ;18 cases) having no gender reported. The mean age was 9.4 years (SD :4.9) with median age of 11.0 (min:0.0/max:17.0). The majority of these cases were reported in children 12-17 years of age (46.2%; 30 cases).

Of the 65 cases, 62 were non-serious and involved product use issues with no AE reported, described events known to occur with elasomeran or contained insufficient information to draw further conclusions.

Three serious cases ([redacted], [redacted], [redacted]) are summarized below.

[redacted] **(WW Identifier** [redacted]**:** This regulatory authority case concerns a 17-year-old female patient with no reported medical history who experienced chest pain (reported as medically significant) 1 day dose 4 elasomeran/davesomeran bivalent vaccine. There was no dyspnea, no palpitation, no fever, or cough. No abnormality was found on electrocardiogram and blood tests. There is no indication that the patient was actually admitted

MAH Comment: Based on the temporal association, a causal association is possible and very probably reactogenicity.

[redacted] **(WW Identifier** [redacted]**):** Concerns a 14-year-old male with no medical history reported, who experienced serious pyrexia and chest pain 1 day after elasomeran/davesomeran vaccination as Dose 4. One day after vaccination, the patient reportedly was admitted for complaints of chest pain, chest distress, suspected cardiogenic chest pain with pain index of 8 points. Troponin value was slightly elevated on the first day and back to normal values afterward. Creatine phosphokinase was elevated at 195 IU/L with other labs unremarkable. An ECG was performed and reported as abnormal but actual results were not provided. After one day patient was transferred to

another hospital and discharged within 3 days with chest pain reported as resolved.

MAH Comment: According to the Brighton Collaboration case definition this case is considered Level 2 for myocarditis. According to the CDC case definition this case is considered Probable, and according to the WHO causality assessment this case is considered possible. The report is lacking important information including medical history, concomitant medications, actual ECG results.

[redacted] **(WW Identifier:** [redacted]**:** Concerns a 13-year-old male with no medical history reported, who experienced chest pain, dizziness and pyrexia one day after elasomeran/davesomeran vaccination as Dose 3. Laboratory results provided showed normal Troponin and negative D-dimer, but elevated CRP with other lab results unremarkable. Electrocardiogram was reported as normal. Patient had high blood pressure and elevated heart rate and was subsequently discharged.

MAH Comment: According to the Brighton Collaboration case definition this case is considered Level 5 – Not a case of myocarditis. According to the CDC case definition this case is considered "Not a case". Given that this is not considered a case of myocarditis the WHO causality assessment was not conducted. Events reported by the patient more likely represent reactogenicity events.

Discussion

Over three-quarters (83.2%) of cases reported in children under the age of 18 years during this reporting period were non-serious and most of the cases (1,543; 60.9%) were reported in adolescents 12 – 17 years. In the 0- 5 months age group, there were 40 cases with most commonly reported events of pyrexia, exposure via breast milk and headache. In 6 months to 5 years (599 cases) product use related events were mostly reported. Among 6 to 11 years age group there were 353 cases where vaccine was administered (as opposed to exposure through breast milk) with AEs typical of reactogenicity predominating. In the12-17-year age group the most frequently reported events of pyrexia, headache and fatigue were in line with reactogenicity of elasomeran, however events of myocarditis/pericarditis/myopericarditis (71 events, 1.6 %) (myocarditis is an Important Identified Risk for elasomeran) continue to be received in the 12–17-year-old age group.

Reports of events following booster doses with elasomeran/imelasomeran and elasomeran/davesomeran were mainly non-serious, involved product use issues or described events associated with vaccine administration or those commonly occurring in this population.

The MAH has observed a marked decrease in the events of Product administered to patient of inappropriate age received during this period (170 events, 2.5%) compared to all prior intervals (4462 events, 30.1%), driving the cumulative reporting rate downwards (4,632 events 21.4%). The vast majority of reports were non-serious and very often did not have associated AEs. When AEs were infrequently reported, they were typically reactogenicity, or other events that did not demonstrate any unusual pattern. With the approval of conditional marketing authorization in adolescents and now in children 6 months-11 years, use will no longer be considered inappropriate in this age group. With greater global awareness and vaccine availability, the MAH expects an increasing amount of information to be received in coming months about the safety of the product in this subpopulation to enable the MAH to further inform vaccination practice.

Overall, the reports received during this period generally described events that were representative of reactogenicity and other systemic events such as pyrexia, headache, fatigue, malaise, and chills and were similar across age groups.

Conclusion

After careful review of all new safety data received during the reporting period and cumulatively, for the

children <18 years, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The safety of vaccination in children <18 years will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

During the reporting period the MAH identified 2,535 cases in children (<18 years of age). This includes 426 serious cases and 12 fatal cases. The fatal cases were assessed by the MAH to be Unlikely related (n=5), Unassessable (n=5) or Conditional (n=2). No information was provided by the MAH concerning any effort to gather additional information in these cases.

It is noted that there is a large proportion of unknown dose number, and large proportion of unknown TTO in the review period.

No specific pattern that warrants further analysis was identified.

However, the Rapporteur noted the following inconsistencies:

The MAH reported on a 4-year-old case ([redacted]) with suspected MIS-C, Kawasaki like disease, and myocardial ischemia following elasomeran. TTO=2. The MAH did not include this case in the section of Multisystem Inflammatory Syndrome. Please see request in the MIS section of the AR (section 2.4.4).

The MAH identified a 14-year-old male considered with BC level 2 myocarditis ([redacted]. This case was neither included in the PSUR section of myocarditis nor myocarditis appendix 11.5. Please see request in the myocarditis section of the AR (section 2.3.1.2).

The MAH reported on a 17-year-old serious case with febrile convulsion ([redacted]) in the presentation of the youngest babies/children (6 months to 5 years of age), which is inconsistent. Furthermore, this case is not included in the annex 11.26a and annex 11.26b (Use in Children (< 18 Years of Old): Serious Cases During the Reporting Period- Case Evaluations and Case Narratives (All) (elasomeran)). **The MAH is requested within the next PSUR to clarify this discrepancy.**

The following three serious cases of elasomeran/davesomeran ([redacted], [redacted], [redacted]) are not found in the appendix 11.26 (Use in children (<18 Years of Old): Serious cases during the reporting period). **The MAH is requested to clarify within the next PSUR this discrepancy.**

In the guidance of assessment and understanding of data the MAH is requested to specify within the next PSUR the MAH's definition of a noteworthy report, which has been used by the MAH as an argument to present cases.

The number of inconsistencies identified in one PSUR section noted. The MAH is once more reminded to be thorough and precise in the presentation and assessment of data.

The provided information is acknowledged.

2.5.10. Bivalent Variant Use

Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTx, Inc. cumulatively from 20 Dec 2020 to 17 Dec 2022 and for the reporting period of 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran booster and elasomeran/davesomeran booster.

Background Relevant to the Evaluation

The MAH received a request from a regulatory authority to summarize cases involving elasomeran, elasomeran/imelasomeran booster and elasomeran/davesomeran booster. Specifically, the regulatory authority requested:

"The MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine – cumulative and booster. Any differences in occurrence of safety issues, when comparing the variant updated vaccines with the original monovalent elasomeran or, indeed, when comparing the two different variants updated bivalent elasomeran vaccines, should be discussed."

Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations (eg, immunocompromised) and/or as a booster dose, including authorization for two bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) continue to expand.

Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB cumulatively from 18 Dec 2020 to 17 Dec 2022 and for the reporting period 19 Jun 2022 through 17 Dec 2022, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The MAH has continued its review and reporting of cases involving booster doses of elasomeran and of the 2 bivalent vaccine boosters (elasomeran/imelasomeran and elasomeran/davesomeran). For cases reporting a third dose with elasomeran, reporting sources rarely identify this third dose as either booster or as part of the primary series in immunocompromised patients. Further, prior vaccination information (i.e., manufacturer) is often not provided. This absence of differentiation confounds the MAH's ability to identify and report clear safety patterns involving booster doses of elasomeran. In comparison, administration information provided by the reporting sources about the 2 bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) supports their use as boosters. Attribution of events to specific doses is provided, when available. Otherwise, analysis is presented in a consolidated manner for ≥ 3 doses of elasomeran.

The MAH is receiving information globally after new authorizations for bivalent boosters. When relevant to vaccine exposure, results are designated as being associated with elasomeran) as the primary series and/or booster, elasomeran/imelasomeran booster and elasomeran/davesomeran booster. If no designation is provided, then data are associated with elasomeran.

Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Refer to Appendix 11.27 for details of the summaries in this section.

<u>Overview of Cases: elasomeran</u>

The majority of case reports were from regulatory authorities (76.0% cumulatively and 84.3% for the reporting period).

Cumulatively, the MAH has received 658,759 cases (2,516,669 events, of which 418,715 events were serious). Of the cumulative reported cases, 310,791 cases were medically confirmed, 134,884 cases were serious, and 6,569 cases had fatal outcomes. The majority of cases were reported in females (444,791; 67.5%) compared to males (186,791; 28.4%) with mean age of 48.9 years (SD: 17.8; median: 48.0 years). A total of 27,177 cases (4.1%) had unknown/unreported gender.

During this reporting period, the MAH received 80,461 cases (327,956 events, of which 37,235 events were serious). Of the total cases during this reporting period, 30,538 cases were medically confirmed, 15,335 cases were serious, and 373 cases had fatal outcomes. The majority of cases were reported in females (53,192; 66.1%) compared to males (23,536; 29.3%) with mean age of 45.0 years (SD: 16.8; median: 44.0 years). A total of 3,733 cases (4.6%) had unknown/unreported gender.

Cumulatively and during the reporting period, the majority of cases received for elasomeran have been non-serious (Table 16.172).

Table 16.172. Post-authorization Cases Received Cumulative and Reporting Period- (elasomeran)

Seriousness	Review Period		Cumulative	
	Cases (N)	Cases (%)	Cases (N)	Cases (%)
Non-Serious	65,126	80.9	523,875	79.5
Serious	15,335	19.1	134,884	20.5
Total	**80,461**	**100.0**	**658,759**	**100.0**

Cumulatively and during the reporting period for cases reported to the MAH for elasomeran with age information, the majority of cases have been reported in adults ≥ 18 years of age (PSUR Table 16.173).

Cumulatively, the majority of all cases for elasomeran have been reported by the EEA (42.9%) and the United States (39.2%) and the majority of serious cases have been reported by the EEA (35.9%), United States, (33.4%), and UK (18.8%). During the reporting period, reports from the EEA accounted for 66.6% of non-serious cases and 69.5% of serious cases.

For the calculation of Time To Onset (TTO) and the attribution of Dose Number to individual events, an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a specific Dose Number was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number. Furthermore, for each event, TTOs were calculated by Dose Number. Therefore, when the Dose Number was "Unknown" for an event, TTO could not be calculated, and the event has a missing TTO.

Event distribution by dose number and seriousness are described in Table 16.174 below. The majority of doses administered cumulatively and during the review period have involved the primary series (ie, Dose 1 and Dose 2 and [for certain subpopulations] Dose 3), when dose information was reported by the source. During this reporting period, event distribution showed that a greater number of events for elasomeran were associated with Dose 2 than with other doses. The section below (Overview of Cases: elasomeran Booster) provides a summary of cases and events for recipients of 3 or more doses.

Table 16.174 Distribution of Events by Dose Number and Seriousness -Cumulative and Reporting Period (elasomeran)

Dose	Review Period		Cumulative
	Non-Serious	Serious	
	Events N (%)	Events N (%)	Events N (%)
Dose 1	39,023 (13.4)	3,808 (10.2)	758,268 (30.1)
Dose 2	51,740 (17.8)	6,786 (18.2)	606,530 (24.1)
Dose 3	40,169 (13.8)	6,582 (17.7)	202,370 (8.0)
Dose 4	4,456 (1.5)	2,068 (5.6)	11,467 (0.5)
Dose 5	272 (0.1)	452 (1.2)	923 (0.0)
Dose 6	7 (0.0)	0 (0.0)	17 (0.0)
Dose 7	1 (0.0)	1 (0.0)	10 (0.0)
Unknown	155,053 (53.3)	17,538 (47.1)	938,084 (37.3)
Grand total	**290,721 (100.0)**	**37,235 (100.0)**	**2,517,669 (100.0)**

Table 16.175 provides the cumulative distribution of events by dose and time to onset. Excepting the events with "Unknown" dose (ie, not reported by the source), substantially more events were reported after Dose 1 compared to Dose 2 and Dose 3.

Table 16.175 Distribution of Events by Dose Number and Time to Onset (TTO) Cumulative and Reporting Period (elasomeran)

		Review Period		Cumulative	
Dose Number	TTO (days)	Events (N)	Events (%)	Events (N)	Events (%)
Dose 1	**Subtotal**	**42,831**	**13.1**	**758,268**	**30.1**
	0 days	17,005	5.2	294,478	11.7
	01-02	12,950	3.9	200,491	8.0
	03-04	1,903	0.6	37,423	1.5
	05-06	1,801	0.5	35,335	1.4
	07-13	6,102	1.9	139,590	5.5
	14-29	1,455	0.4	29,905	1.2
	30+	1,615	0.5	21,046	0.8
Dose 2	**Subtotal**	**58,526**	**17.8**	**606,530**	**24.1**

		Review Period		Cumulative	
Dose Number	**TTO (days)**	**Events (N)**	**Events (%)**	**Events (N)**	**Events (%)**
	0 days	27,875	8.5	253,469	10.1
	01-02	19,168	5.8	219,254	8.7
	03-04	1,604	0.5	21,008	0.8
	05-06	814	0.2	9,885	0.4
	07-13	1,601	0.5	20,662	0.8
	14-29	1,679	0.5	20,621	0.8
	30+	5,785	1.8	61,631	2.4
Dose 3	**Subtotal**	**46,751**	**14.3**	**202,370**	**8.0**
	0 days	17,041	5.2	80,949	3.2
	01-02	16,441	5.0	78,787	3.1
	03-04	2,080	0.6	9,403	0.4
	05-06	1,220	0.4	4,883	0.2
	07-13	3,347	1.0	12,822	0.5
	14-29	2,306	0.7	6,970	0.3
	30+	4,316	1.3	8,556	0.3
Dose 4	**Subtotal**	**6,524**	**2.0**	**11,467**	**0.5**
	0 days	3,017	0.9	5,759	0.2
	01-02	1,987	0.6	3,556	0.1
	03-04	294	0.1	519	0.0
	05-06	192	0.1	258	0.0
	07-13	337	0.1	500	0.0
	14-29	271	0.1	341	0.0
	30+	426	0.1	534	0.0
Dose 5	**Subtotal**	**724**	**0.2**	**923**	**0.0**
	0 days	330	0.1	437	0.0
	01-02	273	0.1	339	0.0
	03-04	28	0.0	36	0.0
	05-06	6	0.0	10	0.0
	07-13	20	0.0	26	0.0
	14-29	25	0.0	27	0.0
	30+	42	0.0	48	0.0
Dose 6	**Subtotal**	7	**0.0**	**17**	**0.0**
	0 days	1	0.0	1	0.0
	01-02	1	0.0	1	0.0

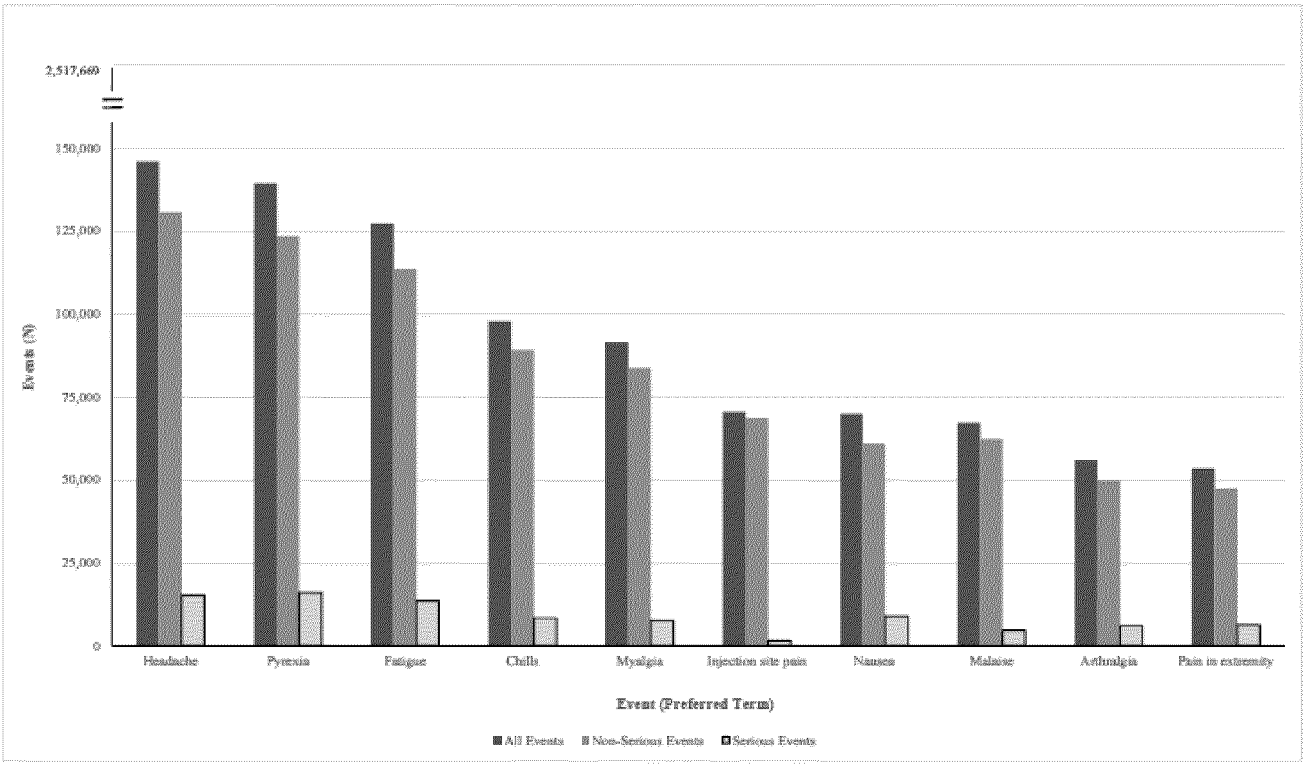
		Review Period		Cumulative	
Dose Number	**TTO (days)**	**Events (N)**	**Events (%)**	**Events (N)**	**Events (%)**
	05-06	0	0	10	0.0
	07-13	5	0.0	5	0.0
Dose 7	**Subtotal**	**2**	**0.0**	**10**	**0.0**
	0 days	0	0	8	0.0
	30+	2	0.0	2	0.0
Unknown	**Subtotal**	**172,591**	**52.6**	**938,084**	**37.3**
	0 days	18,320	5.6	150,617	6.0
	01-02	7,361	2.2	136,447	5.4
	03-04	1,482	0.5	15,885	0.6
	05-06	998	0.3	10,654	0.4
	07-13	2,370	0.7	35,047	1.4
	14-29	2,278	0.7	14,163	0.6
	30+	10,297	3.1	27,603	1.1
	Event onset prior to first dose reported	8,429	2.6	17,218	0.7
	Missing	121,056	36.9	530,450	21.1
Grand Total		**327,956**	**100.0**	**2,517,669**	**100.0**

Interval and Cumulative Spontaneous Adverse Reactions by SOC, HLT, and PT

Overview of Events

The most frequently reported events for elasomeran are presented cumulatively in Figure 16-21. Among all events cumulatively (N=2,517,669), the most frequently reported serious and nonserious events were headache (15,358 serious events, 0.6%; 130,681 non-serious events, 5.2%), pyrexia (16,087 serious events, 0.6%; 123,373 non-serious events, 4.9%), and fatigue (13,569 serious events, 0.5%; 113,615 non-serious events, 4.5%) which are consistent with the expected reactogenicity events associated with elasomeran.

Figure 16-21. Most Frequently Reported Events Reported for elasomeran (Cumulative)



The most frequently reported events for elasomeran during the reporting period are presented in PSUR Figure 16-22. Among all events during the reporting period (N=327,956), the most frequently reported serious and non-serious events were headache (1,070 serious events, 2.9%; 19,256 non-serious events, 6.6%), fatigue (1,118 serious events, 3.0%, 18,126 non-serious events, 6.2%), and pyrexia (967 serious events, 2.6%; 17,759 non-serious events, 6.1%) which are consistent with the expected reactogenicity events associated with elasomeran.

Overview of Serious Cases During the Reporting Period – elasomeran

Of the 80,461 cases during the reporting period, 15,335 cases were serious, and 373 cases had fatal outcomes. There were 327,956 events, of which 37,235 were serious. Outcomes for serious events during the reporting period included 778 fatal events, 6,726 events resolved, 6,313 events resolving, 2,058 events resolved with sequelae, 12,712 events not resolved, and 8,648 events had missing/unknown data.

For serious events whose associated doses were reported, most occurred after receiving Dose 2 (18.2%) compared to Dose 3 (17.7%) and Dose 1 (10.2%). A substantial proportion of serious events (47.1%) were reported without associated doses.

Overview of Cases with Fatal Outcomes – elasomeran

Cumulatively, a total of 6,569 cases (17,751 events, all serious) had fatal outcomes. The majority of cases were in males (3,752 cases, 57.1%) compared to females (2,642 events, 40.2%) with mean age of 70.8 years (SD: 17.0; median: 73.0 years). A total of 175 cases (2.7%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (3,005 events, 16.9%), COVID-19 (696 events, 3.9%), and dyspnoea (534 events, 3.0%). The majority of cases with fatal outcomes were reported from the United States (63.5%), EEA (18.3%), and Asia (13.9%). The majority of events (69.3%) were reported after Dose 1 and Dose 2. During the reporting period, a total of 373 cases (778 events, all serious) had fatal outcomes. The majority of cases were in males (202 cases, 54.2%) compared to females (155 cases, 41.6%) with a mean age of 64.2 years (SD: 20.1; median: 68.0 years).

A total of 16 cases (4.3%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (82 events, 10.5%), COVID-19 (19 events, 2.4%), and myocarditis and cardiac arrest (18 events, 2.3% for each term). The majority of cases were reported from Asia (132 cases, 35.4%) and the EEA (116 cases, 31.1%). The majority of cases (60.4%) were reported with unknown association to dose number. Events with fatal outcomes are summarized in Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

Overview of Cases: Elasomeran Booster

Cumulatively, the MAH has received 70,647 cases (214,787 events, of which 68,016 events were serious) involving recipients of >2 doses of elasomeran. Of the cumulative reported cases, 20,424 cases were medically confirmed, 22,050 cases were serious, and 542 cases had fatal outcomes. The majority of cases were reported in females (45,518; 64.4%) compared to males (22,591; 32.0%) with the mean age of 49.7 years (SD: 16.1; median: 49.0 years). A total of 2,538 cases (3.6%) had unknown/unreported gender.

During this reporting period, the MAH received 16,923 cases (54,008 events, of which 9,103 events were serious) involving recipients of >2 doses of elasomeran. Of the total cases during this reporting period, 5,123 cases were medically confirmed, 3,880 cases were serious, and 100 cases had fatal outcomes. The majority of cases were reported in females (11,054; 65.3%) compared to males (5,555; 32.8%) with mean age of 50.7 years (SD: 15.7; median: 50.0 years). A total of 314 cases (1.9%) had unknown/unreported gender.

Cumulatively and during the reporting period, the majority of cases involving recipients of >2 doses of elasomeran have been non-serious (Table 16.176).

Table 16.176 Post-authorization Cases Involving Recipients of >2 Doses of elasomeran Cumulative and Reporting Period

Seriousness	Review Period		Cumulative	
	Cases (N)	Cases (%)	Cases (N)	Cases (%)
Non-Serious	13,043	77.1	48,597	68.8
Serious	3,880	22.9	22,050	31.2
Total	**16,923**	**100.0**	**70,647**	**100.0**

Cumulatively and during the reporting period for recipients of >2 doses of elasomeran, the majority of cases have been reported in adults ≥ 18 years of age (Table 16.177).

Table 16.177 Distribution of Cases by Age Group and Gender Involving Recipients of >2 Doses of elasomeran Cumulative and Reporting Period

Age Group	Review Period			Cumulative
	Female N (%)	Male N (%)	Unknown N (%)	N (%)
Children (<11 years old)	30 (0.3)	27 (0.5)	7 (2.2)	147 (0.2)
Adolescents (12-17 years old)	10,711 (96.9)	5,367 (96.6)	224 (71.3)	66,157 (93.6)
Adults (≥18 years old)	277 (2.5)	143 (2.6)	81 (25.8)	4,260 (6.0)
Unknown	11,054 (100.0)	5,555 (100.0)	314 (100.0)	70,647 (100.0)
Total	**30 (0.3)**	**27 (0.5)**	**7 (2.2)**	**147 (0.2)**

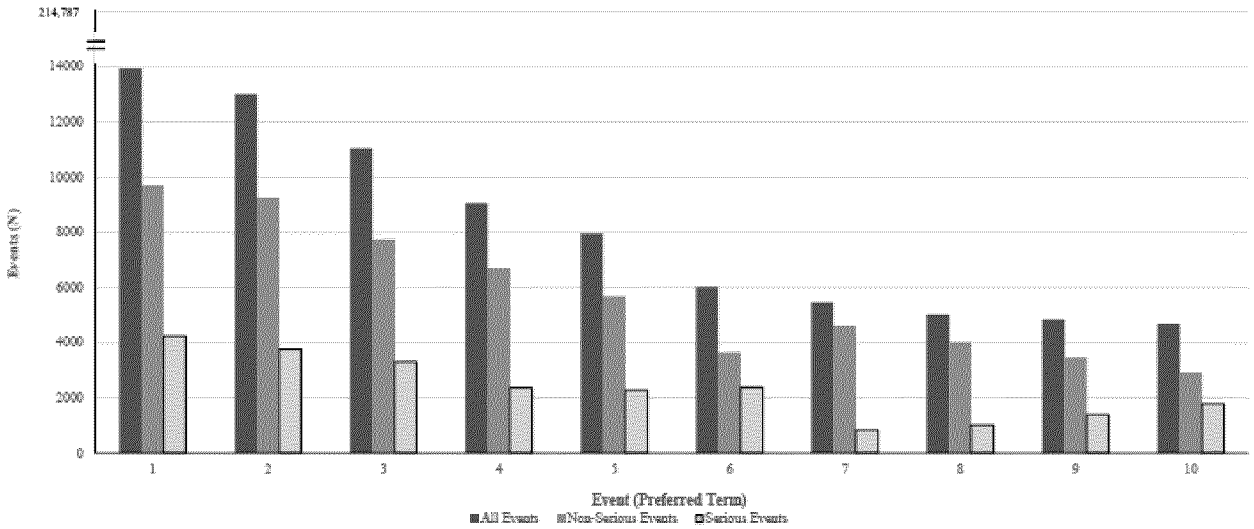
Cumulatively, the majority of all cases have been reported by the EEA (47.2%), UK (26.0%) and United States (16.3%) and the majority of serious cases have been reported by the UK (52.9%) and EEA (30.0%). During the reporting period, the EEA accounted for 75.8% of non-serious cases and 53.9% of serious cases.

Interval and Cumulative Spontaneous Adverse Reactions by SOC, HLT, and PT

Overview of Events – elasomeran) >2 Doses

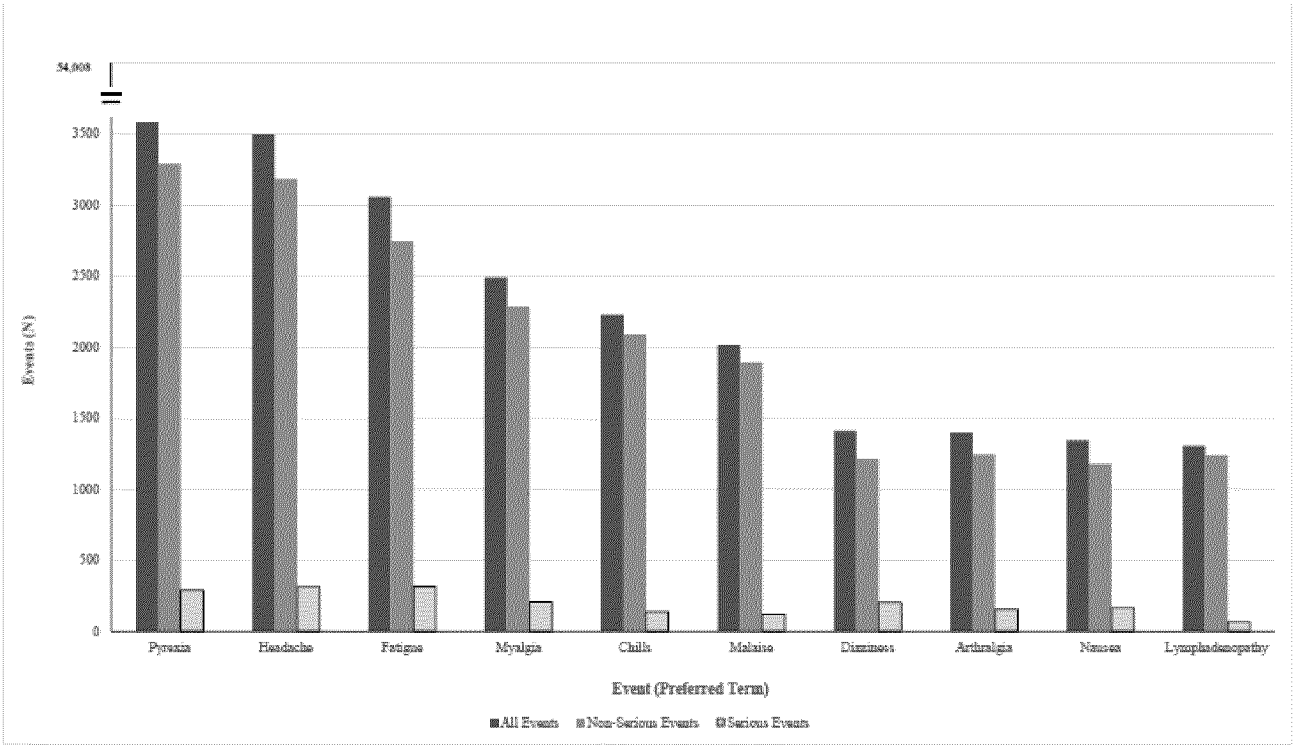
The most frequently reported events reported for recipients of > 2 doses of elasomeran are presented cumulatively in Figure 16-23. Among all events cumulatively (N=214,787), the most frequently reported serious and non-serious events were headache (4,229 serious events, 2.0%; 9,690 non-serious events, 4.5%), pyrexia (3,764 serious events, 1.8%; 9,240 non-serious events, 6.1%), and fatigue (3,303 serious events, 1.5%; 7,737 non-serious events, 1.5%).

Figure 16-23. Most Frequently Reported Events Reported for Recipients of >2 Doses of elasomeran (Cumulative)



The most frequently reported events during the reporting period for recipients of > 2 doses of elasomeran are presented in Figure 16-24. Among all events during the reporting period (N=54,008), the most frequently reported serious and non-serious events were pyrexia (290 serious events, 0.5%; 3,291 non-serious events, 6.6%), headache (313 serious events, 0.6%; 3,182 nonserious events, 5.9%), and fatigue (316 serious events, 0.6%; 2,741 non-serious, 5.1%).

Figure 16-24. Most Frequently Reported Events Reported for Recipients of >2 Doses of elasomeran (Review Period)



During the reporting period, a total of 6,508 events were reported for recipients of >2 doses of elasomeran among which the 3 most frequently reported events by PT were pyrexia (647 events, 9.9%), headache (530 events, 8.1%), and fatigue (401 events, 6.2%). During the reporting period, a total of 726 serious events were reported for recipients of >2 doses of elasomeran among which the 3 most frequently reported serious events by PT were arthralgia (30 events, 4.1%), fatigue (25 events, 3.4%), and headache (25 events, 3.4%) which are consistent with the expected reactogenicity events associated with elasomeran.

Overview of Serious Cases During the Reporting Period – elasomeran >2 doses

Of the 16,923 cases during the reporting period for recipients of >2 doses of elasomeran, 3,880 cases were serious, and 100 cases had fatal outcomes. There were 54,008 events, of which 9,103 were serious. Outcomes for serious events during the reporting period included 201 fatal events, 1,664 events resolved, 1,963 events resolving, 727 events resolved with sequelae, 3,391 events not resolved, and 1,157 events had missing/unknown data.

Overview of Cases with Fatal Outcomes

Cumulatively, a total of 542 cases (1,362 events, all serious) had fatal outcomes. The majority of cases were in males (328 cases, 60.5%) compared to females (211 events, 38.9%) with mean age of 70.7 years (SD: 16.4; median: 73.0 years). A total of 3 cases (0.6%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (174 events, 12.8%), cardiac arrest (49

events, 3.6%), and cardiorespiratory arrest (42 events, 3.1%). The majority of cases with fatal outcomes were reported from Asia (40.4%), EEA (27.3%), and United States (22.1%).

During the reporting period, a total of 100 cases (201 events, all serious) had fatal outcomes. The majority of cases were in males (69 cases, 69.0%) compared to females (30 cases, 30.0%) with a mean age of 68.7 years (SD: 18.0; median: 70.0 years). A total of 1 case (1.0%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (17 events, 8.5%), myocarditis (11 events, 5.5%), and pyrexia (9 events, 4.5%). The majority of cases were reported from Asia (56 cases, 56.0%) the EEA (22 cases, 22.0%), and the United States (10 events, 10.0%).

Events with fatal outcomes are summarized in PSUR Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

Overview of Cases: elasomeran/imelasomeran Booster

Elasomeran/imelasomeran received authorization for use in selected global regions in Sep 2022 and within the review period of this PBRER; therefore, the data received by the MAH during the review period constitute the cumulative data.

Since Sep 2022, a limited number of cases have been reported to the MAH. Important to note is that a substantial number of cases (2,552, 48.8%) were reported to the MAH without information about age and 90.3% of events have been reported to the MAH without information regarding dose number. This limits the MAH's ability to present certain summaries as in other sections of this report.

The majority of case reports were from regulatory authorities for the reporting period (78.9%).

During the reporting period, the MAH has received 5,234 cases (21,578 events, of which 2,130 events were serious) involving the elasomeran/imelasomeran booster. Of the reported cases, 1,271 cases were medically confirmed, 940 cases were serious, and 38 cases had fatal outcomes.

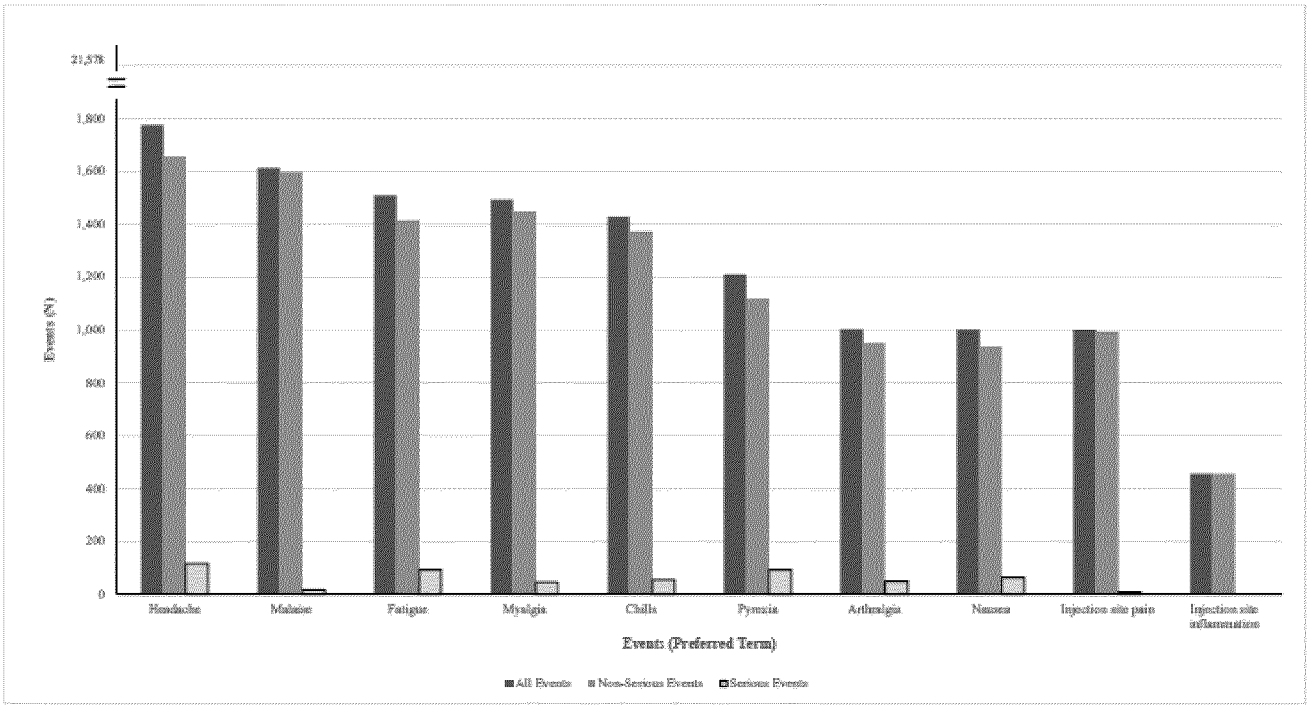
The majority of cases were reported in females (3,129, 59.8%) compared to males (1,591; 30.4%) with mean age of 58.9 years (SD: 14.9; median: 60.0 years). A total of 514 cases (9.8%) had unknown/unreported gender. Of the reported serious cases, the majority of serious cases were reported in females (587, 62.4%) compared to males (317; 33.7%) with mean age of 61.1 years (SD: 16.9; median: 64.0 years). A total of 36 cases (3.8%) had unknown/unreported gender.

During the reporting period, the majority of all cases have been reported from Europe (60.3%), UK (20.3%), and Asia (11.0%). Among the 940 serious cases reports, the majority were reported from the UK (50.5%) and Europe (33.8%).

During the reporting period, for events reported as being associated with a known dose number (2,089 events), the majority (1,743 events, 83.4%) occurred within 2 days after administration of the elasomeran/imelasomeran) booster. Of note, a total of 19,489 events were reported without an associated dose number. Among serious events reported as being associated with a known dose number (1,253 events), the majority (1,051 events, 83.9%) occurred within 2 days after administration of elasomeran/imelasomeran. Of note, a total of 1,899 serious events were reported without an associated dose number.

The most frequently reported events during the reporting period are presented in Figure 16-25. Among all events (N=21,578), headache (7.7%), malaise (7.4%), and myalgia (6.7%) were the most frequently reported non-serious events and headache (0.5%), fatigue (0.4%), and pyrexia (0.4%) were the most frequently reported serious events among 940 serious cases, which are consistent with the expected reactogenicity events associated with elasomeran/imelasomeran).

Figure 16-25. Most Frequently Reported Events During the Review Period



The event outcome most frequently reported outcome during the reporting period was Not recovered/Not Resolved in 31.7% non-serious events and 30.7% of serious events (Table 16.178).

Table 16.178 Event Outcome (Reporting Period) elasomeran/imelasomeran

Event Outcome	Review Period	
	Non-Serious Events, n (%)	Serious Events, n (%)
Fatal	69 (0.3)	69 (2.2)
Not Recovered/Not Resolved	6,836 (31.7)	654 (30.7)
Recovered/Resolved	5,798 (26.9)	553 (26.0)
Recovered/Resolved with Sequelae	48 (0.2)	29 (1.4)
Recovering/Resolving	6,212 (28.8)	589 (27.7)
Unknown	2,615 (12.1)	236 (11.1)
Grand Total	**21,578 (100.0)**	**2,130 (100.0)**

Fatal Cases (Reporting Period) - elasomeran/imelasomeran

During the reporting period a total of 38 cases (69 events, all serious) had fatal outcomes. More cases involving males (20 cases, 52.6%) were reported than for females (14 cases, 36.8%) with mean age of 76.5 years (SD: 14.6; median: 76.0 years). A total of 4 cases (10.5%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (11 events, 15.9%), myocardial infarction (4 events, 5.8%), and the following events each occurring with a frequency of 2 event (2.9%): abdominal pain, acute myocardial infarction, asthma, cardiac arrest, condition aggravated, fatigue, hypoxia, sepsis, and tachycardia. The most cases with fatal outcomes were reported from Asia (16 cases, 42.1%) and EEA (12 events, 31.6%). Among events for which dose number was reported (38 events), the 18 events (47.4%) occurred within 2 days after administration of elasomeran/imelasomeran booster.

Events with fatal outcomes are summarized in Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

Overview of Cases: elasomeran/davesomeran

Elasomeran/davesomeran received authorization for use primarily in the United States in Sep 2022 followed by selected regions thereafter within the review period of this PBRER; therefore, the data received by the MAH during the review period constitute the cumulative data.

Since September, a limited number of cases have been reported to the MAH. Important to note is that a substantial number of cases (801, 34.1%) were reported to the MAH without information about age and 76.0% of events have been reported to the MAH without information regarding dose number. This limits the MAH's ability to present certain summaries as in other sections of this report.

The majority of case reports were spontaneous reports for the reporting period (99.3%).

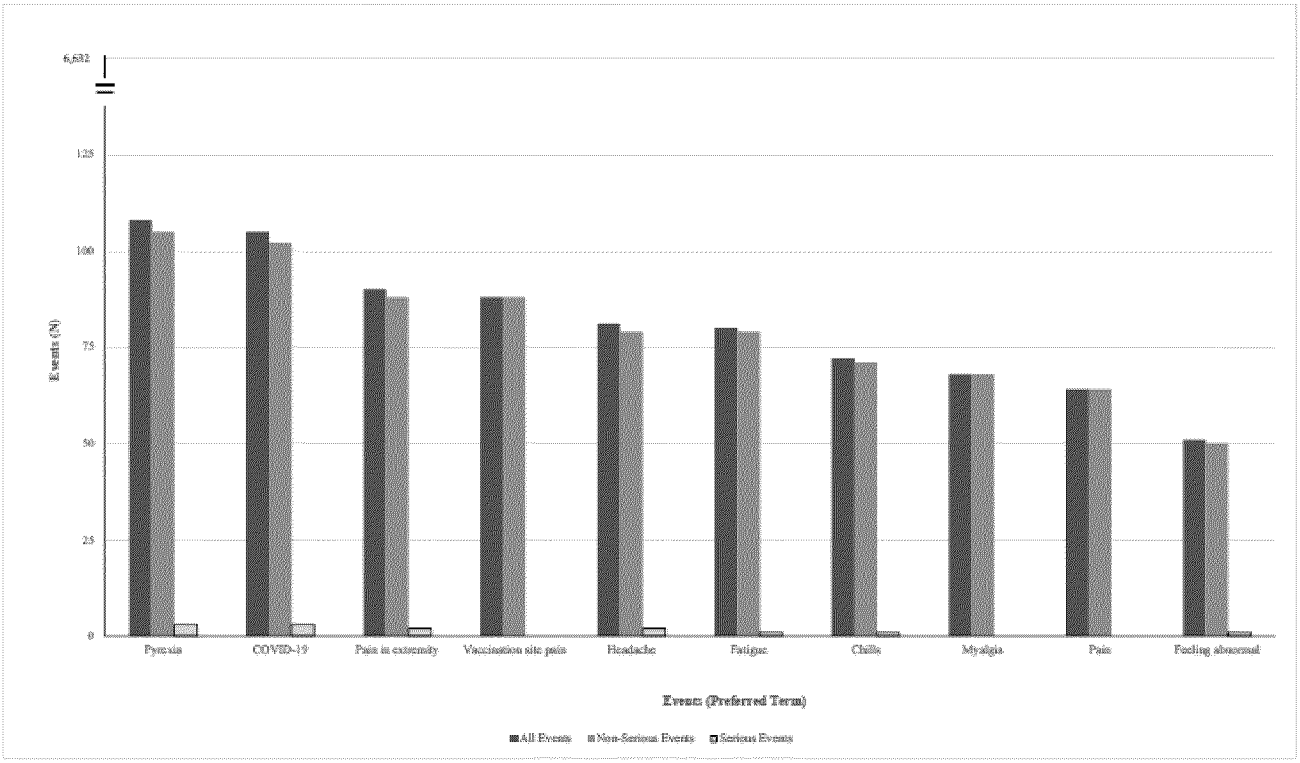
During the reporting period, the MAH has received 2,348 cases (6,632 events, of which 181 events were serious) involving the elasomeran/davesomeran booster. Of the reported cases, 1,709 cases were medically confirmed, 119 cases were serious, and 12 cases had fatal outcomes. More cases were reported in females (951, 40.5%) compared to males (686; 29.2%) with mean age of 57.7 years (SD: 19.7; median: 63.0 years). A total of 711 cases (30.3%) had unknown/unreported gender. Of the reported serious cases, more serious cases were reported in females (58, 48.7%) compared to males (52; 43.7%) with mean age of 62.1 years (SD: 16.8; median: 66.0 years). A total of 9 cases (7.6%) had unknown/unreported gender.

During the reporting period, the majority of all cases (2,101, 89.5%) have been reported from the United States. Among the 119 serious cases reports, the majority were reported from the United States (92.4%).

During the reporting period, for events reported as being associated with a known dose number (1,594 events), the majority (1,405 events, 88.2%) occurred within 2 days after administration of the elasomeran/davesomeran booster. Of note, a total of 5,038 events were reported without an associated dose number. Among serious events reported as being associated with a known dose number (182 events), the majority (150 events, 82.4%) occurred within 2 days after administration of elasomeran/davesomeran booster. Of note, a total of 267 serious events were reported without an associated dose number.

The most frequently reported events during the reporting period that were associated clinically with administration of elasomeran/davesomeran booster are presented in Figure 16-26. Among all events (N=6,632), pyrexia (105 events, 1.6%%), COVID-19 (102 events, 1.6%), and pain in extremity (88 events, 1.3%) were the most frequently reported non-serious events while serious events accounted for ≤ 3 events (< 0.05%) in each of those most frequently reported PTs. Events coded as "No AE" (23.3% of all events during the review period) were often associated with events involving product administration errors (e.g., accidental underdose, wrong product administered, etc.). Among all events, the most frequently reported serious events were syncope (8 events, 0.12%), atrial fibrillation (7 events, 0.11%%), and loss of consciousness (7 events, 0.11%). Both syncope and loss of consciousness may be related to Immunization Stress-Related Responses (ISRR). Immunization Stress-Related Responses is used to describe the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom. Individual responses to stress vary from person to person and may change according to time or context. Immunization Stress-Related Responses may manifest as acute stress responses, vasovagal reactions (syncope/ loss of consciousness) or dissociative neurological symptom reactions [135].

Figure 16-26. Most Frequently Reported Events During the Review Period - elasomeran/davesomeran booster



The event outcome most frequently reported outcomes during the reporting period were Not recovered/Not Resolved for non-serious events (8.6%) and serious events (21.0%) (Table 16.179). Of note, events reported without outcome accounted for 80.5% of non-serious events and 53.6% of serious events.

Table 16.179 Event Outcome Reporting Period - elasomeran/davesomeran booster

Event Outcome	Review Period	
	Non-Serious Events, n (%)	Serious Events, n (%)
Fatal	0 (0)	12 (6.6)
Not Recovered/Not Resolved	558 (8.6)	38 (21.0)
Recovered/Resolved	505 (7.8)	25 (13.8)
Recovered/Resolved with Sequelae	11 (0.2)	3 (1.7)
Recovering/Resolving	181 (2.8)	6 (3.3)
Unknown	5,196 (80.5)	97 (53.6)
Grand Total	**6,451 (100.0)**	**181 (100.0)**

Fatal Cases (Reporting Period) - elasomeran/davesomeran) booster

During the reporting period a total of 12 cases (12 events, all serious) had fatal outcomes. The majority of cases involved males (7 cases, 58.3%) were reported than for females (4 cases, 33.3%) with mean age of 67.8 years (SD: 20.2; median: 79.0 years). A total of 1 case (8.3%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (5 events, 41.7%), myocardial infarction (2 events, 16.7%), and the following events each occurring with a frequency of 1 event (8.3%): abdominal pain, cardiac arrest, cardiac failure, pulmonary thrombosis, and thrombosis. The most cases with fatal outcomes were reported from the United States (11 cases, 91.7%). Among events for

which dose number was reported (2 events), both events occurred within 2 days after administration of elasomeran/davesomeran booster.

Events with fatal outcomes are summarized in Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

Discussion

Review of the post-marketing safety data for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and for both bivalents showed that the majority of reported events were reported in females compared to males, and the majority of reports are in individuals >18 years of age, and more specifically >50 years of age.

It is important to note that this distribution of reported cases by gender for each of the vaccines is similar to the overall distribution of reported cases by gender for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in general in the GSDB. Overall, cumulative as of 17 Dec 2022, a total of 448,846 (67.4%) reports for females are included in the GSDB, with 189,053 (28.4%) reports for males, and 28,399 (4.3%) reports missing sex information. According to the literature, Zucker et al., [185] stated that women experience ADRs nearly twice as often as men, yet the role of sex as a biological factor in the generation of ADRs is poorly understood. In a scoping review conducted by Brabete et al [186] in order to identify sex and gender-related factors that impact the lifecycle management of drugs processes, the authors concluded that observed sex differences in the number of reported ADRs can be linked to sex- or gender-related factors.

Sex-related factors refer to biological differences between women and men, whereas gender-related factors refer to social, behavioral, or cultural differences. They also mentioned that in addition to sex-related factors that affect both ADR occurrence and reporting, there are also gender-related factors such as gender roles, access to resources and opportunities, adherence to gender norms, degrees of commitment to dominant femininities and masculinities, and institutionalized inequities that reinforce sex and gender groups in all cultures and contexts. Women are more interested in and report much more active seeking of health-related information and receive more informal health-related information from close family members, other kin, and friends/workmates than men do [187]. Review of the safety data also showed that for all three vaccines, when dose number and TTO was reported, more events happened after Dose 1 (758,368; 47.9%) and Dose 2 (606,588; 38.3%) than any other dose, and within less than 7 days (1,259,718; 79.6%).

The most common reported events for all three vaccines are consistent with the expected reactogenicity events that have been associated with administration of elasomeran. The majority of the fatal cases reported to the global safety database for all three vaccines were reported in elderly individuals (>65 years of age) (3,536; 73.0%), and after Dose 1 (2,152; 44.4%). Elderly individuals are also considered part of the frail population. Frail patients are considered at higher risk of complications due to coronavirus disease 2019 (COVID-19) infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. The most frequently reported event terms in fatal cases closely match those seen both in the elderly population and in the general population as a whole. Fatal cases are in general strongly confounded by multiple comorbidities and the advanced age in the elderly.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted

for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered. Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 408,226,293 individuals received a first dose, 275,197,667 received a second dose, 166,419,347 received a third dose, and 62,984,506 received a fourth dose, with third and fourth doses including both original elosameran and elosameran bivalent booster dose formulations.

With this large number of doses of elosameran (Original and bivalents) that has been administered worldwide, reported cases included in the MAH's GSDB in the large majority are associated with expected reactogenicity events. The MAH has a comprehensive and systematic approach to evaluating all available safety information, including that pertaining to the administration of the bivalent vaccines as well as new age indications that have been authorized since the beginning of this pandemic. The MAH has monitored safety concerns included in the RMP, as well as AESI, and any other additional medical topic that may trigger in the conduct of the Observe/Expected analysis of the post-marketing safety data in each MSSRs as well as PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elosameran (and other COVID-19) vaccines and boosters, the MAH has found that review of the safety data in all subpopulations, including individuals with AI/ID, immunocompromised individuals, frail individuals, use in pregnancy and while breastfeeding, children, among other, reported in the GSDB indicates that the general pattern of commonly reported AEs is comparable to the general population, rather than as a result of vaccine exposure.

Conclusion

The data provided in this PBRER describe the safety profile of elosameran, elosameran/imelasomeran and elosameran/davesomeran, in the reporting period and cumulatively. A comparison with the cumulative data shows no new safety concerns or change in safety profile of the vaccines and the benefit-risk evaluation remains positive.

Based on the analysis of all the safety data received cumulative and during the reporting period of this PBRER, ModernaTx, Inc. considers that cases reported after vaccination with elosameran/imelasomeran and elosameran/davesomeran) to be consistent with the known safety profile of elasomeran. The MAH will continue to monitor AEs reported after use of any of the elasomeran vaccines using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

In the previous PSUSA the MAH was requested to present postmarketing data from the newly approved bivalent vaccines.

The MAH informs that details in the case reports hampers the MAH's ability to report clear safety patterns involving booster doses of elasomeran. In this review peiod 52.3% of the events the dose number was unknown.

The MAH had reported 16,923 cases (54,008 events; 9,103 (16.9%) events were serious) who had received 2 or more doses of elasomeran during the reporting period. Of the total cases, 5,123 cases were medically confirmed, 3,880 cases were serious, and 100 cases had fatal outcomes.

For the elasomeran/imelasomeran booster the MAH has received 5,234 cases (21,578 events; 2,130 (9.9%) events were serious). Of the reported cases, 1,271 cases were medically confirmed, 940 cases were serious, and 38 cases had fatal outcomes.

For the elasomeran/davesomeran booster the MAH has received 2,348 cases (6,632 events; 181 (2.7%)

events were serious). Of the reported cases, 1,709 cases were medically confirmed, 119 cases were serious, and 12 cases had fatal outcomes.

The overview of data for of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in the first reporting period reporting post marketing data for the bivalent Moderna vaccines targeting SARS-CoV-2 no specific safety patterns were identified.

The data presented is acknowledged.

2.6. MAH responses to requests in previous PSUSA (no 3)

ITEM 1: Thrombosis with Thrombocytopenia Syndrome (TTS): The MAH is requested, in the next PSUR, to provide a discussion on the pattern of TTO in TTS, and whether there are differences in TTO according to dose number.

MAH Response: The question is addressed in PSUR section 16.3.6.2.1 Thrombosis with Thrombocytopenia Syndrome.

Rapporteur assessment comment:

The discussion of the pattern of time to onset in TTS is discussed elsewhere in the AR. Please see section 2.4.1.

Endorsed.

ITEM 2: Fatal cases: It is noted that for several fatal cases, the assessments of cases are often precluded due to limited information. The MAH is encouraged to put an extra effort into retrieving all available information of the fatal cases in order to enable a thorough case assessment. If fatal cases of myocarditis in the age group (5-11 years of age) are identified within the next PSURs, the MAH is requested to provide detailed case information. This is relevant for all topics and not only myocarditis.

MAH Response: The MAH acknowledged the request and made all efforts to collect sufficient information for enabling meaningful assessment of fatal cases. Cumulatively through 17 Dec 2022, there were no fatal cases of myocarditis or pericarditis reported in the age group < 12 years of age.

Rapporteur assessment comment:

The MAH replies that efforts are made to collect sufficient information for fatal case evaluation. The MAH provides information that no fatal cases of myocarditis or pericarditis have been reported in children younger than 12 years of age.

Endorsed.

ITEM 3: Causality assessment: The MAH has applied the WHO-UMC causality assessment criteria in the case reviews, which is acknowledged. It has however been noted that in several cases, the assessment criteria have not been fully complied with. For example, rechallenge is not required for a case to be considered "Probable". Also, the MAH is anticipated to critically assess whether the cases contain information on concomitant disease or drugs, which could explain the occurrence of the event. In the case presentations, this critical assessment leading to a specific causality term, has not been fully transparent. In future PSURs, the MAH is requested to explicitly state the argument(s) in every specific case with possible causality the reason(s) why the specific case does not qualify for probable or certain causality classification.

MAH Response: The MAH acknowledged this request and has made all efforts to provide arguments explaining causality assessment classification.

Rapporteur assessment comment:

The MAH informs that information about arguments explaining causality assessment classification will be of high priority. The MAH is encouraged to continue this work.

Endorsed.

ITEM 4: Mechanical urticaria/Dermatographism: The MAH is requested to provide a cumulative review of the topic "mechanical urticaria/dermatographism" in the next PSUR, including consideration of an inclusion in the Product information. Should the pattern point towards a co-occurrence of mechanical urticaria with chronic urticaria, the MAH should take the opportunity to include chronic urticaria in the review, as appropriate.

MAH Response: The MAH acknowledged this request. Mechanical urticaria/Dermatographism is discussed in section 16.3.6.5.1.1 of the PSUR

Rapporteur assessment comment:

The cumulative review of Mechanical urticaria/Dermatographism is provided and assessed elsewhere in the AR. Please see section 2.5.4.

Endorsed.

ITEM 5: Bivalent variant updated Spikevax vaccines: Approval of bivalent variant updated Spikevax vaccines – assessment: After the DLP of this report, Spikevax has been variant updated (bivalent vaccines), approved and is currently being used in the EU. In light of this, in the next PSUR, the MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine. Any differences in occurrence of safety issues, when comparing the variant updated vaccines with the original monovalent Spikevax or, indeed, when comparing the two different variants updated bivalent Spikevax vaccines, should be discussed.

MAH Response: The MAH acknowledged the request and ensured a transparent presentation of cases reported from the newly approved variant vaccines as well as from the original vaccine. Everywhere possible data are stratified by original monovalent Spikevax or bivalent vaccines.

Rapporteur assessment comment:

The MAH has presented information for the approved bivalent booster vaccines separately in relevant sections, and specific in section 2.5.10 of this AR.

Endorsed.

ITEM 6: In relation to the MAH's review of public available literature (section 11 of the PSUR), the MAH is requested to comment on the following paper published within the PSUR period no 4: "Kwan, A.C., Ebinger, J.E., Wei, J. et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. Nat Cardiovasc Res (2022). https://doi.org/10.1038/s44161-022-00177-8".

MAH Response: Postural tachycardia syndrome (POTS) is a chronic debilitating condition characterized by symptoms of lightheadedness, fatigue, palpitations, pre-syncope, sleep disturbances, cognitive impairment and brain fog in conjunction with an exaggerated increase in heart rate (HR) when upright, despite maintenance of a normal blood pressure (Garland et al. 2015).

The pathophysiology underlying POTS remains incompletely understood, is likely to be multifactorial and varies in different subgroups of POTS patients. Factors such as moderate autonomic dysfunction,

increased sympathetic tone, severe deconditioning, inadequate venous return or excessive blood venous pooling may contribute to POTS symptoms. Autoimmunity and mast cell activation syndromes have been postulated as contributing to the development of POTS in some patients, but immunotherapy is rarely indicated and the relevance of autoantibodies and mast cells in most patients with POTS remains controversial.

Kwan et al. (Kwan et al. 2022), conducted a retrospective observational cohort study of 284,592 COVID-19-vaccinated individuals, age 52 ± 20 years; 57% female, who received at least one dose of COVID-19 vaccine in the Cedars-Sinai Health System in US from 2020 to 2022, to compare odds of postural orthostatic tachycardia syndrome (POTS) diagnosis identified by International Classification of Diseases (ICD) codes in the outpatient encounters within 90 days post the first dose of COVID-19 vaccine with odds of POTS 90 days pre-vaccination in a sequence symmetry analysis (SSA). Similar analyses were conducted for myocarditis, common primary care (CPC) diagnoses, and post Dose 2 in the vaccinated cohort and another retrospective cohort of patients with SARS-CoV-2 infection. The vaccines administered to this cohort included 62% Pfizer-BioNTech (BNT162b2); 31% Moderna (mRNA-1273); 6.9% Johnson & Johnson/Janssen (Ad26.COV2.S); and <0.1% other vaccines, including AstraZeneca (ChAdOx1-S), Novavax (NVX-CoV2373) and Sinovac (CoronaVac).

The authors used a sequence – symmetry analysis, to evaluate the relation between COVID-19 vaccination and new POTS-related diagnoses by assessing the odds of diagnosis in the baseline 90 days before first vaccine exposure versus the subsequent 90 days after vaccine exposure. The authors compared new POTS-related diagnosis odds to those for myocarditis and for common primary care (CPC) diagnoses to provide benchmarks accounting for potential confounding from changes in patient engagement with the healthcare system during the pandemic as well as detection bias from the provider standpoint. Then the authors compared the risks of new POTS diagnoses arising after vaccination compared to new POTS diagnoses arising after natural infection.

The authors found the post-Dose 1 odds ratio (OR) of POTS-associated diagnoses (1.33, 95% confidence interval=1.25–1.41) was slightly higher than for CPC diagnoses (OR=1.21, 95%CI=1.18–1.23) but lower than for myocarditis (OR= 2.57, 95%CI=1.02–6.77) in the vaccinated cohort, and post-infection OR of new POTS-associated diagnoses (1.52, 95%CI=1.33–1.72) was slightly higher than that for CPC diagnoses (OR = 1.40, 95%CI=1.31– 1.50) in the infected cohort.

MAH Comment: Although this study identified lightly elevated risk of receiving a POTS diagnosis after COVID-19 vaccination, the interpretation of the results requires cautions given the following limitations, and additional studies are required to verify the association as the authors recommended. First, the primary analysis restricted to vaccinated persons and may bias the association away from the null, as people who experienced a POTS may delay or did not receive a COVID-19 vaccine, violating one of the assumptions for SSA (i.e., events do not alter the probability of subsequent exposure). No distribution of POTS diagnoses pre- and post- vaccination is presented to evaluate. Healthy vaccinee effect, however, was reflected by the also elected OR for CPC diagnoses. The authors attempted to address this bias by reporting the crude ratio of ORs between POTS diagnosis and CPC diagnosis (1.10, 95%CI 1.03–1.17). However, such estimate was likely confounded, and the significance was likely driven by the large sample size. Second, POTS diagnoses were not fully adjudicated and are subject to outcome misclassification, as the author mentioned "a significant degree of non-POTS diagnoses were captured within our International Classification of Diseases (ICD) codes". The degree of misclassification pre- and post-vaccination may not necessarily non-differential as diagnostic vigilance of POTS may be intensified after vaccination, biasing the association away from the null. Furthermore, it was unclear how "new diagnosis" of POTS was identified and whether patients with a previous code related to POTS were included in the analysis and whether the distribution differed in the pre- and post-vaccination events, biasing the association in either direction depending on the distribution of prevalent events. Third, the OR estimates and ratios of ORs

were crude without adjustment for confounding. The confounding distribution, such as risk factors for POTS, may be different in events occurred pre and post vaccination.

Rapporteur assessment comment:

As requested, the MAH has reviewed and commented on the Kwan Nat Cardiovasc Res (2022) paper regarding the potential association of POTS with COVID-19 vaccination and with SARS-CoV-2 infection. The summary of the study design and results are acknowledged.

The MAH commented on the study focus and the limitations of the study, which is acknowledged. It is agreed that while statistically significant, in this large cohort the odds ratio (OR) of post-vaccine diagnoses of POTS-associated conditions versus common primary care (CPC) conditions was small (OR=1.10 (95% CI: 1.03–1.17), p=0.003). The results were obtained by pooling all vaccinations, of which elasomeran contributed 31% (mRNA vaccines though 93%). No specific data on elasomeran were available.

Of note, the post COVID-19 OR of POTS-related diagnoses was estimated to be 5.35 (95% CI: 5.05-5.68) when compared to post COVID-19 vaccination.

In conclusion, this study points to the importance of further research and routine pharmacovigilance on POTS, while not questioning the importance of COVID-19 vaccination in general nor with elasomeran specifically.

Issue is resolved, no further action is needed. The MAH will continue to monitor POTS via routine pharmacovigilance.

ITEM 7: The MAH is requested with the next PSUR to perform a cumulative review including a comprehensive review of published literature on arrythmias potentially associated with Spikevax, and based hereon, if considered warranted, to draft an update for the PI.

MAH Response: The MAH acknowledged the request. A cumulative analysis of arrythmias is presented in section 16.3.6.1.1 of the PSUR. No update of the PI was deemed warranted.

Rapporteur assessment comment:

The MAH presented a cumulative review on arrythmias as requested in the previous PSUR. In addition, the MAH presented response to EMAs request for supplementary information for study p903 (procedure MEA003.9), where the MAH was requested to perform a Self-controlled risk interval (SCRI) analysis of arrhythmia. The data and assessment are presented elsewhere in the AR. Please see AR section 2.5.1.

Endorsed.

ITEM 8: The MAH is requested to be thorough, precise in the reporting and proof-read the table concerning O/E analysis concerning ADEM in the next PSUR.

MAH Response: The MAH acknowledged the request. Information presented in this PSUR, including the tables presented for the O/E analysis do go through review and proof-read before publishing.

Rapporteur assessment comment:

The MAH has provided data for *acute disseminated encephalomyelitis (ADEM)* for the interval period 19 June 2022 to 17 December 2022, as well as cumulative data covering the complete data collection period from 18 December 2020 to 17 December 2022.

The MAH has presented data in tables. The MAH was requested to be precise in the reporting and to proof-read the table presenting the O/E analysis.

Results

From the global safety database

Cumulatively from 18 December 2020 through 17 December 2022 in total 107 cases of ADEM were reported, of these 14 were in interval period.

Cases and distribution by gender and age

The gender distribution of all cases was 55 females (51%), 51 males (48%), leaving 1 (1%) of unknown gender. 54 cases (50%) were patients ≥ 50 years of age.

Children and adolescents

In total 3 cases were reported among children and adolescents < 18 years of age, hereof 2 were children in the age group 2-11 years, 1 was an adolescent in the age group 12-17 years. These 3 cases were all reported in the interval period being the first reported cases of ADEM in children or adolescents following elasomeran.

Observed/Expected analysis

The 107 cases correspond to a cumulative reporting rate of 0.20 cases per 100,000 person-years, which is below all listed incidence estimates; the expected Spanish (2019) incidence estimates being 0.50, RR = 0.41 [0.33, 0.51], the US (2018) estimates of 0.49, RR = 0.42 [0.33, 0.52] and the US (2021) estimates of 0.40, RR = 0.51 [0.40, 0.64].

Conclusion

The cumulated data from the complete 2-year-period does not give rise to specific concern about a causal association between ADEM and elasomeran. The numbers of reported observed cases are generally much below expected numbers. It appears that the rollout of the vaccination programme is reflected in the pattern of reported cases by age groups; as the vaccine over time is more widely distributed also to younger age groups, the number of cases can be expected to settle with a somewhat more even age distribution, this may explain why there for the first time have been reported cases among children and adolescents.

Issue is resolved. Monitoring through routine pharmacovigilance is supported.

ITEM 9: The MAH is requested for the next PSUR with DLP 17 Dec 2022 to submit a cumulative review of the HLT Hearing loss including review of postmarketing cases, cases from clinical trials, literature review, and disproportionality analysis. Based on the conclusions from the cumulative review the MAH is requested to discuss the need for an update of the Product Information and a suggestion of wording.

MAH Response: The MAH acknowledged the request. A cumulative analysis of the HLT Hearing loss is presented in section 16.3.6.6.2 of the PSUR. No update of the PI was deemed warranted.

Rapporteur assessment comment:

The MAH presented a cumulative reviewof the HLT Hearing loss. The assessment is found elsewhere in the AR. Please see AR section 2.5.2.

Endorsed.

ITEM 10: In relation to the risk of acquired haemophilia, the MAH is requested to comment upon the recently published paper by Franchini et al., and also the paper by Hirsiger et al., as this has apparently not been included in the review presented in this PSUR. The comments should be provided in the next PSUR. The MAH should clearly state whether the information provided in the articles gives rise to an in-

depth evaluation of the topic of Spikevax and acquired haemophilia.

Franchini M, et al. Investigating a Signal of Acquired Hemophilia Associated with COVID- 19 Vaccination: A Systematic Case Review. Semin Thromb Hemost 2022 Sep 2. doi: 10.1055/s-0042-1754389.

Hirsiger JR, et al. Investigating potential mechanisms underlying FVIII inhibition in acquired hemophilia A associated with mRNA COVID-19 vaccines. J Thromb Haemost. 2022 Feb 2. doi: 10.1111/jth.15665).

MAH Response: Acquired hemophilia A (AHA) is a rare bleeding disorder caused by functional insufficiency of coagulation factor VIII (FVIII). Autoantibodies targeting FVIII may neutralize its procoagulant effect, thereby causing severe bleeding. Such inhibitory autoantibodies have been detected in autoimmune diseases, pregnancy, infections, or malignant diseases. Older age and certain drugs are known co-risk factors.

Franchini et al. conducted a disproportionality analysis (Franchini et al. 2022) on 96 unique cases of interest of Acquired Hemophilia A (AHA) following COVID-19 vaccines from the World Health Organization (WHO) database of spontaneous reports of adverse drug reactions (ADRs) and adverse events following immunization (AEFIs) (VigiBase), and integrating VigiBase information with those available in cases published in medical literature or recorded in the U.S. Vaccine Adverse Events Reporting System (VAERS) database.

The authors reported a majority (79%) of the cases reviewed were elderly (65 years and above), reported after 5 days and a median time to diagnosis of 18 days and 40% of cases were reported after the second dose. There was no report of vaccine associated AHA observed during pregnancy or postdelivery period. The authors also reported 73% of cases received the Pfizer/BNT162b2 vaccine, while 20 % received Moderna mRNA1273 vaccine. Twenty-one percent of reviewed cases had at least one pre-existing condition/ risk factor for AHA (including history of AHA, cancer, autoimmune disorder). No reported concomitant medications had AHA as a possible adverse event, and mortality was 11%.

According to the authors the most obvious mechanism could involve serological cross-reactivity between SARS-CoV-2 Spike protein (the active ingredient and common denominator for all COVID-19 vaccines associated with AHA) and FVIII.

This study has several limitations, including those inherent to evaluation of spontaneous reports. This study has two main limitations. The signal detection analysis conducted by the authors included duplicate cases, which can certainly lead to identification of false signals, especially with conditions as rare as AHA. The second limitation could be the heterogeneity in accuracy of information provided in individual case reports, with consequent risk of misclassification.

However, the authors believe that the number of good-quality reports is quite high to support a probable causal relationship, to such an extent to consider the generation of a signal of risk that deserves discussion. What the authors fail to take into consideration is the large number of COVID-19 vaccines that have been administered in the context of their evaluation. With the 19 case reports after mRNA-1273 vaccination that the authors are including in their article, as of 17 December 2023 [ed. TYPO, should be 2022], that would represent a reporting rate of 0.02 cases per million doses of mRNA-1273 administered.

Hirsiger et al. (Hirsiger et al. 2022) conducted a non-clinical study for the purpose of evaluated the binding, function, and cross-reactivity of the vaccine-induced anti-S-IgG for the mRNA COVID-19 vaccines, using serum from three previously reported cases of AHA diagnosed in temporal association with COVID vaccination. The authors were investigating the potential mechanisms underlying FVIII inhibition in acquired hemophilia A associated with mRNA COVID-19 vaccines. The study main goal was to determine if "the vaccine-induced antibody response against the SARS-CoV2 spike protein may exhibit FVIII inhibitory functions". The authors reported "the likelihood of cross-reactive epitopes between the spike protein and FVIII was low based on in silico protein structures; the anti-S-IgG enriched fraction

showed weak FVIII cross-reactivity in binding assays; and weak cross-binding of the anti-S-IgG enriched fraction did not translate into FVIII inhibition".

The authors also explained "the FVIII binding in the enriched anti-S-IgG fraction may have been due to residuals of anti-FVIII-IgG with low cross-reactivity against the spike protein. The amount of total IgG measured in this fraction indeed indicated a substantial non-anti-S-specific IgG". The authors concluded that "AHA associated with mRNA COVID vaccination was likely not due to vaccine-induced cross-reactive, FVIII inhibiting anti-S-IgG. Alternatively, the broad toll-like-receptor stimulation by mRNA vaccines may cause polyclonal B cell activation and thereby trigger autoantibody production in pre-existing self-reactive B cell clones in persons predisposed to AHA".

In conclusion, the authors explained that the data presented in their study, combined with their epidemiological analysis, demonstrates that immunological phenotypes occurring related to vaccination may occur unrelated to the vaccine-antigen. Detailed epidemiological and immunological studies, rather than single clinical case reports, are needed to advance the understanding of adverse events following vaccination.

MAH Comment: A causality relationship between mRNA 1273 and AHA could not be established using the available information in these articles, due to detection bias, existing risk factors that provides plausible explanation and study limitations. Hirsiger et al hypothesized a trigger of autoantibody production in individuals predisposed to AHA.

Based on the analysis of all the global safety database available as of 17 December 2022, ModernaTX Inc considers that cases included under the Acquired Hemophilia related events did not raise any safety concerns and the information provided is inadequate to provide evidence of causality with Spikevax exposure.

The benefit-risk evaluation of Spikevax remains positive. The information provided in these 2 articles does not trigger an in-depth evaluation of the topic of Spikevax and acquired haemophilia. The MAH will continue monitoring events of acquired hemophilia-related events using routine surveillance.

Rapporteur assessment comment:

In the last PSUR the MAH presented a cumulative review of acquired haemophilia (AH) and a literature-based overview of plausible mechanisms for AH. For this, the MAH stated that 11 manuscripts about "Acquired Hemophilia" were retrieved in a literature search on PubMed and Google. Nevertheless, the MAH had only presented the search string for PubMed. Furthermore, the MAH had missed to include the following paper which was published as freely available in February 2022: *Hirsiger JR, Martinez M, Tsakiris DA, Cittone MG, Graf L, Oldenburg J, Pezeshkpoor B, Recher M, Mueller J, Gerber B, Berger CT. Investigating potential mechanisms underlying FVIII inhibition in acquired hemophilia A associated with mRNA COVID-19 vaccines. J Thromb Haemost. 2022 Apr;20(4):1015-1018. doi: 10.1111/jth.15665. Epub 2022 Feb 13.* The MAH has therefore been requested to comment upon this paper in this present PSUR, and also upon a paper from September 2022, namely: *Franchini M, Cappello E, Valdiserra G, Bonaso M, Moretti U, Focosi D, Tuccori M. Investigating a Signal of Acquired Hemophilia Associated with COVID-19 Vaccination: A Systematic Case Review. Semin Thromb Hemost. 2023 Feb;49(1):15-26. doi: 10.1055/s-0042-1754389. Epub 2022 Sep 2. PMID: 36055265.*

The MAH has now given a resume of these two papers, but the discussion/assessment of the papers is sparse. The following details are noted by the rapporteur:

Firstly, concerning the study by Franchini et al (2022), which identified cases from medical literature, VAERS and VigiBase. A disproportionality analysis was applied to a larger dataset than referenced by the MAH. In total, 146 cases of acquired haemophilia in relation to COVID-19 vaccines overall were included, and an estimate of 1.1 was calculated, which means that there is in this data a significant overreporting

for acquired haemophilia. When stratifying by vaccine the overreporting was also significant for BNT16b2 (n=112) but not for mRNA-1273 (n=26).

For the case review, 96 unique cases of interest of AHA following COVID-19 vaccines were identified. Of these, 73% had received the Pfizer/BNT162b2 vaccine and 20% (n=19 cases) the Moderna mRNA1273 vaccine. This ratio seems to correspond to the ratio of the distribution of administered COVID-19 vaccine doses by manufacturer.

Only 21% of the reviewed cases had at least one pre-existing condition/risk factor for AHA (including history of AHA, cancer, autoimmune disorder). None of the reported concomitant medications had AHA as a possible adverse event. This corresponds to, that for most cases, in total 79%, no risk factors for AHA were described.

The majority of the cases, also 79%, were ≥ 65 years of age. It is noted that this is not only in concordance with the typical presentation of AH, but that it also matches the findings from the GSDB where events mostly occurred in adults above 60 years of age.

The median time to diagnosis was 18 days, and 40% of cases were reported after the 2nd dose (30% had no information available on vaccine dose number). It is considered, that this many cases after 2nd dose should call for consideration and preferably a discussion of whether this might be influenced by exposure and re-exposure to the vaccine, just as whether the median time of 18 days could fit temporally with an immune-mediated reaction.

AHA is known to occur in women during pregnancy and following delivery. There was however no report of vaccine associated AHA observed in relation to pregnancy or the postdelivery period. The value of this seems limited, as the number of women vaccinated during pregnancy or close to delivery is not reported.

The authors state that the number of good-quality reports is quite high, and that it supports a probable causal relationship. The MAH does not agree to this and argues, that the authors fail to take into consideration the large number of administered COVID-19 vaccines. The MAH also argues that the 19 cases associated with elasomeran represent a reporting rate of 0.02 cases per million doses of mRNA-1273 administered. It is noted, that a low reporting rate itself does not define causality or not. The low number of AHA reports could also be caused by underreporting. Furthermore, it should be kept in mind, that 79% of the patients had no described risk factors for AHA.

Secondly, the study of Hirsiger et al. which studied mechanism possibilities for AHA. The authors concluded that AHA associated with mRNA COVID vaccination was likely not due to vaccine-induced cross-reactive FVIII-inhibiting anti-S-IgG. Alternatively, the broad toll-like-receptor stimulation by mRNA vaccines may cause polyclonal B-cell-activation and thereby trigger autoantibody production in pre-existing self-reactive B cell clones in persons predisposed to AHA.

Conclusion

The non-clinical study by Hirsiger et al. did not contribute with an explainable mechanism for AHA after COVID-19 vaccination. However, the study by Franchini found well-described AHA cases with no pre-existing risk factors described, and found that 40% occurred after 2nd dose (30% had unknown dose number) and with a time to onset with a median of 18 days.

At present there is insufficient data to support a causal role in the association between elasomeran and acquired haemophilia. Therefore, no further actions beyond routine pharmacovigilance are considered warranted at this point. Issue is resolved.

ITEM 11: In relation to the risk of hepatitis, the MAH is requested to comment upon the paper by Codoni et al, in the next PSUR. The MAH is reminded to include other subtypes of hepatitis in their routine pharmacovigilance activities (Codoni G, Kirchner T, Engel B. et al. "Histological and serological features of

acute liver injury after SARS-CoV-2 vaccination, JHEP Reports (2022), doi: https://doi.org/10.1016/j.jhepr.2022.100605.)

MAH Response: Codoni et. al.(Codoni et al. 2022), conducted and observational cohort study on individuals with acute hepatitis arising after SARS-CoV-2 vaccination, focusing on histological and serological features. Cases were collected from members of the International AIH Group (IAIHG) and the European Reference Network on Hepatological Diseases (ERN RARE-LIVER). Inclusion criteria were: elevation of transaminase levels >−5x the upper limit of normal (ULN) occurring within 3 months from any vaccination against SARS-CoV-2 with available liver biopsy for central review and a clinical follow-up of at least 3 months or until liver transplantation (LT)/death, whichever came first, from diagnosis of acute liver injury. Exclusion criteria were: a known history of autoimmune liver disease (AIH; primary biliary cholangitis; primary sclerosing cholangitis); acute or chronic viral hepatitis including hepatitis A, B, C, D or E; history of LT.

Fifty-nine patients, from 26 centers in 11 countries were recruited according to the inclusion and exclusion criteria. The majority were female, median age at diagnosis of hepatitis was 54 years. Five had a history of COVID-19 before hepatitis. Patients were exposed to seven different SARS-CoV-2 vaccines (mRNA-based vaccines: mRNA-1273 [Moderna] and BNT162b2 [BioNTech/Pfizer]; non-replicative virus vector vaccines: AZD1222 [AstraZeneca], Ad26.COV2.S [Johnson & Johnson] and Gam-COVIDVac [Sputnik V]; vaccinewith inactivated SARS-CoV-2: BBIBP-CorV [Sinopharm]; and protein-based vaccines: NVX-CoV2373 [Novavax]) in various combinations before the diagnosis of liver injury.

Hepatitis was diagnosed after the second vaccine dose in the majority of patients. The median time from last vaccine dose to diagnosis of hepatitis was 24 days. Thirty-six patients (61%) were on other medications and/or had a history of other medications in the 12 weeks preceding the liver injury; none was on steroids, while three were on immunosuppressants (azathioprine, anti-CD20, anti-IL23). Eighteen (31%) had an extrahepatic autoimmune comorbidity. Five took medications to treat vaccine side effects, including acetaminophen at a dose of 1–1.5 g/day in all cases, and diclofenac in one case. Laboratory test values obtained at presentation in the participating centers were normalized to the local ULN. The liver enzyme pattern was hepatocellular in the vast majority of cases and mixed in a small minority; none had a cholestatic pattern. Total IgG was elevated (>16 g/L) in two thirds of cases. Acute liver failure including hepatic encephalopathy manifested in a single patient, the only one to require LT (113 days after re-exposure to BNT162b2 vaccine). Fifteen patients were re-exposed to a SARS-CoV-2 vaccine after the diagnosis of hepatitis. Ten received the same vaccine class, of whom six had no relapse (five on and one off immunosuppression), three relapsed (one on and two off immunosuppression), and one was re-vaccinated while transaminase levels were still elevated and showed improvement upon subsequent corticosteroid treatment. Only one patient, who was rechallenged with the BNT162b2 vaccine, relapsed on immunosuppression, finally requiring a LT, and none of the four patients who had been rechallenged with heterologous vaccination while in remission (three on low-dose immunosuppression) relapsed.

Regarding patient outcomes, liver tests improved after 3 months in all patients. There were no significant differences between treated and untreated participants in terms of demographics and clinical characteristics, vaccine type, time from vaccination to liver injury, histological and serological features, and outcome. ALT at 3 months after the onset of liver injury was normal in 24/58 patients (one patient died of cardiac decompensation 2 months after the onset of liver injury); 6-month data, available for 46 patients (80%), showed normal ALT levels in 30 patients (64%), of whom 23 were still on treatment. The three patients on long term immunosuppression before vaccination were treated with steroids; two are still on treatment without complete ALT normalization after 3 months, and one could discontinue steroids after 5 months without relapse.

The authors reported that liver histology showed a picture of predominant lobular hepatitis in three-quarters of cases, while predominant portal hepatitis was present in fewer than one-fifth of patients,

supporting an acute onset of liver injury. Almost all patients in the study were seropositive locally and at centralized testing for autoantibodies associated with AIH, frequently at high titers, and had high IgG, collectively suggesting a diagnosis of AIH or AIH-like DILI. According to the authors, given that only few of the patients had advanced liver fibrosis, would support that elevation of transaminase levels following SARS-CoV-2 vaccination reflects acute liver injury in the absence of pre-existing unrecognized chronic liver damage, and therefore would favor AIH like DILI. But as the authors presented in their report, criteria for differentiating classical AIH from AIH-like DILI has not been established and while AIH is characterized by long-term immunosuppression dependency and frequent presence of advanced fibrosis at diagnosis, the latter is characterized by a low relapse rate after withdrawal of a short- term steroid course. Ninety-two percent of the patients in the study were treated with steroids, with or without azathioprine, and showed an excellent response, liver enzymes improving in all cases and normalizing in two-thirds after 6 months; however, as most of them are still on immunosuppression and the cohort follow-up is too short according to the authors, it is impossible to determine whether they suffer from AIH-like DILI or classical AIH purely based on their response to treatment.

The authors concluded that their study cannot prove or refute a causal relationship between SARS-CoV-2 vaccines and liver injury with autoimmune features, especially because most patients received other drugs during the 3 months preceding liver injury, other DILI triggers cannot be excluded.

MAH Comment: A causality relationship between SPIKEVAX and AIH could not be established using the available information in this study as explained by the authors. The MAH has reviewed cases of AIH in the global safety database, and no new safety concern has been identified.

Based on the analysis of all the global safety database available as of 17 December 2022, ModernaTX Inc considers that cases included under the Autoimmune Hepatitis related events do not raise any safety concerns and the information provided is inadequate to provide evidence of causality with SPIKEVAX exposure.

The benefit-risk evaluation of SPIKEVAX remains positive. The MAH will continue monitoring events of AIH using routine surveillance.

Rapporteur assessment comment:

In the previous PSUR, the MAH searched their clinical trials safety database, the global safety database, VAERS and EVDAS for autoimmune hepatitis (AIH) and cases where diagnosis of AIH could be suspected. -suspected diagnoses. Data did not indicate a causal association between AIH and elasomeran, and no new and concerning safety information was identified.

In the previous PUSA, the MAH was requested to comment on the paper by Codoni et al. regarding the risk of hepatitis, and to include other subtypes of hepatitis in their routine pharmacovigilance activities.

As requested, information from the paper Codoni G, Kirchner T, Engel B. et al. "Histological and serological features of acute liver injury after SARS-CoV-2 vaccination, JHEP Reports (2022), doi: https://doi.org/10.1016/j.jhepr.2022.100605 was included in this PSUR. Overall, the study supports the conclusion that causal association between COVID-19 vaccines and liver injury with autoimmune features cannot be established.

Most of the case reports in the global safety database could not be classified as cases of AIH, according to the Simplified Classification Guidelines, or were unassessable due to lack of information. In the cohort study mentioned above, several patients had received other drugs within 3 months prior to their liver injury and thus other DILI triggers could not be excluded.

All in all, no new and significant safety information was identified regarding AIH. The current evidence is insufficient to establish causal association between AIH and elasomeran.

Continue monitoring of AIH and related events by use of routine surveillance is acknowledged.

Endorsed.

ITEM 12: For the purpose of improving overview of data, the MAH is requested to put an effort into presenting exposure data for the age category of for children (5-11 years of age) and adolescents (12-17 years of age) separately.

MAH Response: The MAH acknowledged the request and has made all effort to present separately exposure data for children and adolescents.

Rapporteur assessment comment:

The MAH presented age-stratified exposure data for the <18 year old vaccinees for some countries/regions. Endorsed.

ITEM 13: Concerning Single Organ Cutaneous Vasculitis (SOCV), the MAH is requested to make an extra effort to provide the information missing to assess causality regarding the 2 cases deemed unassessable, and to update and reevaluate all cases in the SOCV case listings in the next PSUR. The DLP of PSUR no 4 should be applied, and the MAH is requested to add clear argumentation where the MAH does not agree with the reporter or the description in the case narrative. Also, the MAH is requested to comment on the apparent discrepancy between the total number of literature reports on SOCV (n=47), the number of cases previously listed in PSUR Appendix 11.22a (n=30) and the number of listed cases in the new appendices 1 and 2 (n=12).

MAH Response: The MAH acknowledged the request and responded in section 16.3.6.6.3 of the PSUR.

Rapporteur assessment comment:

Please see AR section 2.4.2 for the evaluation of the submitted data concerning Single Organ Cuteneous Vasculitis (SOCV).

REFERENCES:

Codoni G, Kirchner T, Engel B, Villamil AM, Efe C, Stättermayer AF, et al. Histological and serological features of acute liver injury after SARS-CoV-2 vaccination. Jhep Reports. 2022;5(1):100605.

Franchini M, Cappello E, Valdiserra G, Bonaso M, Moretti U, Focosi D, et al. Investigating a Signal of Acquired Hemophilia Associated with COVID-19 Vaccination: A Systematic Case Review. Semin Thromb Hemost. 2022;49(01):015–26.

Garland EM, Celedonio JE, Raj SR. Postural Tachycardia Syndrome: Beyond Orthostatic Intolerance. Curr Neurol Neurosci. 2015;15(9):60.

Hirsiger JR, Martinez M, Tsakiris DA, Cittone MG, Graf L, Oldenburg J, et al. Investigating potential mechanisms underlying FVIII inhibition in acquired hemophilia A associated with mRNA COVID-19 vaccines. J Thromb Haemost. 2022;20(4):1015–8.

Kwan AC, Ebinger JE, Wei J, Le CN, Oft JR, Zabner R, et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-Cov-2 Infection. Nat Cardiovasc Res. 2022;1(12):1187–94.

2.7. Characterisation of risks

Rapporteur assessment comment:

The MAH proposed changes to the RMP list of safety concerns (see section 3.1.). Regarding the assessment of proposed changes to the list of safety concerns in the PSUR, please refer to section 2.3. The following topics shall be removed and an evaluation of new information on these topics in future PSURs is not expected:

- Important potential risk: Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
- Missing information: Interaction with other vaccines

The following missing information topics shall remain in the PSUR list of safety concerns and an evaluation of new information on these topics is required with future PSURs:

- Use in pregnancy and while breast-feeding
- Use in immunocompromised subjects
- Use in frail subjects with unstable health conditions and co-morbidities
- Use in subjects with autoimmune or inflammatory disorders

For the important identified risks myocarditis and pericarditis the following is noted: The MAH has strived to present a thorough overview of myocarditis and pericarditis. These two heart-related conditions are often discussed together and also can be overlapping as either perimyocarditis or myopericarditis.

A few comments concerning the table for myocarditis are mentioned here: Regarding "Potential mechanism". In the explanation box is written "Infectious causes include viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa." Chlamydia and Rickettsia are bacteria and can be deleted here. Regarding "Evidence source(s) and strengths of evidence": In the explanation is stated "Data to evaluate safety concern were derived from CTs and the post-authorization safety.". "Post-authorization safety" should be clarified, maybe it should be "post-authorization safety studies".

Furthermore, the MAH is reminded in the next PSUR to reflect the potential upcoming change to the PI in the characterisation of risk.

The information provided concerning characterisation of risks is acknowledged.

3. Update of the Risk Management Plan

The MAH submitted an updated RMP version 7.0 with data lock point of 01 February 2023 and final sign off date of 21 February 2023 with this PSUR. The (main) proposed RMP changes were the following:

- To update the Products Overview (Part I) with the current indication and posology for Spikevax bivalent Original/Omicron BA.1 for individuals 6 years of age and older
- To update the epidemiology in Module SI with cumulative data through 01 February 2023
- To update SIV.1 to highlight the areas of missing information that are no longer safety concerns
- To update the exposure of special populations in SIV.3 with post-authorisation exposure data up to 17 January 2023
- To update the post-authorisation exposure data in Module SV up to 13 January 2023
- To update Module SVII.2 to justify the removal of VAED including VAERD as an important potential risk

- To update Module SVII.2 to justify the removal of use in pregnancy and while breast-feeding, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as missing information
- To update Module SVII.3 to remove VAED including VAERD as an important potential risk and to remove use in pregnancy and while breast-feeding, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as missing information
- To update Module SVIII to remove VAED including VAERD, use in pregnancy and while breast-feeding, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns
- To update Part III.1 to remove the COVID-19 / Vaccine Failure Questionnaire as a routine pharmacovigilance activity and to remove VAED including VAERD, use in pregnancy and while breast-feeding, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns
- To update study milestones for studies mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901 in Part III.2, Part III.3 and Annex 2
- To update the Summary Table of Additional Pharmacovigilance Activities in Part III.3 to highlight the removed safety concerns associated with the relevant studies
- To update Part III.2, Part III.3 and Annex 2 to reflect administrative updates for studies mRNA-1273-P901, mRNA-1273-P910, mRNA-1273-P911 and mRNA-1273-P919
- To update Risk Minimisation Measures (Parts V.1 and V.3) to remove VAED including VAERD, use in pregnancy and while breast-feeding, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns
- To update Summary of the Risk Management Plan (Part VI) to remove VAED including VAERD, use in pregnancy and while breast-feeding, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns
- To update Part V.3 and Part VI to include mRNA-1273-P910 as a study for characterising pericarditis
- To update Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program in Annex 2 to highlight the removed safety concerns associated with the relevant studies
- To remove the COVID-19/Vaccine Failure Questionnaire in Annex 4
- To update the list of references in Annex 7 associated with the updates in the RMP

3.1. Safety Specification

3.1.1. Epidemiology of the indications and target population

The module has been updated with cumulative data through 01 February 2023. This is acceptable.

3.1.2. Populations not studied in clinical trials

The module has been updated to highlight the areas of missing information that are no longer safety concerns (as proposed by the MAH). While this is in principle acceptable, not all areas of missing information are to be removed from the list of safety concerns (see section SVII.2) and the MAH is reminded to update Table 83 in the RMP accordingly.

3.1.3. Post-authorisation experience

The module has been updated to reflect the post-authorisation exposure data up to 13 January 2023. This is acceptable.

3.1.4. Identified and potential risks

3.1.4.1. New Safety Concerns and Reclassification with a Submission of an Updated RMP

3.1.4.1.1. Removal of vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) as an important potential risk

Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) was included as an important potential risk in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021).

The MAH has closely monitored VAED including VAERD and presented cumulative reviews in Monthly Safety Summary Reports (MSSRs) as well as in Periodic Safety Update Reports (PSURs) since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of VAED including VAERD as an important potential risk. A summary of the data is presented below.

Vaccine-associated enhanced disease was raised as a safety concern for COVID-19 vaccines early in the pandemic, but current evidence does not suggest that this hypothetical construct presents a confirmed risk. More than 772 million Spikevax doses are estimated to have been administered since the first EUA up to 17 December 2022, and it is likely that VAED would have been observed and reported if it were both confirmed and more than a very rare event. Motivation to monitor COVID-19 vaccine recipients for possible VAED arose from sources such as animal models in which pathogenesis suggested a common potential mechanism producing VAED related to respiratory syncytial virus (RSV) vaccines in MERS and SARS-CoV-1 (Lambert 2020). To date, no pathognomonic presentation of VAED has been recognised following immunisation of >902 million individuals with Spikevax vaccines. Furthermore, analysis of the immune profile of Spikevax in a mouse model shows elicitation of a protective immune profile that is not associated with vaccine-enhanced disease upon SARS-CoV-2 challenge (DiPiazza 2021).

There is currently no widely accepted case definition for VAED; however, a recent publication by the Brighton Collaboration provides some guidance for assessment of potential VAED in COVID-19 (Munoz 2021). In this guidance, it is suggested that VAED may be identified first as a vaccine failure (i.e., VAED requires exposure to and infection by SARS-CoV-2 in a person who has been fully immunised). The authors acknowledge that there is presently no pathognomonic set of clinical findings to characterise VAED. Furthermore, case classifications that can be readily applied to individual-level data from spontaneous reporting are not defined. The Brighton Collaboration working group states that a definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. Probable cases must show an increase in severity or rates of atypical findings when compared to a non-vaccinated control group, however this criterion must be considered at a population or group level rather than an individual level. Given that there have been numerous epidemiologic studies evaluating effectiveness of mRNA vaccines in millions of vaccinees and that there have not been findings showing an increased risk of COVID-19 disease in vaccinees (or a subgroup of vaccinees) compared to those not vaccinated, real world evidence for occurrence of VAED is lacking. Moreover, there is an absence of medical literature supporting the existence of VAED due to Spikevax or mRNA vaccines against COVID-19.

The removal of VAED including VAERD as an important potential risk is supported by the following considerations:

- The MAH has monitored VAED in each PSUR since EUA (18 Dec 2020) at the request of the EMA and other health authorities. Over the years of analysis and given the amount of safety data accumulated given the unprecedent use of these vaccines, the MAH has found no evidence to support the hypothesis that this phenomenon exists or that there is a causal relationship to the vaccine.
- Despite the large number of doses of Spikevax that has been administered worldwide, no cases of VAED have been reported to the MAH's global safety database.
- As of 17 December 2022, SARS-CoV-2 vaccines have not been associated with VAED in preclinical studies or clinical use. Even with the emergence of multiple new variants/serotypes of SARS-CoV-2, with their potential to provoke sub-neutralising antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as was the case for SARS-CoV-2 variant Omicron, no enhancement of disease has been reported.
- Despite widespread use of the Spikevax vaccines (>800 million individuals vaccinated with at least one dose) there is no convincing evidence to support the hypothesis that VAED exists or that it has a causal relationship to the vaccine.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to VAED.

In conclusion, the MAH considers there is sufficient justification for removing VAED including VAERD as an important potential risk from the RMP and proposes to continue monitoring VAED including VAERD through routine surveillance and ongoing post-authorisation safety studies as applicable.

Rapporteur assessment comment:

The theoretical concern of Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) was based on previous experience with RSV and measles vaccines which triggered disease enhancement in persons later infected by the natural virus. Since pathology consistent with the RSV vaccine enhanced disease has been demonstrated for some SARS-CoV-1 vaccine

candidates in animal models, there was also a concern that a similar syndrome could occur in humans immunized with SARS-CoV-2 candidate vaccines [1]. VAED including VAERD was therefore included in the initial RMP as an important potential risk. Analysis of the immune profile of Spikevax in a mouse model did not demonstrate any evidence of vaccine-enhanced disease [2].

Considering that >800 million individuals have been vaccinated with at least one dose of a Spikevax vaccine, the Rapporteur agrees with the MAH that it is likely that VAED including VAERD would have been observed and reported if it were an actual risk. The fact that not a single case has been reported strengthens the view that this is a purely hypothetical concern, despite the challenges in defining and reporting VAED. Moreover, numerous epidemiological studies evaluating effectiveness did not reveal any evidence of an increased risk of COVID-19 disease in vaccines compared to individuals not vaccinated.

It is furthermore agreed that there is no reasonable expectation that the existing or future pharmacovigilance activities could further characterise the safety profile of Spikevax with respect to VAED. The MAH's proposal to remove VAED including VAERD from the list of safety concerns in the RMP is endorsed.

3.1.4.1.2. Removal of use in pregnancy and while breast-feeding as missing information

Use in pregnancy and while breast-feeding was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021) as pregnant or lactating females were excluded from the pivotal clinical trials (Table 83).

The MAH has closely monitored use in pregnancy and while breast-feeding and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of use in pregnancy and while breast-feeding as missing information. A summary of the data is presented below.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition, or postnatal development.

Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications in this population (WHO 2022b; Berman 2022). However, there was recognition that in absence of clinical trials, vigilant post-EUA passive report monitoring, real world evidence, and pregnancy registries were needed to continue monitoring the safety of COVID-19 vaccination in pregnant women. To date there have been no specific safety concerns identified for COVID-19 maternal immunisation. Epidemiological studies have not indicated any increased risk of adverse perinatal outcomes including spontaneous abortion, preterm birth, small-for-gestational-age birth, stillbirth, or neonatal intensive care admission after COVID-19 vaccination during pregnancy (Fell 2022; Magnus 2021; Kharbanda 2021; Lipkind 2022; Shimabukuro 2021; Magnus 2022; Ruderman 2022; Trostle 2021).

Reported cases reflect obstetric events observed after administration of Spikevax. Pregnancy- specific reports had limited information about past medical and obstetric history, gestational age at time of

[1] Lambert PH, Ambrosino DM, Andersen SR, Baric RS, Black SB, Chen RT, Dekker CL, Didierlaurent AM, Graham BS, Martin SD, Molrine DC, Perlman S, Picard-Fraser PA, Pollard AJ, Qin C, Subbarao K, Cramer JP. Consensus summary report for CEPI/BC March 12-13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines. Vaccine. 2020 Jun 26;38(31):4783-4791. doi: 10.1016/j.vaccine.2020.05.064. Epub 2020 May 25. PMID: 32507409; PMCID: PMC7247514.
[2] DiPiazza AT, Leist SR, Abiona OM, Moliva JI, Werner A, Minai M, et al. COVID-19 vaccine mRNA-1273 elicits a protective immune profile in mice that is not associated with vaccine- enhanced disease upon SARS-CoV-2 challenge. Immunity. 2021;54(8):1869-1882.e6.

vaccination, onset of AE, diagnostics, treatment and/or outcome. Where data was available, noted confounding factors for spontaneous abortion/foetal deaths and complications of pregnancy included advanced maternal age, in vitro fertilisation, intrauterine insemination, concomitant medications, co-morbidities (such as hypothyroidism), previous relevant obstetric history, and congenital anomalies which predated the vaccination.

In-depth literature reviews performed have not identified any safety concerns for the use of Spikevax during pregnancy. Thus far, published literature has not identified any evidence of an subpopulation increased risk of pregnancy, foetal or neonatal complications related to Spikevax maternal immunisation. Furthermore, there is transfer of maternal antibodies, a reduction in COVID-19 in vaccinated pregnant women, early evidence that infants benefit from passive protection from SARS-CoV-2 infection and severe disease following maternal COVID-19 vaccination, recognition that COVID-19 may be more serious and cause complications for both the mother and the foetus; and thus, in summary, published literature supports the favourable benefit/risk profile of maternal Spikevax immunisation. Data on use of Spikevax bivalent vaccines during pregnancy, continues to provide supporting evidence for health authorities recommendations for the use of COVID-19 vaccines including Spikevax during pregnancy.

A review of the literature to date has likewise not identified any safety concerns related to Spikevax vaccination during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated breast-feeding women and/or their breast-fed children as well as transfer of maternal SARS-CoV-2 antibodies induced by vaccination to infants via breastmilk, supporting the favourable benefit/risk profile of COVID-19 vaccination during lactation which continues to provide supporting evidence for health authorities recommendations for the use of COVID-19 vaccines including Moderna COVID-19 vaccines during lactation.

While vaccination can induce cytokines, which can be passed via breast milk, vaccination while breast-feeding has not been linked to adverse events in infants (Sachs 2013). In fact, women with fever and illness are encouraged to continue breast-feeding given the positive impact of the transfer of antibodies, which has also been reported for COVID-19 vaccines, as well as to support infant nutritional needs (UpToDate 2021).

Reports of vaccinated lactating women, and children exposed to Spikevax, Spikevax Bivalent .214 (Original/BA.1) and Spikevax Bivalent .222 (Original/BA.4/5) through breast milk (referred to as lactation cases) were identified from the ModernaTx global safety database (GSDB). Both in the GSDB and in the literature, reports of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhoea, and pyrexia are consistent with the safety profile of Spikevax or what is expected in the general population (ACOG 2007; UpToDate 2021; UpToDate 2022).

After careful review of all new safety data for the safety topic of use in pregnancy and while breast-feeding, the benefit-risk profile for Spikevax remains favourable. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the congenital anomalies reported in the global safety database indicates that the anomalies are varied in type, aetiology, and critical gestational age at exposure; this data would seem to indicate that the anomalies have occurred as part of the background incidence rather than as a result of vaccine exposure.
- Review of the post-marketing safety data does not support a causal relationship between Spikevax, and the birth defects reported to the global safety database.
- It remains difficult to interpret the significance of malformations when they are rare.
- All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug or vaccine exposure.

- Review of the reports of exposure to Spikevax while breastfeeding reported in the global safety database indicates no increased risk in short-term adverse effects. In several epidemiological studies of breastfeeding mothers, very few reported to have concerns about the infant after the first dose and second dose. Few infant events are reported, with the majority of them non-serious and the most common side-effects seen among nursing children are poor sleep and irritability, which indicates they may have occurred as part of the background incidence rather than as a result of vaccine exposure.
- Review of the post-marketing safety data does not support a causal relationship between Spikevax, and adverse events reported in breastfed infants to the global safety database.
- At the request of the EMA the following recommendations are included in the SmPC: "Spikevax can be used during pregnancy" and "Spikevax can be used during breastfeeding".
- The MAH continues to evaluate the pregnancy outcomes and reported outcomes in infants while breastfeeding in reports of Spikevax (Original and Bivalent Boosters) use during pregnancy via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- Use of Spikevax in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.

The removal of use in pregnancy and while breast-feeding as missing information is supported by the following considerations:

- Use of the vaccine in pregnant individuals is already included in the product's labelling, and it is embedded in clinical practice and has been recommended by major public health authorities.
- Use of the vaccine in breastfeeding individuals is already included in the product's labelling, and it is embedded in clinical practice and included in relevant health guidelines.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to use in pregnancy and while breast-feeding as long-term safety is being maintained as missing information.

In conclusion, the MAH considers there is sufficient justification for removing use in pregnancy and while breast-feeding as missing information from the RMP and proposes to continue monitoring use in pregnancy and while breast-feeding through routine surveillance and the ongoing post-authorisation safety studies as applicable.

Rapporteur assessment comment:

Pregnant or lactating women were excluded in clinical trials and due to the gaps in knowledge about the safety of Spikevax in this population, 'use in pregnancy and while breast-feeding' was included as missing information in the initial RMP.

Regarding use in pregnancy, the following is stated in SmPC section 4.6:

A large amount of observational data from pregnant women vaccinated with Spikevax during the second and third trimester has not shown an increase in adverse pregnancy outcomes. While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Spikevax can be used during pregnancy.

The MAH did not propose an update of this.

The MAH argued that a removal of this area of missing information is supported by the fact that use in pregnancy and while breast-feeding is embedded in clinical practice, has been recommended by major public health authorities/health guidelines and is included in the product's labelling.

Within this PSUR, the MAH provided an analysis of pregnancy cases from the company safety database (see section 2.3.3.1.). Cases were either confounded or had insufficient information precluding a meaningful medical assessment. No significant new safety information emerged from the evaluation of cases from the company safety database. As routine pharmacovigilance activities were not deemed sufficient to establish the safety of Spikevax in use in pregnancy, the following additional pharmacovigilance activities were requested to address this:

- P905 (EU) – Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries. **The final study report is expected 31 December 2023**.
- P919 (US) - An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy. **The final study report is expected 31 March 2024**.

In contrast to the epidemiological studies referenced by the MAH, these studies assess a causal association of Spikevax and **all relevant maternal and neonatal outcomes**. However, the MAH argues that there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to use in pregnancy and while breast-feeding. The PRAC Rapporteur disagrees with this. The data from epidemiological studies presented by the MAH do not allow to conclude that there is robust scientific evidence showing that use of Spikevax in pregnancy is safe **with regards to all relevant outcomes**.

Several studies addressed outcomes such as spontaneous abortion, stillbirth, preterm birth and small-for-gestational-age and no increased risk following vaccination with Spikevax was observed.[3,4,5,6] While typical limitations of (retrospective) observational studies such as information bias and residual confounding challenge the validity of these studies, the PRAC Rapporteur considers there to be an acceptable level of evidence to conclude that Spikevax is not associated with any of these outcomes. Nevertheless, corroboration of these estimates with data from the ongoing PAS studies in the EU and the US is considered highly valuable.

One of the main outcomes of interests following vaccination with Spikevax during pregnancy is major congenital malformation (MCM). In this regard, the epidemiological data presented by the MAH is not considered sufficiently robust to be able to conclude that there is no association between Spikevax and MCM. Ruderman et al (2022) performed a cohort study to evaluate the association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies compared with unvaccinated controls.[7] However, the main threat to the validity of this study is the ascertainment of the outcome: EMR of structural anomalies identified on ultrasonography, which has a low sensitivity and non-differential misclassification may therefore have biased estimates towards the null. Moreover, this was a single-centre study and the Spikevax exposure during the teratogenic risk window was limited.

[3] Magnus MC, Örtqvist AK, Dahlqwist E, Ljung R, Skår F, Oakley L, et al. Association of SARS-CoV-2 vaccination during pregnancy with pregnancy outcomes. Jama 2022;327(15):1469-77
[4] Kharbanda EO, Haapala J, DeSilva M, Vazquez-Benitez G, Vesco KK, Naleway AL, et al. Spontaneous abortion following COVID-19 vaccination during pregnancy. Jama 2021;326(16):1629-31.
[5] Lipkind HS, Vazquez-Benitez G, DeSilva M, Vesco KK, Ackerman-Banks C, Zhu J, et al. Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at birth–eight integrated health care organizations, United States, December 15, 2020- July 22, 2021. Morbidity and Mortality Weekly Report 2022;71(1):26.
[6] Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB, Håberg SE. Covid-19 vaccination during pregnancy and first-trimester miscarriage. New England Journal of Medicine 2021;385(21):2008-10.
[7] Ruderman RS, Mormol J, Trawick E, Perry MF, Allen EC, Millan D, et al. Association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies. JAMA pediatrics 2022;176(7):717-9.

Shimabukuro et al (2021) reported an analysis of events following vaccination during pregnancy based on spontaneous reporting databases.[8] In view of the absence of a denominator and comparison group, these findings are considered preliminary and cannot be viewed of evidence of an absence of an association between Spikevax and MCM.

Moreover, based on the overall data provided by the MAH, there still seems to be a lack of knowledge regarding exposure during the first trimester, as currently reflected in the SmPC: '*While data on pregnancy outcomes following vaccination during the first trimester are presently limited, no increased risk for miscarriage has been seen.'*

Conclusion

Overall, a number of epidemiological studies provided reassuring data regarding the safety of Spikevax during pregnancy. However, the level of evidence varies considerably depending on the outcome of interest and there is a lack of valid studies on the association between Spikevax and major congenital malformations, one of the primary outcomes of interest. Moreover, there still is a lack of knowledge regarding exposure during the first trimester, in line with the wording of the current SmPC. As the ongoing PAS studies P905 and P919 are expected to provide additional evidence in this regard, 'use in pregnancy and while breast-feeding' shall remain in the RMP list of safety concerns.

3.1.4.1.3. Removal of Use in immunocompromised subjects as missing information

Use in immunocompromised subjects was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021) as immunocompromised and/or immunosuppressed people were excluded from the pivotal clinical trials (Table 83).

The MAH has closely monitored use in immunocompromised subjects and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of use in immunocompromised subjects as missing information. A summary of the data is presented below.

Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date.

Epidemiological studies have not indicated any significantly increased risk of side-effects in immunocompromised individuals after vaccination with Spikevax, and they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving Spikevax (Sáez-Peñataro 2022; Napuri 2022). Analyses have found a higher risk of hospitalisation or death from COVID-19 in those with a variety of immunocompromising conditions, including rheumatic diseases, haematological malignancies, solid organ transplants, and HIV (Vijenthira 2020; Ao 2021). Factors that increase the risk of severe COVID-19 in the general population, such as older age, chronic kidney disease, cardiovascular disease, and other co-morbidities, are significant drivers of risk in immunocompromised individuals. Moreover, some immunodeficiencies seem to increase the risk above and beyond traditional risk factors.

[8] Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons [published correction appears in N Engl J Med. 2021 Oct 14;385(16):1536]. *N Engl J Med*. 2021;384(24):2273-2282. doi:10.1056/NEJMoa2104983

Cumulative review of post-marketing safety data has not identified any patterns/trends or specific safety concerns in the immunocompromised population. Serious events and fatal reports are heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported adverse events in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population.

In general, public health and professional groups recommend COVID-19 vaccination for immunocompromised patients. These recommendations highlight the likely potential benefits of COVID-19 vaccines in this population with the potential risk of more severe COVID-19 infections, sequelae, and impact on underlying immune-mediated diseases (Botwin 2021; Briggs 2021; Izmirly 2022; Tang 2021).

Currently, some countries have approved/authorised/recommend a third dose in the primary series as well as a fourth "booster" dose and fifth "second booster" in severely immunocompromised individuals, as well as a third booster dose in mildly immunosuppressed individuals (and the general population) due to waning of immunity and the emergence of new variants. A higher percentage of reports for Dose 3 and Dose 4 during the review period of PSUR #4 (19 Jun 2022 to 17 Dec 2022) compared to the cumulative period (18 Dec 2020 to 17 Dec 2022) likely reflects increased booster vaccination uptake and reporting of booster cases in the immunocompromised during this period.

After careful review of all new safety data for the safety topic of use in immunocompromised individuals, and given that this population is at an increased risk for severe COVID-19 infection, the benefit-risk profile for Spikevax remains favourable. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data in immunocompromised subjects reported in the global safety database indicates that the general pattern of commonly reported adverse events in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population, rather than as a result of vaccine exposure.
- The MAH continues to evaluate use in immunocompromised subjects in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- Throughout the world all the EUA received for Spikevax includes recommendations for additional doses for immunocompromised subjects
- Use of Spikevax in immunocompromised subjects is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.

The removal of use in immunocompromised subjects as missing information is supported by the following considerations:

- Extended use of the Spikevax vaccines in immunocompromised individuals has provided extensive safety information in this sub-population group to no longer be considered missing information.
- Use of Spikevax in immunocompromised individuals is already included in the SmPC and embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to use in

immunocompromised subjects as long-term safety is being maintained as missing information.

In conclusion, the MAH considers there is sufficient justification for removing use in immunocompromised subjects as missing information from the RMP and proposes to continue monitoring use in immunocompromised subjects through routine surveillance and ongoing post-authorisation safety studies as applicable.

Rapporteur assessment comment:

Immunocompromised subjects were excluded in clinical trials and due to the gaps in knowledge about the safety of Spikevax in this population, 'use in immunocompromised subjects' was included as missing information in the initial RMP.

As immunocompromised individuals are at increased risk for severe COVID-19 infection, use of Spikevax in this patient population is embedded in clinical practise and included in relevant health guidelines. The MAH further argued that use in immunocompromised individuals is already included in the SmPC. While it is agreed that a recommendation regarding a third dose in this population is included in the SmPC, use in immunocompromised individuals is still reflected as an area of missing information in section 4.4 of the current SmPC:

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Spikevax may be lower in immunocompromised individuals.

The MAH did not propose an update of this.

The Rapporteur agrees that in view of the extensive exposure and recommendations to vaccinate immunocompromised individuals, the gaps in knowledge about the safety of Spikevax in this population very likely have been filled. This is for example suggested by a relatively large prospective epidemiological study showing a lower risk of short-term adverse reactions in a hospital cohort of solid-organ transplant recipients as compared to a control cohort of HCPs from the same hospital.[9] However, no other relevant real-world data regarding **safety** has been presented by the MAH. A review article is referenced, which synthesises data from studies on vaccination responses in various immunocompromised populations.[10] However, most studies were exclusively focused on efficacy outcomes, and the limited safety data available was mostly obtained in individuals vaccinated with the Comirnaty COVID-19 vaccine. One study investigated safety following mRNA vaccination in individuals with chronic inflammatory disease compared to healthy controls; however, details on vaccine brand amongst the 26 individuals who received an mRNA vaccine are missing.[11]

Within this PSUR, the MAH provided an analysis of cases from the company safety database reporting adverse events in immunocompromised individuals (see section 2.3.3.4.). A comparison of cases reporting the most frequently reported PTs in this population with those of the general Spikevax vaccinated population suggested a comparable reactogenicity profile. However, the interpretation of such comparison is limited based on lack of adjustment for any biases including the fact that spontaneous

[9] Sáez-Peñataro J, Torres F, Bartra J, Bascuas J, Vilella A, Tortajada M, Quesada S, González E, López-Suñé E, Castells A, Serrano S, Camacho C, Trilla A, Calvo G; VigilVacCOVID Group. Tolerability and Reactogenicity Profile of mRNA SARS-Cov-2 Vaccines from a Mass Vaccination Campaign in a Tertiary Hospital: Between-Vaccine and Between-Population Prospective Observational Study (VigilVacCOVID Study). BioDrugs. 2022 Jul;36(4):509-520. doi: 10.1007/s40259-022-00543-9. Epub 2022 Jun 28. PMID: 35764768; PMCID: PMC9243773.

[10] Napuri NI, Curcio D, Swerdlow DL, Srivastava A. Immune Response to COVID-19 and mRNA Vaccination in Immunocompromised Individuals: A Narrative Review. *Infect Dis Ther*. 2022;11(4):1391-1414. doi:10.1007/s40121-022-00648-2

[11] Geisen UM, Berner DK, Tran F, et al. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. *Ann Rheum Dis*. 2021;80(10):1306-1311. doi:10.1136/annrheumdis-2021-220272

reporting in these different populations may differ substantially. Cases reporting severe adverse events were heavily confounded by the underlying conditions in immunocompromised individuals. As routine pharmacovigilance activities were not deemed sufficient to answer whether the safety profile of Spikevax in immunocompromised individuals differs from that of the general Spikevax-vaccinated population, additional pharmacovigilance activities were requested to address this (among other safety concerns), including the following studies:

- P304 (US) - A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARSCoV- 2 mRNA- 1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls. Interventional. The next interim report is expected 31 March 2023 and the **final CSR 31 March 2024**.
- P904 (EU) - Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU. The next interim report is expected 31 March 2023 and the **final study report 31 December 2023**.

Although not specified in the RMP, study P903 (US) also includes analyses of relative risks of AESI in a subgroup of immunocompromised individuals. **The final study report is expected 30 June 2023**.

Moreover, real-world study P901 evaluates the effectiveness of Spikevax in immunocompromised subjects.

The MAH did not provide any data from these aPhV activities that would support the removal of use in immunocompromised subjects from the list of safety concerns. The MAH argued that public health and professional groups recommend COVID-19 vaccination for immunocompromised patients, based on the likely benefit for patients at risk for a more severe COVID-19 infection. However, from a risk management perspective, gaps in knowledge regarding the effectiveness is not of concern and the MAH did not present compelling evidence supporting safe use of rituximab in immunocompromised patients, apart from the Sáez-Peñataro et al (2022) study. While the PRAC rapporteur agrees that extensive safety information in this population should be available, the MAH's evaluation of cases from the company safety database is not considered sufficient in view of ongoing additional PhV activities specifically designed to address this concern.

Therefore, the MAH is requested to present (interim) data from these studies to support removal of the missing information 'use in immunocompromised subjects' from the RMP. As the data from literature regarding safety was limited to one relevant epidemiological study, the MAH should also consider a comprehensive cumulative review of the literature. Moreover, if the evidence indeed supports the removal of this safety concern in the RMP, this should be reflected in the product information accordingly. Therefore, the MAH is also requested to propose an update of the wording in SmPC section 4.4 regarding the safety of Spikevax in immunocompromised individuals if considered applicable. (RSI)

3.1.4.1.4. Removal of Interactions with other vaccines as missing information

Interactions with other vaccines was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021).

The MAH has closely monitored interactions with other vaccines and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of interactions with other vaccines as missing information. A summary of the data is presented below.

The safety profile of Spikevax when co-administered with non-COVID-19 vaccines is being monitored, including their use with the new Spikevax bivalent vaccines. As COVID-19 vaccines become available to

children who are also being vaccinated against childhood infectious diseases, the safety and efficacy of coadministration is being evaluated with routine surveillance activities.

Overall, cumulatively up to 17 December 2022, adverse events reported for individuals receiving non-COVID-19 vaccines concomitantly with Spikevax, were generally comparable to those seen in the general population after vaccination with non-COVID-19 vaccines and were related to reactogenicity events commonly seeing after vaccination with Spikevax. A review of the data showed that events reported in individuals receiving concurrent vaccines with Spikevax continue to primarily occur in individuals >50 years of age, with a higher number of reports involving females, as it is seeing in the general population, with a time to onset (TTO) of less than 7 days. Reports in the paediatric population comprised mainly product administration errors. The highest reported events were seen with coadministration with the influenza vaccine.

Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show increased adverse events. Therefore, WHO considers that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

The cumulative review of the safety information did not identify any patterns/trends or specific safety concerns in individuals receiving concurrent vaccines with Spikevax. Serious events and fatal reports were heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported adverse events in those individuals receiving concurrent vaccines with Spikevax was comparable to the general population. No interactions between Spikevax and other non-COVID-19 vaccines have been observed.

After careful review of all new safety data received for the safety topic of interaction with other vaccines, the benefit-risk profile for Spikevax remains favourable. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data on individuals receiving concurrent vaccines with Spikevax reported in the global safety database indicates that the general pattern of commonly reported adverse events are consistent with expected reactogenicity events and are comparable to events observed in the general population receiving other widely used vaccines.
- Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show an increase in reporting of adverse events. Health authorities consider that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.
- Use of Spikevax with other vaccines, including childhood immunisation vaccines is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.

The removal of interaction with other vaccines as missing information is supported by the following considerations:

- Extended use of the Spikevax vaccines in conjunction with other vaccines has provided extensive safety information for interactions with other vaccines to no longer be considered missing information.
- Concomitant use of other vaccines with Spikevax is included in the SmPC: High dose quadrivalent influenza vaccine can be concomitantly administered with Spikevax.

- The MAH continues to evaluate interaction with other vaccines in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- Concomitant use of the vaccine with the influenza vaccine is already included in the product's labelling, and the use of Spikevax with other vaccines is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to interaction with other vaccines as long-term safety is being maintained as missing information.

In conclusion, the MAH considers there is sufficient justification for removing interactions with other vaccines as missing information from the RMP, and proposes to continue monitoring interactions with other vaccines through routine surveillance and ongoing post-authorisation safety studies as applicable.

Rapporteur assessment comment:

No subjects concomitantly exposed to another vaccine were included in clinical trials and due to the gaps in knowledge about the safety of Spikevax in this population, 'interaction with other vaccines' was included as missing information in the initial RMP.

One additional pharmacovigilance activity addresses this safety concern. However, study P901 is a real-world study to evaluate Spikevax **effectiveness** and there are no outcome measures related to the safety of interaction with other vaccines. From a risk management perspective, gaps in knowledge regarding the effectiveness of Spikevax in a population of individuals who concomitantly received other vaccines is not driving inclusion of this area of missing information in the list of safety concerns. Moreover, the evaluation of effectiveness of Spikevax when given concomitantly with another vaccine is one of many secondary objectives of this study and the protocol specifies that this objective may not be feasible.

No additional risk minimisation measures are in place for this safety concern.

The MAH's review of safety data reported for heterologous vaccines interchange is acknowledged, and it is agreed that no new safety issues were identified and that the safety profile of Spikevax products is not different when used with other heterologous vaccines. The MAH's proposal to remove 'interaction with other vaccines' from the list of safety concerns in the RMP is endorsed.

3.1.4.1.5. Removal of use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) as missing information

Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021).

The MAH has closely monitored use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to

17 December 2022, presents detailed data supporting the removal of use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as missing information. A summary of the data is presented below.

Frail patients are considered at higher risk of complications due to COVID-19 infection including hospitalisations and deaths; and for this reason, are prioritised candidates for vaccination. Since frail subjects with unstable health conditions and co-morbidities were excluded from the registration trials, ModernaTx, Inc is characterising safety through post-marketing routine monitoring of adverse events in this special subpopulation. Frailty refers to a state of vulnerability to stressors characterised by a decreased physiological reserve, resulting in poor health outcomes compared to individuals of the same chronological age (Rockwood 2018).

There is growing evidence to supporting the safety profile of the COVID-19 vaccine in immunocompromised patients, such as HIV-infected patients, diabetics, and patients with cardiopulmonary diseases, is similar to that in the general population. Presently, the US Centers for Disease Control and Prevention, British Society for Immunology, and various other governmental and professional societies and organisations endorse COVID-19 vaccination in the immunocompromised population. Overall, recommendations for use in patients with immunocompromising medical conditions and immunosuppressing medications on the efficacy of the vaccine may support the extrapolation into the frail subpopulation indicating potential benefits to outweigh theoretical risks. The frail population was the first sub-population group vaccinated with Spikevax and other COVID-19 vaccines given that this population was recognised to have the potential for more severe complications due to COVID-19 infection. This same recommendation is still in place for vaccination against SARS-CoV2 and its variants.

Overall, the general pattern of commonly reported adverse events in the frail subpopulation is consistent with expected Spikevax reactogenicity and comparable to those events observed in the general population and in patients with these underlying conditions, especially the elderly. This is to be expected, as the elderly comprise 30.2% of the frail subpopulation in the reporting period of PSUR #4.

As expected with the time course of reactogenicity events observed in the general population, event clustering in the frail subpopulation was observed in the three-day window after vaccination, irrespective of dose number. Notably, reports of event term COVID-19 were much less prevalent in serious cases in the frail subpopulation (1.3%) compared to the general population (2.0%). This is likely due to the preferential roll out of boosters to this frail subpopulation in many countries. The most frequently reported event terms in serious cases in the frail subpopulation closely match those seen both in the elderly population and in the general population as a whole. Fatal cases in the frail subpopulation in the reporting period (2.0%) were strongly confounded by multiple co-morbidities and the advanced age in the elderly, which comprise a little less than a third of the frail subgroup.

Case reports across all available vaccines after doses 3 and above have increased as expected with uptake of booster doses administered in many countries in the period of PSUR #4. With this increase in booster dosing, more events were reported after dose 3 than any other dose in this reporting period. The adverse event profile observed after booster doses in the frail subpopulation is similar to that seen in the general population, notably as reactogenicity events with similar time to onset for dose 3 as after dose 1 and dose 2.

The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events.

With the scale in distribution of Spikevax bivalent vaccines to frail and vulnerable groups globally, the accumulated safety data have not revealed any safety concerns or significant novel events in the frail

subpopulation or key differences among the various types of vaccines, compared to the general population.

The MAH has monitored use in frail subjects with unstable health conditions and co-morbidities in each MSSR as well as PSURs since EUA (18 Dec 2020) at the request of the EMA and other health authorities. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data in frail subjects with unstable health conditions and co-morbidities reported in the global safety database indicates that the general pattern of commonly reported adverse events in those frail subjects with unstable health conditions and co-morbidities is comparable to the general population, rather than as a result of vaccine exposure.
- The MAH continues to evaluate use in frail subjects with unstable health conditions and co-morbidities in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- Use of Spikevax in frail subjects with unstable health conditions and co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines and no longer constitutes missing information in the safety profile of Spikevax.

The removal of use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as missing information is supported by the following considerations:

- Extensive use of the Spikevax vaccines (>800 million individuals vaccinated with at least one dose), including in frail subjects with unstable health conditions and co-morbidities, has provided extensive safety information in this sub-population group to no longer be considered missing information.
- The MAH continues to evaluate use in frail subjects with unstable health conditions and co-morbidities in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of Spikevax with respect to use in frail subjects with unstable health conditions and co-morbidities as long-term safety is being maintained as missing information.
- In conclusion, the MAH considers there is sufficient justification for removing use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as missing information from the RMP, and proposes to continue monitoring use in frail individuals with unstable health conditions and co-morbidities through routine surveillance and ongoing post-authorisation safety studies as applicable.

Rapporteur assessment comment:

Frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) were excluded in clinical trials and due to the gaps in knowledge about the safety of Spikevax in this population, 'use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders)' was included as missing information in the initial RMP.

As frail patients are considered at higher risk of complications due to COVID-19 infection, they are prioritized candidates for vaccination. The MAH argued that the evidence of the safety profile of Spikevax

in immunocompromised patients can be extrapolated into the frail subpopulation. However, as discussed in the section on use in immunocompromised subjects, the MAH has not presented comprehensive evidence demonstrating that the safety profile in this population is comparable to the general population.

The MAH presented 3 relevant articles of studies investigating the safety of Spikevax in this population.[12,13,14] Two of these studies assessed the reactogenicity profile based on questionnaires without a comparison group of healthy individuals. Cavanna et al included a comparison group in a prospective observational study; however, this was primarily focused on immunogenicity. The reactogenicity profile appeared comparable between the two groups, but details on individual adverse reactions were lacking. Moreover, the definition of frailty varies substantially, and it is unclear if any of these studies or the sum of data from these adequately reflect the population of frail subjects for which the use of Spikevax is considered missing information.

The MAH presented an evaluation of the cumulative evidence from the company's safety database (see section 2.3.3.6.), indicating that the general pattern of commonly reported AEs in the frail subpopulation is consistent with expected Spikevax reactogenicity and comparable to those events observed in the general population.

In contrast to use in immunocompromised subjects, there is no mentioning of the lack of knowledge of use in frail subjects with unstable health conditions and co-morbidities in the SmPC. Moreover, additional PhV activities to further characterise the safety profile in this area of missing information are limited to study P904 in which an increased risk of AESI in this subpopulation will be assessed as a secondary objective.

The PRAC Rapporteur agrees with the MAH that the cumulative evidence supports that use in frail subjects with unstable health conditions and co-morbidities no longer should be considered missing information and that there is no reasonable expectation that the existing pharmacovigilance activities could further characterise the safety profile in this population. The MAH's proposal to remove use in frail subjects with unstable health conditions and co-morbidities from the list of safety concerns in the RMP is endorsed. Continued monitoring through routine pharmacovigilance as well as the ongoing PASS p904 is acceptable.

3.1.4.1.6. Removal of use in subjects with autoimmune or inflammatory disorders as missing information

Use in subjects with autoimmune or inflammatory disorders was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021). The MAH has closely monitored use in subjects with autoimmune or inflammatory disorders and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of use in subjects with autoimmune or inflammatory disorders as missing information. A summary of the data is presented below.

[12] Lupo-Stanghellini MT, Di Cosimo S, Costantini M, et al. mRNA-COVID19 Vaccination Can Be Considered Safe and Tolerable for Frail Patients. *Front Oncol*. 2022;12:855723. Published 2022 Mar 17. doi:10.3389/fonc.2022.855723.
[13] Connolly CM, Ruddy JA, Boyarsky BJ, et al. Safety of the first dose of mRNA SARS-CoV-2 vaccines in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis*. 2021;80(8):1100-1101. doi:10.1136/annrheumdis-2021-220231
[14] Cavanna L, Citterio C, Biasini C, et al. COVID-19 vaccines in adult cancer patients with solid tumours undergoing active treatment: Seropositivity and safety. A prospective observational study in Italy. *Eur J Cancer*. 2021;157:441-449. doi:10.1016/j.ejca.2021.08.035

Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/effectiveness of the vaccine in the immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date.

In general, public health and professional groups recommend COVID-19 vaccination for patients with autoimmune or inflammatory disorders (AI/ID). These recommendations highlight the likely potential benefits of COVID-19 vaccines in this population with the potential risk of more severe COVID-19 infections, sequelae, and impact on underlying immune-mediated diseases (Botwin 2021; Briggs 2021; Izmirly 2022; Tang 2021).

Of note, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine and may be a risk factor for more severe COVID-19 disease (Duly 2022; Tallantyre 2022).

Exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID-19 vaccines (Torres-Aguilar 2019; Watad 2021; Ishay 2021). While decreased immunogenicity for those on immunosuppressive therapies and the hypothetical risk of disease exacerbation have been recognised by professional and public health organisations, given the risk of more severe COVID-19 and sequelae, vaccination is generally recommended with monitoring and management of any potential flare or exacerbation after vaccination.

Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with Spikevax. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving Spikevax (Giannoccaro 2022; Machado 2021; Sattui 2021; Lupo-Stanghellini 2022).

In the review period for PSUR #4 and cumulatively, the most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among medical history of autoimmune and/or inflammatory disease (MedHx AI/ID) cases receiving Spikevax (both Original and Bivalents) represent expected reactogenicity. The types and distribution of the most frequently reported events is comparable to those observed with Spikevax (Original) in MedHx AI/ID cases and those receiving Spikevax Bivalent .214 (Original/BA.1) or SPIKEVAX Bivalent.222 (Original/BA.4/5).

During the reporting period for PSUR #4, the potential cases of exacerbation of underlying autoimmune and inflammatory disorders reported after vaccination with Spikevax (Original and bivalent vaccines) may have limited information and lack a description of the baseline disease status or historic pattern of flares, the clinical course, diagnostics/labs/imaging, treatment, outcome, clear time to onset and/or dose number. Those reports also include signs and symptoms of reactogenicity that could mimic signs and symptoms of autoimmune disease (such as fever, myalgia, fatigue, arthralgia, headache), and thus it may be difficult to fully differentiate transient reactogenicity from AI/ID reactivation/flare. Given the natural waxing and waning course of AI/ID, and that there are no reliable reference data of the background rates of respective flares, the cases do not represent a safety concern at this time.

The MAH has monitored use in individuals with AI/ID in each MSSR as well as PSURs since EUA (18 Dec 2020) at the request of the EMA and other health authorities. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data individuals with AI/ID reported in the global safety database indicates that the general pattern of commonly reported adverse events in those with a medical history of autoimmune/inflammatory disorder is comparable to the general population, rather than as a result of vaccine exposure.
- Exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID-19 vaccines. This has been recognised by professional and public health organisations; yet, given the risk of the potential consequences of COVID-19 infection, some are recommending vaccination with monitoring and management of any potential flare or exacerbation occurring after vaccination. In addition, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine, and/or make them more susceptible to infections.
- Use of Spikevax in individuals with AI/ID is embedded in clinical practice and included in the SmPC and relevant health guidelines.
- The MAH continues to evaluate use in individuals with autoimmune and inflammatory disorders (AI/ID) in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.

The removal of use in individuals with autoimmune and inflammatory disorders as missing information is supported by the following considerations:

- Extended use of the Spikevax vaccines (>800 million individuals vaccinated with at least one dose) has provided extensive safety information including individuals with autoimmune and inflammatory disorders (AI/ID) to support the removal of this population as missing information.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to individuals with autoimmune and inflammatory disorders.

In conclusion, the MAH considers there is sufficient justification for removing use in subjects with autoimmune or inflammatory disorders as missing information from the RMP, and proposes to continue monitoring use in individuals with autoimmune or inflammatory disorders through routine surveillance and ongoing post-authorisation safety studies as applicable.

Rapporteur assessment comment:

Subjects with autoimmune or inflammatory disorders (AI/ID) were excluded in clinical trials and due to the gaps in knowledge about the safety of Spikevax in this population, 'use in subjects with autoimmune or inflammatory disorders' was included as missing information in the initial RMP.

As individuals with AI/ID are at increased risk for severe COVID-19 infection, including the impact on the underlying immune-mediated diseases, use of Spikevax in this patient population is embedded in clinical practise and included in relevant health guidelines. Moreover, individuals with AI/ID may be on immunosuppressive medications, which may impact the efficacy of the vaccine but also is a risk factor for more severe COVID-19 disease. Thus, there is substantial overlap between the population of subjects with AI/ID and immunocompromised subjects.

However, the anticipated risk of use of Spikevax in subjects with AI/ID differs from that of use in

immunocompromised subjects (in general) in that vaccination could trigger an exacerbation of the underlying autoimmune conditions and this safety aspect is of particular interest. The MAH presented a cumulative evaluation of data from the company's safety database and identified 2,437 potential cases of exacerbation of underlying AI/ID reported after vaccination with Spikevax. However, due to lack of information and the limitation to differentiate between transient reactogenicity from AI/ID exacerbation no conclusions can be drawn from these data.

The MAH stated that epidemiologic studies have indicated that the safety/tolerability profile of Spikevax in individuals with AI/ID is consistent with that observed in the general population and referenced four studies.[15,16,17,18] As discussed in the section on use in frail subjects with unstable health conditions and co-morbidities, the interpretation of the findings by Lupo-Stanghellini et al is limited since no comparison group was included and otherwise non-informative to the safety concern of use in patients with AI/ID, since no data on exacerbation of the underlying disease were collected.

In a prospective cohort study, Giannoccaro et al assessed the safety profile of COVID-19 vaccines in 300 individuals with autoimmune neurological conditions. Use of Spikevax increased the risk of local and systemic adverse reactions as compared a control group of vaccinated healthcare workers. The incidence of relapse did not differ in the two months before and after vaccination; however, for Spikevax this was based on only 8 and 11 events before and after vaccination, respectively.

In a large registry-based study, Machado et al assessed the reactogenicity profile following Spikevax vaccination in patients with inflammatory/autoimmune rheumatic and musculoskeletal disease (I-RMD) as compared to patients with non-inflammatory RMD (NI-RMD). The risk of AEs was similar between these groups; however, no inferential statistics were performed. Flares following vaccination occurred rarely (4.4%) and this was consistent between different vaccines.

Sattui et al performed a survey among adults with systemic rheumatic diseases who received COVID-19 vaccination (Spikevax n=610). Among all participants, 382/2860 (13.4%) reported flares of existing systemic rheumatic disease lasting at least 2 days post-COVID-19 vaccine, and for 132 (4.6%) this required a new or increased dose of medication to treat the flare.

In addition, the assessor identified another relevant study not mentioned by the MAH. Geissen et al assessed the safety profile of mRNA COVID-19 vaccines in patients with chronic inflammatory diseases (CID) compared to healthy control subjects. Side effects were comparable between the two groups and no inflammatory flares were observed in any of the 26 patients with CID.

Overall, the evidence provided suggests that the safety profile of Spikevax in individuals with AI/ID does not differ from that of the general population. Moreover, the descriptive data from epidemiological studies suggest that the incidence of flares following Spikevax is compatible with the natural history of AI/ID diseases. Despite the above-discussed limitations of these data, in view of the overall evidence, the PRAC Rapporteur considers that use in subjects with autoimmune or inflammatory disorders can no longer be viewed as missing information and the MAH's proposal to remove this from the list of safety concerns in the RMP is endorsed. Continued monitoring through routine pharmacovigilance as well as the ongoing PASS p904 is acceptable.

[15] Lupo-Stanghellini MT, Di Cosimo S, Costantini M, Monti S, Mantegazza R, Mantovani A, et al. mRNA-COVID19 Vaccination Can Be Considered Safe and Tolerable for Frail Patients. Front Oncol 2022;12:855723.
[16] Giannoccaro MP, Vacchiano V, Leone M, et al. Difference in safety and humoral response to mRNA SARS-CoV-2 vaccines in patients with autoimmune neurological disorders: the ANCOVAX study. *J Neurol*. 2022;269(8):4000-4012. doi:10.1007/s00415-022-11142-7
[17] Machado PM, Lawson-Tovey S, Strangfeld A, et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. *Ann Rheum Dis*. 2022;81(5):695-709. doi:10.1136/annrheumdis-2021-221490
[18] Sattui SE, Liew JW, Kennedy K, et al. Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. *RMD Open*. 2021;7(3):e001814. doi:10.1136/rmdopen-2021-001814

Of note, outcomes reported in the epidemiological studies were mostly limited to reactogenicity or flares, while the occurrence of adverse events of special interest was not a primary focus. Ongoing PAS Study p904 will investigate the occurrence of AESI in the subpopulation of individuals with AI/ID and compare these with unvaccinated individuals. This will remain an additional PhV activity as it addresses also other safety concerns (e.g. long-term safety) and results for the AI/ID subpopulation should be reported as outlined in the study protocol.

3.1.4.2. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The module has been updated in line with the proposal to remove the above-mentioned safety concerns. Removal of the safety concerns 'use in immunocompromised subjects' and 'use in pregnancy and while breast-feeding' is currently not supported and the MAH should update this section of the RMP accordingly.

3.2. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Myocarditis Pericarditis
Important potential risks	None
Missing information	Long-term safety

Based on the data provided by the MAH and as outlined in the section above, removal of the following safety concerns is acceptable:

- Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
- Interaction with other vaccines
- Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in subjects with autoimmune or inflammatory disorders

Removal of the following safety concern is currently not supported and awaits supplementary information to be provided by the MAH:

- Use in immunocompromised subjects

Removal of the following safety concern is currently not acceptable:

- Use in pregnancy and while breast-feeding

The MAH is requested to update Table 87 of the RMP accordingly.

3.3. Pharmacovigilance plan

3.3.1. Routine Pharmacovigilance activities

This section has been updated to remove the specific adverse reaction follow-up questionnaire related to the important potential risk Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD). As removal of this safety concern from the RMP is accepted, removal of the follow-up questionnaire is endorsed.

3.3.2. Additional Pharmacovigilance activities

Ongoing and Planned Additional Pharmacovigilance Activities

Study Number, Title, and Categories **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances				
None				
Category 3 – Required pharmacovigilance activities				
Study mRNA-1273-P301 Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Study Status: Ongoing	Evaluate long-term safety data and durability of vaccine effectiveness (VE)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Myocarditis Pericarditis Long-term safety	Interim CSR	15 Oct 2021
			Long-term follow-up Part B & C Interim CSR	31 Dec 2022
			Final CSR	19 Dec 2023
Study mRNA-1273-P203 A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age	Evaluate the safety, reactogenicity, and effectiveness of Spikevax. Assess safety and immunogenicity of mRNA-1273.222	Myocarditis Pericarditis Long-term safety	Interim long-term safety CSR for Part A & B	31 Oct 2022
			Final CSR	15 Jul 2025

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study Status: Ongoing				
Study mRNA-1273-P204 Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age Study status: Ongoing	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of elasomeran administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Long-term safety	Study start Final CSR	15 Mar 2021 31 Mar 2024
Study mRNA-1273-P205 Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants Study status: Ongoing	Evaluate the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS CoV-2 variants including mRNA-1273.211, Spikevax, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA-1273.222 (Spikevax bivalent Original/Omicron BA.4-5).	Long-term safety	Study start Interim report: Final CSR	28 May 2021 30 Jun 2022 30 Apr 2024
Study mRNA-1273-P304 A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls Study status: Ongoing	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of elasomeran. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.	Myocarditis Pericarditis Use in immunocompromised subjects* AESI	Protocol submission Interim report Final CSR	05 Feb 2021 31 Mar 2023 31 May 2024
Study mRNA-1273-P903 Post-Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety	Myocarditis Pericarditis Vaccine-associated enhanced	Protocol submission Interim updates	31 Jan 2021 30 Apr 2021, 31 Jul 2021, 31 Oct 2021, 31 Jan 2022,

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity Study status: Ongoing	signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Long-term safety AESI and emerging validated safety signals		30 Apr 2022, 31 Jul 2022, 31 Oct 2022, 31 Jan 2023
			Final study report	30 Jun 2023
Study mRNA-1273-P904 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Study status: Ongoing	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: - To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group. Secondary objective: - To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Long-term safety Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)* Use in subjects with autoimmune or inflammatory disorders*	Protocol submission	30 Jun 2021
			Interim Updates	30 Sep 2021, 31 Mar 2022, 30 Sep 2022 31 Mar 2023,
			Final study report	31 Dec 2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study mRNA-1273-P905 Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries Study status: Ongoing	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax? Primary objectives: - To determine whether exposure to the Moderna COVID-19 vaccine during pregnancy is associated with an increased risk of: a. Pregnancy complications b. Adverse pregnancy outcomes c. Major congenital malformations in the offspring (overall and organ-specific if feasible) d. Adverse neonatal outcomes Secondary objectives: - To describe utilization of COVID-19 Vaccine Moderna in pregnancy	Use in pregnancy*	Protocol submission	30 Jun 2021
			Interim updates	31 Mar 2022, 30 Sep 2022 31 Mar 2023
			Final study report	31 Dec 2023
Study mRNA-1273-P901 Real-world study of the effectiveness of the Moderna COVID-19 Vaccine Study Status: Ongoing	Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) in a large integrated healthcare system in the United States Primary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease Secondary Objectives	Use in immunocompromised subjects* Interaction with other vaccines, as possible* Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disorders)* Use in subjects with autoimmune or	Protocol submission	01 Mar 2021
			Interim updates	14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 30 Jun 2022; 31 Jul 2022; 14 Dec 2022; 30 Jun 2023; 20 Dec 2023
			Final study report	14 Apr 2025

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection by age and by sex 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection by race/ethnicity groups 3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals with chronic diseases (e.g., chronic kidney disease, lung disease including chronic obstructive pulmonary disease [COPD] and asthma, diabetes) 4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals who are immunocompromised (e.g., HIV, cancer, transplant, immunosuppressive medications) 5. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals with autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus) 6. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in frail individuals 7. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine administered during pregnancy in preventing SARS-CoV-2 infection in pregnant women	inflammatory disorders*		

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	8. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection among individuals with a history of SARS-CoV-2 infection 9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection when given concomitantly with another vaccine 10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic SARS-CoV-2 infection 11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic SARS-CoV-2 infection 12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection 13. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease 14. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection 15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease. 16. To assess the effectiveness of two doses of Moderna COVID-19 vaccine against SARS-CoV-2 variants (test-negative design) 17. To assess the effectiveness of one dose of Moderna COVID-19 vaccine against			

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	SARS-CoV-2 variants (test-negative design) 18. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection and severe COVID-19 disease in non-immunocompromised individuals 19. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection and severe COVID-19 disease in immunocompromised individuals			
mRNA-1273-P910 Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2 Study status: Planned	Describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.	Myocarditis, pericarditis	Protocol submission	26 Apr 2022
			Interim report	30 Aug 2022 31 Jan 2023 30 Jun 2023 31Jan 2024 30 Jun 2024 31 Jan 2025
			Final study report	30 Jun 2025
mRNA-1273-P911 Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) Study status: Ongoing	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasomeran (SPIKEVAX).	Myocarditis	Protocol submission	30 Apr 2022
			Interim report	31 Oct 2022 31 Oct 2023 31 Oct 2024 31 Oct 2025 31 Oct 2026 31 Oct 2027
			Final study report	31 Oct 2028
mRNA-1273-P919 An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy Study status: Planned	This observational post-marketing safety study will evaluate the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to Spikevax during pregnancy.	Use in pregnancy*	Protocol submission	28 Oct 2022
			Study completion	30 Sep 2023
			Final study report	31 Mar 2024

* No longer safety concerns in the RMP.

Rapporteur assessment comment:

The summary table of aPhV activities was updated to highlight the removed safety concerns associated with the relevant studies. As outlined above, the removal of some of these safety concerns is not endorsed and the MAH should update this table accordingly.

The MAH also updated study milestones for studies mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901. As these changes were not previously agreed with the Rapporteur, the MAH is requested to provide a justification for the changes of milestones for each of these studies within this procedure. (**RSI**)

The table was also updated to reflect administrative updates for studies mRNA-1273-P901, mRNA-1273-P910, mRNA-1273-P911 and mRNA-1273-P919. This has been agreed in previous procedures and is acceptable.

3.4. Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety Concern	**Routine Risk Minimisation Activities**
Myocarditis	Routine risk communication: SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC Section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Other routine risk minimisation measures beyond the Product Information: None.
Pericarditis	Routine risk communication:

	SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. (SmPC Section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Other routine risk minimisation measures beyond the Product Information: None.
Long-term safety	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.

Rapporteur assessment comment:

The description of routine RMMs was updated in line with the MAH's proposal to remove a number of safety concerns. As outlined above, the removal of some of these safety concerns is not endorsed and the MAH should update this table accordingly.

3.5. Elements for a public summary of the RMP

The summary of the RMP has been updated in line with the MAH's proposal to remove a number of safety concerns. As outlined above, the removal of some of these safety concerns is not endorsed and the MAH should update the summary of the RMP accordingly.

3.6. Annexes

The annexes have been updated in line with the MAH's proposal to remove a number of safety concerns. As outlined above, the removal of some of these safety concerns is not endorsed and the MAH should update the annexes accordingly.

4. Benefit evaluation

[From the PSUR section 17.2 and 17.3].

Newly Identified Information on Efficacy and Effectiveness

Study mRNA-1273-P204 is an ongoing Phase 2/3 study conducted to evaluate the safety, tolerability, reactogenicity, and effectiveness of elasomeran in healthy children 6 months through 11 years of age. The study enrolled children in 3 age groups: 6 years through 11 years; 2 years through 5 years; and 6 months through 23 months.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cut-off date of 21 Feb 2022 was performed in 5,476 participants 6 months through 5 years of age who received two doses (at 0 and 1 month) of either elasomeran (n=4,105) or placebo (n=1,371) and had a negative baseline SARS-CoV-2 status (referred to as the Per Protocol Set for Efficacy).

Between participants who received elasomeran and those who received placebo, there were no notable differences in demographics.

The median length of follow-up for efficacy post Dose 2 was 71 days for participants 2 through 5 years of age and 68 days for participants 6 months through 23 months of age.

Vaccine efficacy in this study was observed during the period when the B.1.1.529 (Omicron) variant was the predominant variant in circulation.

For children aged 2 years through 5 years of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n = 264; 25 micrograms) to those of young adults (n=295; 100 µg) demonstrated a GMR of 1.014 (95% CI: 0.881, 1.167), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The geometric mean fold rise (GMFR) from baseline to Day 57 for these children was 183.3 (95% CI: 164.03, 204.91). The difference in SRR between the children and young adults was -0.4% (95% CI: -2.7%, 1.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the SRR difference > -10%).

For infants and toddlers from 6 months through 23 months of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n=230; 25 µg) to those 24 of young adults (n=295; 100 µg) demonstrated a GMR of 1.280 (95% CI: 1.115, 1.470), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The difference in SRR rates between the infants/toddlers and young adults was 0.7% (95% CI: -1.0%, 2.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the seroresponse rate difference > -10%).

Accordingly, the pre-specified success criteria for the primary immunogenicity objective were met for both age groups, allowing efficacy of 25 µg to be inferred in both children 2 years through 5 years and infants and toddlers aged 6 months through 23 months (please see Table 17.6 and Table 17.7 in the PSUR).

Characterisation of Benefits

From the study mRNA-1273-P204, Vaccine efficacy (VE) in Part 2 for the Per Protocol Set for Efficacy for COVID-19 cases 14 days or more after dose 2 using the "COVID-19 P301 case definition" (i.e., the definition employed in the pivotal adult efficacy study) was 36.8% (95% CI: 12.5, 54.0) for children 2 through 5 years of age and 50.6% (95% CI: 21.4, 68.6) for children 6 months through 23 months of age.

Rapporteur assessment comment:

In section 17.3 of the PSUR, the MAH summarized information from the study mRNA-1273-P204on the efficacy of elasomeran in children aged <12 years. The MAH is reminded that, as per the GVP module

VII.B.5.17.3, section 17.3 should include an integrated benefit analysis in the authorized indications, i.e. baseline information and the newly identified benefit information that became available during the reporting interval. The MAH is reminded to comply with the requirements of the GVP module VII in future PSUR.

5. Benefit-risk balance

Elasomeran is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults (18 years and above), adolescents (12-17 years of age), and children (6 months of age and older) in the EU at the time of DLP of this PSUR. In addition, two bivalent vaccines, elasomeran/imelasomeran, and elasomeran/davesomeran, are approved.

No new significant information that would impact the benefit-risk balance was identified during the assessment of the data in this PSUR.

No new important identified or potential risks were identified in the presented data from the reporting interval. Based on the cumulative evidence, the important identified risk 'vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)' is refuted and no longer considered important in the context of the PSUR. Moreover, based on the cumulative evidence, the knowledge gaps regarding the missing information 'interaction with other vaccines' have been filled and it has not been shown to constitute an important risk. Therefore, it is no longer considered important in the context of the PSUR. These topics should be removed from the PSUR list of safety concerns and evaluations of new information in future PSURs are not required.

During the reporting interval, new information concerning the important identified risks myocarditis and pericarditis was identified that warrants an amendmend of the warning included in the PI for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran with more details about the course and the outcome of these two conditions.

Based on the presented data in the PSUR, the PRAC rapporteur concludes that the benefit-risk balance remains unchanged for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in the approved indications.

Given the extensive experience with elasomeran-containing vaccines gathered since its marketing authorisation in the EU on the 6th of January 2021 and lack of new safety issues identified during the assessment of the current PSUR, the PRAC Rapporteur recommends to change the frequency of PSUR submission for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran from 6 months to one year (see section 5 of this AR).

6. Rapporteur Request for supplementary information

6.1. Request no 1: Anaphylaxis

The MAH did not state clearly whether they propose to remove 'anaphylaxis' from the safety concerns in the PSUR, in line with the changes to the RMP. Within the current PSUSA, the MAH is requested to clarify whether they propose to remove 'anaphylaxis' from the safety concerns in the PSUR. If yes, the MAH should provide justification for the proposed change applicable in the context of PSUR.

6.2. Request no 2: Arrhythmias

In Appendices 11.12g/h, 162 "uncharacterized" serious cases are listed, comprising 133 WHO-UMC "Possible", 1 "unlikely", and 28 "Unassessable" cases.

The MAH is requested within the current procedure to 1) clarify the definition of an uncharacterized serious case and also clarify the difference in case selection criteria for the tables in Appendix 11.12c (N=134, MAH serious) and 11.12g (N=162, All serious).

The MAH is also requested, within this procedure to

2) explain the differences in case counts attributed to the various WHO-UMC categories in Appendix 11.12c compared to the PSUR text description, and update the Appendices if so indicated.

3) account for the causality evaluation algorithm leading to the WHO-UMC classification "Possible" in an apparently automatic fashion, precluding higher classifications for individual cases, even though "the underlying cause of the reported events was not generally available".

4) account for each and all cases that according to the WHO-UMC classification may qualify for higher classification, i.e. "Probable" or "Certain", and update the relevant Appendices accordingly.

6.3. Request no 3: Hearing loss

The MAH did not provide any information on the causality of the 2,116 cumulative case reports. The MAH is requested to present in details (including case narratives and MAH's causality assessment) all reports that fulfil level 1-3 BC case definition of sudden hearing loss AND that can be considered as 'index cases'*. If no index cases can be identified by the MAH, it should be clearly stated in the response.

6.4. Request no 4: IgA Nephropathy (IgAN)

A. The MAH is requested to provide literature references that are not readily accessible to the rapporteur in full-text format in English. The request concerns the following two publications:

- Fukuda Y, Namiki M, Taniguchi M, Takata F, Osaki K, Taro Y et al. A case of recurrence of IgA nephropathy induced by vaccination with the COVID- 19 vaccine. The Japanese Journal of Nephrology. 2022;64 (6-W):173

- Higashi T, Ko T, Nakamura K, Adachi M, Mukoyama M. A case of IgA nephropathy diagnosed after gross hematuria after SARS-CoV-2 vaccination. The Japanese Journal of Nephrology. 2022;64 (6-W):P-174.

B. In addition, the MAH is requested to provide English translation of the abstracts that were used as a source for cases number [redacted], [redacted] and [redacted], and that were published in:

- The 65th Annual Meeting of the Japanese Society of Nephrology published in The Japanese Journal of Nephrology, 2022; 64(3)

6.5. Request no 5: Mechanical urticaria

A. The MAH stated that 363 literature articles were identified in the literature search, however only 161 articles are described by the MAH. This discrepancy should be clarified within the current procedure.

B. The MAH is, within this procedure, requested to provide the literature review again and to be clear in how many case reports concerning Spikvax and mechanical urticaria or dermatographism that were identified in the literature review.

C. The MAH is requested, within this procedure, to provide an overview of the co-occurrence of mechanical urticaria/dermatographism and chronic urticaria for all cases with reported mechanical urticaria/dermatographism. The MAH should discuss potential underreporting as cases reported as "urticaria" with a prolonged course of >6 weeks, may not have been updated as chronic urticaria in the reporting system.

6.6. Request no 6: Myocarditis

A. The MAH presented results from a case-control study which finds an increased risk of myocarditis for the 3rd dose compared with the 1st dose, but with a lower incidence than for 2nd dose. However, the PRAC rapporteur could not identify these results online (Ref 29. Epi-Phare. Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France Study based on data from the National Health Data System (SNDS).). The MAH is requested in the current procedure to point directly to where these study results can be found. The provided information will be taken into consideration for the update of the SmPC/PIL text when the PRAC rapporteur has been presented to the results in details.

B. The MAH is requested to comment on the suggested PI changes to the text concerning risk of myocarditis (please, see section 3 of this AR).

C. In the subpopulation analysis of children < 18 years, the MAH presented a 14-year-old male considered with BC level 2 myocarditis ([redacted]). This case was neither included in the present PSUR section of new information on myocarditis nor in the PSUR appendix 11.5 myocarditis/pericarditis. The MAH is requested to clarify this discrepancy in the current procedure and once more the MAH is requested to be thorough and precise in the presentation of data.

6.7. Request no 7: Single organ cutaneous vasculitis (SOCV)

The MAH is requested within the current procedure to give full reference to and comment on any new articles (compared to PSUR#3) considered among the 47 publications cumulatively referred to.

6.8. Request no 8: RMP

A. The MAH is requested to provide an updated RMP according to the PRAC Rapporteur's comments on the safety specification.

B. In the pharmacovigilance plan, the MAH updated study milestones for studies mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901. As these changes were not previously agreed with the Rapporteur, the MAH is requested to provide a justification for the changes of milestones for each of these studies within this procedure.

C. Regarding the proposal to remove the missing information 'use in immunocompromised subjects' from the RMP, the MAH is requested to present (interim) data from additional pharmacovigilance activities addressing this safety concern (P304, P904 and P903). As the data from literature regarding safety was limited to one relevant epidemiological study, the MAH should also consider a comprehensive cumulative review of the literature. Moreover, if the evidence indeed supports

the removal of this safety concern in the RMP, this should be reflected in the product information accordingly. Therefore, the MAH is also requested to propose an update of the wording in SmPC section 4.4 regarding the safety of Spikevax in immunocompromised individuals if considered applicable.

7. MAH responses to Request for supplementary information

7.1. MAH's response to request no 1: Anaphylaxis

Request to MAH: The MAH did not state clearly whether they propose to remove 'anaphylaxis' from the safety concerns in the PSUR, in line with the changes to the RMP. Within the current PSUSA, the MAH is requested to clarify whether they propose to remove 'anaphylaxis' from the safety concerns in the PSUR. If yes, the MAH should provide justification for the proposed change applicable in the context of PSUR.

Response from MAH:

The MAH is requesting removal of "Anaphylaxis" as a safety concern from the PSUR, in line with changes from the RMP. While anaphylaxis, remains as an identified risk for the product, as with any other biologicals, it does not have a considerable impact on the benefit-risk balance of the vaccine.

Anaphylaxis is a known rare risk that require no further characterisation and are followed up via routine pharmacovigilance, including signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers.

The MAH has monitored events of anaphylaxis since the initial Emergency Use Authorization on 18 Dec 2020. Based on cumulative exposure and published background rates, ~6,277 cases of anaphylaxis were expected <21 days post-vaccination. As of 17 Dec 2022, there were 2,588 reported cases (2,651 events) of anaphylaxis (0.4% of all reported cases); most were in women (73.6%). Of these cases, 67 (2.6%) reported a fatal outcome; however, most cases (98.5%) were unrelated to vaccination. When examined by dose number, 47.0% of cases occurred after dose 1, 19.7% after dose 2, 8.3% after dose 3, and 0.8% after dose 4; 24.2% did not indicate dose number. Most events occurred on the same day of vaccination (63.3%) regardless of the dose number. The reporting rate of anaphylaxis was 3.58 cases per 1 million doses administered, with a higher rate in adults (18-64 years old; 4.23 cases per 1 million doses).

Rapporteur assessment comment:

The MAH requested to remove an important identified risk 'anaphylaxis' from the safety concerns in the PSUR. The MAH argued that the risk is well-characterized and appropriately managed via the existing risk minimization measures.

The PRAC Rapporteur does not endorse the MAH's proposal. Given that Spikevax is administered to healthy individuals, anaphylaxis, a potentially fatal ADR, can be considered a defining risk for the safety profile of Spikevax and as such it should remain in the PSUR safety concerns for Spikevax. **The MAH is requested to keep 'anaphylaxis' as an important identified risk in the PSUR.**

7.2. MAH's response to request no 2: Arrhythmias

Request to MAH: In Appendices 11.12g/h, 162 "uncharacterized" serious cases are listed, comprising 133 WHO-UMC "Possible", 1 "unlikely", and 28 "Unassessable" cases.

The MAH is requested within the current procedure to 1) clarify the definition of an uncharacterized serious case and also clarify the difference in case selection criteria for the tables in Appendix 11.12c (N=134, MAH serious) and 11.12g (N=162, All serious).

The MAH is also requested, within this procedure to

2) explain the differences in case counts attributed to the various WHO-UMC categories in Appendix 11.12c compared to the PSUR text description, and update the Appendices if so indicated.

3) account for the causality evaluation algorithm leading to the WHO-UMC classification "Possible" in an apparently automatic fashion, precluding higher classifications for individual cases, even though "the underlying cause of the reported events was not generally available".

4) account for each and all cases that according to the WHO-UMC classification may qualify for higher classification, i.e. "Probable" or "Certain", and update the relevant Appendices accordingly.

Response from MAH:

1. The term "uncharacterized" did not appear in the text of the Arrhythmia section of PBRER #4. This term only appeared in the title of the Excel file that composed Appendix 11.12g. This file was a preliminary draft "working file" that was not finalized and was inadvertently submitted with PBRER #4. The extra 28 cases in the file of Appendix 11.12g (that had "uncharacterized" in its title) were not included in the final data of Appendix 11.12c because their specific MedDRA Preferred Terms (PTs) that met the search criteria for arrhythmia were not coded as serious.

2. As requested, an updated Appendix is submitted with this response. This updated Appendix comprises the same cases as Appendix 11.12c; however, the WHO-UMC causality classifications in Appendix 11.12c composed an inadvertently submitted preliminary draft version that was not final. The updated Appendix provides the final version and is consistent with the text description that was submitted.

3. The MAH has not categorized individual cases of arrhythmia as having Certain or Probable WHO-UMC Causality for the following reasons:

a. Clinical trial data have not shown an association between Spikevax and arrhythmia. In addition, as noted below, the population-based epidemiological findings are mixed and inconclusive.

b. There is no demonstrated biological mechanism for Spikevax to directly cause arrhythmia.

c. There is no demonstrated "time window" or time to onset when arrhythmia occurs following vaccination with Spikevax.

d. Pathognomonic characteristics (whether clinical, laboratory or diagnostic) of vaccine-associated arrhythmia have not been identified.

e. No demographic group or comorbid condition has been clearly shown to be associated with increased risk.

f. Arrhythmia is a heterogenous entity; there are numerous types of arrhythmias, and no specific type or types have been clearly linked to Spikevax.

g. There is a background rate of arrhythmia. With administration of more than 900 million doses of Spikevax noted in PBRER #4, there was ample time-at-risk for etiologically unrelated events to occur coincidentally in temporal association with Spikevax administration.

h. The limited amount of clinical and historical detail that is provided in the individual case safety reports in the MAH's Global Safety Database substantially hinders causality assessment for individual cases.

i. For the reasons noted above, temporal association is the main information that can be utilized for assessing causality. The MAH considers that temporal association alone is insufficient to assess WHO-UMC Causality for a case of arrhythmia as Probable or Certain.

4. As explained in the response directly above, no cases qualified for higher classification as "Probable" or "Certain", according to the WHO-UMC classification.

5. Dickerman et al noted in their article:

"The interventions of interest were vaccination with either the BNT162b2 vaccine with a second dose scheduled 21 days later or the mRNA-1273 vaccine with a second dose scheduled 28 days later"

"Adherence to vaccine protocols was strict. Among persons who received a dose of the BNT162b2 vaccine and had at least 21 days of follow-up, 98% received a second dose of the vaccine (of whom 92% received it before day 24 and 96% received it before day 28). Among persons who received a dose of the mRNA-1273 vaccine and had at least 28 days of follow-up, 98% received a second dose of the vaccine (of whom 92%received it before day 31 and 97% received it before day 35)."

"We also conducted secondary analyses evaluating 14-day and 42-day risk to distinguish adverse events that might be documented in the weeks after the first dose and after the second dose of the vaccine, respectively." The table below shows the results of the analyses evaluating 42-day risk to distinguish arrhythmia events that might be documented in the weeks after the second dose, according to Dickerman et al.

eTable 7: Secondary Analysis: Evaluating 42-Day Risk

eTable 7. Secondary Analysis: Evaluating 42-day Risk: Estimated Comparative Safety of the BNT162b2 and mRNA-1273 Vaccines. Veterans Health Administration (January 4-0Ctober 5. 2021).'

	No. ol persons	No. of events		42-<lay risk *no. of events/10,000 persons (95% CI)*		Risk difference *no. of events/ 10,000 persons (95% CI)*	Risk ratio *(95% CI)*
Event		**BNT162b2**	**mRNA-1273**	**BNT162b2**	**mRNA-1273**		
Neurologict	233.970	565	567	48.5 (47.0. 54.3)	48.7 (44.5, 52.3)	-0.2 (-3.4. 8.2)	1.00 (0.93, 1.18)
Hematologicl:	279.014	731	681	52.6 (47.6. 55.7)	49.0 (45.7, 53.1)	3.6 (-2.9, 7.7)	1.07 (0.94, 1.17)
Hemorhagic stroke	431.508	15	15	0.7 (0.3.1.1)	0.7 (0.3. 1.0)	0.0 (-0.4. 0.6)	1.00 (0.50, 2.38)
Ischemic stroke	392.262	205	168	10 5 (9.3. 11.9)	8.6(7.7.103)	1.9(-0 3. 34)	1.22 (0.97. 142)
Myocardial infarction	406.136	167	120	8.3 (69. 93)	5.9 (55. 77)	2.3(-0.1.32)	139 (099. 156)
Other thromboembolic§	402.126	189	154	9.5 (8.9. 11.6)	7.7 (6.8. 9.4)	1.8 (0.2, 4.2)	1.23 (1.02. 1.59)
Myocarditis or pericarditis	429.564	12	7	0.6 (0.3. 1.0)	0.3 (0.1. 0.6)	0.2 (-0.1. 0.7)	1.72 (0.78. 5.78)
Arrhythmia	277,438	596	492	43.2 (39.0. 46.2)	35.6 (32.9. 39.8)	7.5 (1.9, 11.5)	121 (1.05. 1.34)
Kidney injury	356.008	315	247	17.8 (16.6. 21.0)	13.9 (12.0. 15.6)	3.8 (2.1, 8.0)	1.28 (1.14. 1.63)
AppendiCllis	428.856	16	13	08 (04. 12)	06 (03. 10)	01 (-03. 06)	1.23 (062. 256)
Autoimmune,i	376,088	169	179	9.0 (8.3. 10.9)	9.6 (7.9. 10.6)	-0.5 (-1.5. 2.2)	0.94 (0.85. 1.27)
Herpes zoster or simplex	387.056	133	124	6.9 (5.6. 8.0)	64 (54. 7.7)	0.5(-1.4.1.9)	1.07 (0.80. 1.31)
Arthritis ar arthropathy	397.732	182	145	9.2 (74, 10.1)	7.3(5.9. 8.3)	1.9 (-0.2. 3.6)	1.25 (0.98, 1.61)
Pneumonia	379.978	206	183	10.9 (9.2. 12.3)	9.7 (8.7. 115)	1.2(-1.7. 2.7)	1.13 (0.85. 1.30)

Abbreviation: CI, confidence interval.

"Persons newly vaccinated with the BNT162b2 vaccine were matched in a 1:1 ratio to persons new1y vaccinated with the mRNA-1273 vaccine according to the folloINing variables: calendar date. age, sex, race, urbanicity of residence, and geographic location coded as categories of Veterans Integrated Services NetworK. Follow-up af a matched pair ended when either member developed a documented SARS-CoV-2 infection.

t Neuralogic events included Bell's palsy, non-facialparalysis, paresthesia, seizure. syncope, and vertigo.

:t: Hematologic events included anemia, lymphopenia, neutropenia, and thrombocytapenia.

§ Other thromboembolic events included cerebral venaus sinus thrombosis, deep venous thrombosis ar thrombophlebitis, pulmonary embolism, and other thrombosis (arterial embolism and thrombosis, vascular insufficiency af the intestine).

11Autoimmune events included Guillain-Barre syndrome, innammatary bowel disease, multiple sclerasis, peoriasis, rfleumatoid arthritis, systemic lupus erythematosus, and uveitis.

Conclusions Regarding the study by Dickerman et al.

This was a large, population-based epidemiological study that included a comparison of the incidence of arrhythmia in Spikevax (mRNA-1273) vs. BNT162b2. An overview of the study was included in PBRER #4. Briefly, there was matching on important covariates to minimize confounding. Nearly all vaccinees received a second dose and received it near the recommended time frame. A secondary analysis was performed that, according to the investigators, used a 42-day risk window to address adverse events after the second dose. Shown above is eTable 7, which is reproduced from the Dickerman et al article. This table compares the risk of arrhythmia for the two mRNA vaccines. The risk of arrhythmia for BNT162b2 was 43.2 per 10,000 persons, whereas for Spikevax (mRNA-1273 in the table) the risk was lower, 35.6 per 10,000 persons. The higher risk for BNT162b2 compared to Spikevax was statistically significant: risk ratio 1.21 (95% CI, 1.05-1.34). These findings by Dickerman et al are not consistent with, and do not confirm, the reported findings of the Patone et al study.

Rapporteur assessment comment:

Re. 1) The MAH has explained that the term "uncharacterized" only appeared in the heading of preliminary draft "working file" that was not finalized and was inadvertently submitted with PBRER #4, Further, the MAH has accounted for the discrepancy in case numbers between cases listed in submitted listings of Arrhythmia cases. This is endorsed.

Re. 2) The updated version of Appendix c submitted with this response, including revised WHO-UMC causality classifications, provides the final version consistent with the text description that was submitted. This is noted.

Re. 3) The MAH has listed a number of reasons (a-i) for not categorizing individual cases of arrhythmia as having Certain or Probable WHO-UMC Causality. In general, the list is not endorsed. The reasons mentioned are not relevant for the assessment of individual cases, but will be considered in a final overall assessment of potential causality. However, for the specific purpose of assessing individual cases it is important, that the MAH strictly adhers to the exact definitions as published.

Thus, the MAH is therefore expected to be fully compliant with the WHO-UMC causality assessment criteria as explained and listed at https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf. In the next PSUR, the MAH is requested **to reevaluate cumulatively the WHO-UMC classification of all serious cases of Arrhythmias in the next PSUR, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e. Possible vs Probable and Probable vs Certain), and to discuss the result in the context of the totality of evidence on the subject.**

Re. 4) Not endorsed, see above.

Re. 5) Further, the MAH has spontaneously commented on the study by Dickerman et al. indicating a small but significant difference in the post-second dose risk of Arrhythmias with the 2 mRNA COVID-19 vaccines in favour of elasomeran (eTable 7: Secondary Analysis: Evaluating 42-Day Risk). This is noted. A similar comparison was previously published by Patone et al, indicating the opposite comparative result regarding arrhythmias following a second dose within 28 days. Both publications are noted. However, comparations between vaccines are beyond the scope of the product specific PSUSAs.

7.3. MAH's response to request no 3: Hearing loss

Request to MAH: The MAH did not provide any information on the causality of the 2,116 cumulative case reports. The MAH is requested to present in details (including case narratives and MAH's causality assessment) all reports that fulfil level 1-3 BC case definition of sudden hearing loss AND that can be

considered as 'index cases'*. If no index cases can be identified by the MAH, it should be clearly stated in the response.

Response from MAH:

A cumulative review of the Moderna GSDB for reports under the HLT of "Hearing losses" received after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran was conducted, as per request received from a PRAC.

Methodology:

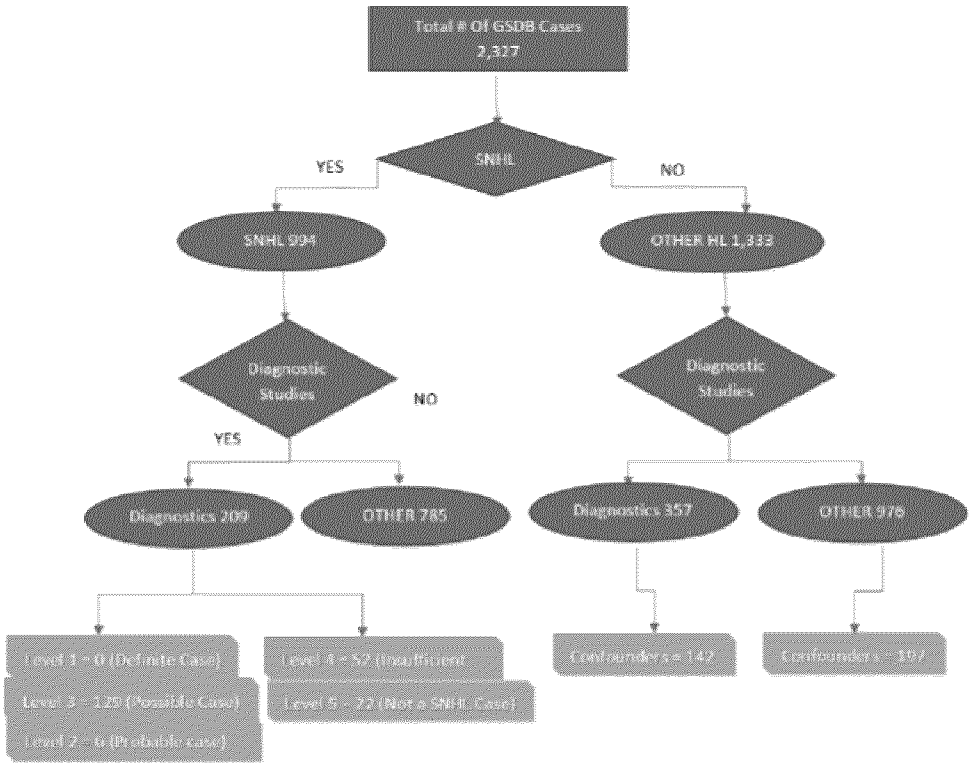
In response to the PRAC's request to perform medical review of Level 1-3 Brighton collaboration (BC) cases, the MAH developed an algorithm in SAS (See Appendix A to the PSUR) to further characterize the 2,327 (there were 2,327 cases identified under PBRER 4) cumulative cases of sensorineural hearing loss (SNHL) (including assessment of BC, WHO causality, associated confounders/risk factors, treatment, outcomes, and review of events of HL alone compared to hearing loss (HL) with other preferred terms (PTs) to provide potential insight into benefit:risk for cases with mixed symptomology (e.g., reactogenicity, immunogenicity, etc). Below describes the criteria for Level 1-3 BC:

• LEVEL 1 (Definite Case): defined as a physical examination excluding conductive hearing loss and audiometry consistent with SNHL.

• LEVEL 2 (Probable case) defined a physical examination excluding conductive hearing loss and an Auditory Brainstem Response (ABR) test consistent with SNHL or a Tuning fork exam consistent with SNHL.

• LEVEL 3 (Possible case): defined as a physical examination excluding conductive hearing loss and an Otoacoustic Emissions (OAE) test consistent with hearing loss or a behavioral or neurodevelopmental testing questionnaire concerning hearing loss or remote screening using telehealth technology concerning hearing loss. Figure 1 below presents the process the MAH utilized to identify and evaluate SNHL/hypoacusis (994 cases) and other HL (1333 cases).

Figure 1 Overview of MAH HLT of Hearing Loss Case Evaluation Strategy



SNHL Sensorineural hearing losses
GSDB Global Safety Database

Summary of Cumulative HLT Hearing Loss Cases

Of the 2,327 cases (2,589 events) identified, 25.2% (586) of cases were reported as non-serious and 74.8% (1,741) were reported as serious, of which 3 were fatal cases. There were 1,254 (53.9%) medically confirmed cases. Gender distribution was highest among women (57.5%) with 40.4 % in men and 2.1 of unknown gender. The mean age was 52.0 years (SD: 17.0) and the median age was 52.0 years (range: 0.3 to 101.0 years, noting that the cases in very young children were found to have age coding discrepancies which are being corrected). The highest proportion of cases occurred in the 50–64-year age group (28.5%) followed by the elderly 65 years and older (24.4%), and the 25-39-year age group (18.3%). There were 16 cases (0.6%) in the pediatric age group. The majority of these cases originated from the United States (51.6%), followed by EEA countries (35.5%) and the United Kingdom (5.8%). The highest events were for the PTs of hypoacusis (33.3%) followed by deafness (25.9%). Table 1 below presents the PTs for the cumulative events (2,589) of hearing loss.

Table 1 Preferred Term Events for HLT of Hearing Loss (Cumulative)

PT	Total # Events	% Total Events
Hypoacusis	861	33.3
Deafness	670	25.9
Deafness unilateral	480	18.5
Sudden hearing loss	346	13.4
Deafness neurosensory	139	5.4
Deafness bilateral	50	1.9
Deafness transitory	23	0.9
Neurosensory hypoacusis	7	0.3
Conductive deafness	5	0.2
Deafness permanent	5	0.2
Presbyacusis	2	0.1
Mixed deafness	1	0.0
Grand total	**2,589**	**100.0**

When time to onset (TTO) was reported, most events occurred after Dose 1 (30.1%), with Dose 2 (28.9%), and Dose 3 (7.6%) with TTO not reported in 32.9% of the events. The time to onset of all doses was on average 13.7 days (SD: 33.9) with a median of 3.0 days (range of -217 to 379). Almost 60% of the 2,589 events (59.6%; 1,544) were not resolved, 14.4% (372 events) resolved, and 8.6% (224) were either resolving or resolved with sequelae. Note: Not resolved outcomes must be interpreted with caution as most reports do not have follow-up. Serious events represented 65.3% (1,220) of the "not resolved" outcomes; 44.9% (324) of the "not resolved" events were non-serious. Most cases were confounded by extensive medical history and or concomitant medication use. Table 2 represents the types of confounders for the cumulative 2,327 cases.

Table 2 Overview of Confounders for Cases of HLT of Hearing Loss

Infective: viral/bacterial (human immunodeficiency virus [HIV], cytomegalovirus [CMV], herpes simplex [HSV], mumps, rubella, syphilis)
Noise induced
Trauma (temporal bone fracture)
Ototoxic drugs (aminoglycosides, NSAIDs, loop diuretics)
Autoimmune disorders (systemic lupus erythematosis [SLE], granulomatosis with polyangiitis [formerly Wegener], Cogan syndrome, relapsing polychondritis, ulcerative colitis, rheumatoid arthritis)
Tumour (vestibular schwannoma, leukaemia, myeloma)
Vascular (cerebrovascular disease, sickle cell disease)
Perilymphatic fistula
Barotrauma
Neurological (deafness, Meniere's disease, hypoacusis, multiple sclerosis, cerebrovascular accident, migraine, transient ischemia attack)
Other (diabetes mellitus, hypertension, hypothyroidism, hyperthyroidism, sarcoidosis, chronic kidney disease)

Overview of Neurosensorial/Hypoacusis Hearing Loss Cases Analysis

The MAH conducted a detailed evaluation of the cases of Sensorineural hearing loss (SNHL) by searching both the narratives and filtering for the MedDRA PTs which contained verbatim combinations of SNHL or hypoacusis. SNHL is defined as a hearing loss of 30 dB or more in three sequential frequencies in the standard pure tone audiogram. Using the results from the MAH SAS algorithm (Appendix 3A in the PSUR), of the 2,327 cases, there were 994 cases of SNHL/hypoacusis and 1333 cases of 'Other hearing loss (HL)' identified. Appendix 3B and 3C present the detailed assessment of these cases of SNHL/hypoacusis and other HL, respectively.

Of the 994 cases, most cases (474; 46.7%) derived from the USA followed by the UK (50; 5.0%), and Japan (18; 1.8%). Gender distribution was highest among women (599; 60.3%) with 380 (38.2%) in men and 15 (1.5%) of unknown gender. There were 689 cases (69.3%) in the adult age group, 254 cases (25.6%) in the elderly 65 years and older population, and 51 cases (5.1%) in the pediatric age group with a mean age of 49.6 years and median age of 50 years. See Table 3 below for overview of SNHL demographics.

Table 3: Cumulative Analysis of Demographics for SNHL Cases

Gender	Age Group	Total		Gender	Age Group	Total
Female	Adult	425		Female	Adult	548
	Children	24			Children	29
	Elderly	150			Elderly	161

Gender	Age Group	Total		Gender	Age Group	Total
Female Total		**599**		**Female Total**		**738**
Male	Adult	263		Male	Adult	389
	Children	17			Children	22
	Elderly	100			Elderly	149
Male Total		**380**		**Male Total**		**560**
Unknown	Adult	1		Unknown	Adult	10
	Children	10			Children	21
	Elderly	4			Elderly	4
Unknown Total		**15**		**Unknown Total**		**35**
Total for SNHL/Hypoacusis Cases		**994**		**Total for Other Hearing Loss Cases**		**1333**

Over 76% of the cases reported treatment with steroids, antibiotics or other medications; the remaining cases had (237) missing/unknown treatment information. There were 242 cases, which had confounders of either medical history, concurrent illnesses, or concomitant medications.However, 432 cases had missing or unknown medical history. A total of 785 cases did not report diagnostic studies (e.g., audiogram/acoustic test, magnetic resonance image [MRI], computerized tomography) information. The remaining 209 cases were identified with diagnostic studies and underwent medical review and assessment (BC case definitions for acute neurosensory hearing loss and WHO causality). Of these 209 diagnostics cases, 64% met the Level 3 criteria, refer Table 4 below.

Table 4 NSHL BC and WHO Case Assessment with Diagnostic Studies:

BC Level	WHO Causality Assessment					Total Cases
	Certain	Probable / Likely	Possible	Unlikely	Unassessable	
Level 1	0	0	0	0	0	0
Level 2	0	1 (16.7%)	5 (83.3%)	0	0	6 (2.9%)
Level 3	0	0	**64 (47.8%)**	**20 (15.0%)**	**45 (34.9%)**	**129 (61.7%)**
Level 4	0	0	0	7 (13.5%)	**45 (86.5%)**	**52 (24.9%)**
Level 5	0	0	0	22 (100%)	0	22 (10.5%)
Total						**209**

Summary of Potential NSHL Cases with Diagnostic Studies (209 Cases)

Of the 209 cases identified using the SAS algorithm, 129 were Level 3 and 80 were assessed as either Level 2, 4 or 5. Overall cases were reported across all regions, had higher rates in females, and were seen in older adults and elderly population. Only 4 cases were identified in the < 18 years population. Majority of cases had plausible temporal associations and supported by physical examinations, diagnostic studies, doctor visits, or ENT specialist visits/consultations. However, many presented with confounders in medical history, concurrent illnesses, or concomitant medications associated with ototoxicity.

Overview of Level 1 to 3 Cases

Level 1: Upon medical review of these cases, there were no index cases identified based on the current information that was provided.

Level 2: Among the 6 Level 2 cases, all cases were in adult age range 38 to 67 years. Cases meeting BC criteria Level 2 had no relevant medical history of hearing disorders. However, 2 cases had a history of high cholesterol, 4 had histories of other vaccines (Shingles), severe hypersensitivity reactions and allergies/respiratory problems. All cases had documented abnormal audiograms of >30db-71db. Of the 4 cases that reported treatment, 2 cases did not resolve, and 2 cases were resolving/resolved after receiving therapy for the event. All cases were assessed as possible except for one case assessed as likely, which did not resolve with treatment.

Note: Previously reported Level 1 index case ([redacted]) was reassessed as Level 2 per SPEAC definition and medical assessment. *An index case is defined as a case report that cannot be excluded due to confounding by disease, concomitant medicines, or comorbidities, and has a plausible time to onset and a plausible mechanism of action.

[redacted] (WWID: [redacted]): 11 Zoccali F, Cambria F, Colizza A, Ralli M, Greco A, Vincentiis M de, Petrella C, Fiore M, Minni A, Barbato C. Sudden Sensorineural Hearing Loss after Third Dose Booster of COVID-19 Vaccine Administration. Diagnostics. 2022;12(9):2039. This literature case report concerned a 67-yearold female patient with no history of vertigo, dizziness, or tinnitus, or any previous hearing loss or ear discharge, who experienced sudden hearing loss of the left side seven days after the patient had received the third dose of the mRNA-1273 vaccine. Relevant medical history included tested positive for coronavirus one year before the administration of the third dose, and allergies and reported the use of an antihistaminic during periods of allergies; however, a complete medical history and concomitant medications were not provided. Otoscopy was unremarkable on both ears, while Weber test was lateralized to the right ear and a Rinne test was positive on both sides. Pure tone audiometry was performed and showed profound right sensorineural hearing loss of at least 60 dB in every frequency. The patient did not have any other neurological deficits and the remaining investigations (e.g., otoscopy, chest x-ray, blood examination, MRI and "MRA") were normal. The patient was treated with intra-tympanic dexamethasone injection and had almost full recovery from the event at the time of this report.

WHO-UMC Causality: According to the WHO causality assessment this case is considered possible. The history of COVID-19 infection is an important risk factor and confounder in this case. Sensorineural hearing loss (SNHL), tinnitus, and/or vertigo have been described to occur during and following COVID-19 infection12. Fancello V, Fancello G, Hatzopoulos S, Bianchini C, Stomeo F, Pelucchi S, Ciorba A. Sensorineural Hearing Loss Post-COVID-19 Infection: An Update. Audiology Res. 2022;12(3):307–15. . To date, different hypotheses have been proposed to explain the etiopathogenesis of neurological symptoms reported during the acute and postacute phases of the infection. It is likely that many factors, or a combination of mechanisms, may be involved in the etiopathogenesis of different symptoms, including SNHL. These could consist of hypoxia, immune-mediated damage, coagulative disorders, and viral direct invasion/damage13. Fancello V, Hatzopoulos S, Corazzi V, Bianchini C, Skarżyńska MB, Pelucchi S, Skarżyński PH, Ciorba A. SARS-CoV-2 (COVID-19) and audio-vestibular disorders.

Int J Immunopath Ph. 2021;35:20587384211027372. No additional information was presented in this report.

Level 3: All Level 3 cases had diagnostics studies (e.g., audiogram, MRI, etc). In the 129 cases, the ages ranged from 27 to 90 years in 39 female and 24 males. Overall, although the majority of cases presented with a plausible temporal association; however, there were 63 cases that had confounders (medical history and/or concomitant medications). The outcomes reported in these cases were "not resolved" (111 cases), "resolved" (10), and "resolving" (8). In 49 cases, the patients received steroid treatment (either oral steroids and/or intra-tympanic steroid injections) in which 42 were not recovered/resolved and 7 resolved or resolving after treatment at the time of the PBRER report).

Adults: Among the 14 cases of younger patients (ages 27-39 years old), 8 were in females and 6 were in males. Confounders included missing specific diagnostic studies (14 cases), known medical history of hypersensitivity reactions to vaccines (3 cases), pre-existing vestibular neuronitis (1 case), pre-existing tinnitus (1 case), unknown TTO (2 cases), and implausible temporal relationship (TTO between > 14 days after their vaccines) (4 cases). Half (7) of the patients received steroid treatment, of which 5 patients had an outcome of "recovered", 6 patients had "unknown" outcomes, and the remaining patient had an outcome of "resolving".

Elderly: Among the 44 cases in the elderly population >65 years and older, 20 were in females and 24 in males. Confounders included advanced age, relevant pre-existing conditions (hypertension, diabetes, hypothyroidism, migraine, meningioma, chronic kidney disease, dementia, vertigo), history of hearing loss disorders (Meniere's disease, deafness, acoustic neuroma, tinnitus, hearing aid user), and concomitant medication associated with ototoxicity (non-steroidal inflammatory drugs [NSAIDs], hydrochlorothiazide, furosemide). All of the events resolved except in 2 cases. Of the 13 cases which reported treatment with steroids, only 1 case resolved after treatment.

Summary of All Other Hearing Loss Cases (1333 cases without SNHL or Hypoacusis)

Methodology: Appendix C to th PSUR presents a summary of the remaining cases (1333 cases) assessed as "other hearing loss", which were heavily confounded by known risk factors associated with acute sensorineural hearing loss. Overview of these cases retrieved from the SAS algorithm were analyzed by demographics, diagnostic studies, risk factors/confounders, and other available data (e.g., treatment, outcome). Note: Only cases with diagnostic studies (e.g., audiogram/acoustic tests, MRI, computerized tomography) were evaluated. Overall cases were reported across all regions, had higher rates in females, and were seen in older adults and elderly population.

Of the 1333 cases, there were 738 (55.4%) female cases, 560 (42.0%) male cases, and 35 (2.6%) unknown cases. The mean age was 49.5 years and the median age was 52 years (0.3 to 101 years). There were 947 cases (71.0%) in the adult age group, 314 cases (23.6%) in the elderly 65 years and older population, and 72 cases (5.4%) in the pediatric age group.

Of the 270 cases that received treatment, 245 resolved and 25 did not resolve with treatment (See PSUR Appendix A: Methods). Only 357 (26.8%) had diagnostic studies information. There were 142 cases assessed as Level 3 (possible case). There were 197 cases assessed as Level 3a, and 994 cases were assessed as Level 4 (Insufficient Information). Note: The Level 3a cases are defined as probable cases of other hearing loss that had no diagnostics studies; however, these cases all had confounders.

Of the 1333 cases, 357 cases had diagnostic studies, of which, there were 195 (54.6%) female cases, 158 (44.3%) male cases, and 4 (1.1%) of unknown gender. Of the 357 cases, 142 cases were assessed as Level 3 (possible case) and 215 cases were assessed as Level 4 (insufficient information). No Level 3a cases had diagnostic studies. All Level 3 and Level 3a cases had confounders. Confounders included concomitant medications associated with ototoxicity and/or relevant medical history that are risk factors

for hearing loss. Of the 142 Level 3 cases, there were 72 (50.7%) female cases, 67 (47.2%) male cases, and 3 (2.1%) of unknown gender. A total of 73 cases (51.4%) represented Hearing Loss (HL) with other PTs (mixed symptomology) and 69 cases (48.6%) represented only events of HL related PTs. Only events of HL related PTs include deafness unilateral, deafness bilateral, sudden hearing loss, deafness, deafness permanent, conductive deafness, tinnitus, hyperacusis, vertigo, vertigo positional, labyrinthitis, condition aggravated, middle ear effusion, vestibular neuronitis, auditory disorder and ear discomfort. The outcome reported in the 142 cases were as follows: "not resolved" (120), "resolved"/"resolving" (13), and "unknown" (9).

Summary of Hearing Loss in Patients After a Bivalents

Cumulative review of SPIKEVAX (Bivalent .214 and Bivalent .222) covers the period from the 18 Dec 2020 to 17 December 2022.

Cumulatively, a total of 11 cases (7 serious, 4 non-serious, 2 medically confirmed) of hearing loss-related PTs were identified for SPIKEVAX (.214) including 11 events. Among the 11 events, 7 were reported as serious. The distribution of cases was slightly higher in females (6; 54.5%) compared to males (5; 45.5%). The median age of patients was 65.5 years (range of n: 57.0 to 75.0 years) with a mean age of 66.3 years (SD: 9.1). The highest proportion of cases occurred in the 50–64-year-old age group (18.2%) followed by the 65-74 year-old age group (9.1%) and 75-year-old age and older group (9.1%) (See Table 5). Most of the cases were received from regulatory authorities (90.9%) and the remaining from spontaneous source (9.1%). The majority of the hearing loss cases were reported in the EEA (54.5%).

Cumulatively, a total of 5 cases (4 serious, 2 medically confirmed, 1 non-serious) of hearing loss-related PTs were identified for SPIKEVAX (.222) including 5 events. Among the 5 events, 4 were reported as serious. The distribution of cases was higher in females (4; 80.0%) compared to males (1; 20.0%). The median age was 68.0 (range of 48.0 to 69.0 years) with a mean age of 63.0 years (SD: 9.0). The highest proportion of cases occurred in the 65–74-year-old age group (60.0%) followed by the 40–49-year-old age group (20.0%) and 50–64-year-old age group (20.0%) (See Table 5). All of the cases were received from spontaneous source (100.0%) and reported in the United States (100%).

Table 5. Number and Percentage of Hearing Loss Cases by Age and Gender (Reporting Period) – SPIKEVAX (.214 and .222)

Age Group	Female		Male		Total # .214 Cases (%)	Total # .222 Cases (%)
	# .214 Cases (%)	# .222 Cases (%)	# .214 Cases (%)	# .222 Cases (%)		
40-49Y	0	0	0	1 (20.0%)	0	1 (20.0%)
50-64Y	1 (9.1%)	1 (20.0%)	1 (9.1%)	0	2 (18.2%)	1 (20.0%)
65-74Y	0	3 (60.0%)	1 (9.1%)	0	1 (9.1%)	3 (60.0%)
75Y+	1 (9.1%)	0	0	0	1 (9.1%)	0
Missing	4 (36.4%)	0	3 (27.3%)	0	7 (63.6%)	0
Total	**6 (54.5%)**	**4 (80.0%)**	**5 (45.5%)**	**1 (20.0%)**	**11 (100.0%)**	**5 (100.0%)**

For SPIKEVAX (.214), the reported MedDRA PTs for hearing loss included hypoacusis (4, 36.4%), deafness (3, 27.3%), sudden hearing loss (3, 27.3%), and deafness unilateral (1, 9.1%). When TTO was reported, 2 events occurred after Dose 4 (18.2%) and 9 occurred after an unknown dose (81.8%). The TTO of all doses was on average 2.3 days (SD: 3.2) with a median of 1.0 days (range of 0 to 6 days). The event outcomes reported were as follows: 6 events (54.5 %) were "not resolved", 3 (27.3%) events were "resolving," 1 event (9.1%) "resolved," and 1 event (9.1%) did not report an outcome. There were no events with fatal outcome.

For SPIKEVAX (.222), the reported MedDRA PTs for hearing loss included deafness (3, 60.0%), deafness unilateral (1, 20.0%), and hypoacusis (1, 20.0%). When TTO was reported, 1 event occurred after Dose 3 (20.0%), 1 event occurred after Dose 4 (20.0%), 1 event occurred after Dose 5 (20.0%), and 2

occurred after an unknown dose (40.0%). The TTO of all doses was on average 13.0 days (SD: 16.8) with a median of 7.0 days (range of 0 to 32 days). The event outcomes reported were as follows: 3 events (60.0 %) were "not resolved" and 2 events (40.0%) did not report an outcome. There were no events with fatal outcome.

Conclusions

In general, it is difficult to adequately analyze post-authorization data due to inherent limitations in spontaneous reporting. Evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomernan and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

The MAH was requested to clearly state whether any cases were identified that could be classified as 'index cases' AND were fulfilling the BC collaboration definition for hearing loss. An index case is defined as a case report that cannot be excluded due to confounding by disease, concomitant medicines, or comorbidities, and has a plausible time to onset and a plausible mechanism of action.

In response to the request, the MAH stated the following:

1) Cumulatively, the MAH identified 135 Level 1-3 BC cases of sensorineural hearing loss (SNHL), whereof 69 cases were assessed by the MAH as WHO-possible and one as WHO-probable.

- Level 1 cases of SNHL: no cases identified

- Level 2 cases of SNHL: 6 cases; 1 WHO probable and 5 WHO-possible

The MAH did not state case numbers for these six cases, apart from case no.: [redacted], which was presented in the preliminary AR and assessed by the PRAC Rapporteur as WHO-probable. It is unclear whether the MAH considered all 6 cases as 'index cases'.

- Level 3 cases of SNHL: the MAH identified 64 WHO-possible cases. The MAH did not state their case numbers and whether they can be classified as 'index cases'.

2) The MAH identified 357 cases of 'other hearing loss' (cases without SNHL or hypoacusis) with relevant diagnostic tests. Of these, 142 complied with the definition of Level 3 cases (possible cases of hearing loss). According to the MAH, all Level 3 cases had confounders. The MAH neither stated causality assessment for these 142 cases nor specififed whether any of the cases could be considered as 'index cases'.

The MAH did not clearly state whether/how many 'index cases' could be identified among the cumulative cases of hearing loss that fulfilled Level 1-3 BC definition of hearing loss. Based on the information presented, the PRAC Rapporteur counted 69 Level 1-3 cases assessed as WHO-possible and one case classified as WHO-probable, which was already presented in the preliminary AR. In light of the extensive global exposure to Spikevax, the numbers can be considered low. The data presented above does not change the PRAC Rapporteur's opinion that the available evidence is insufficient to establish causal association between 'hearing loss' and Spikevax. No further actions beyond routine PV are thus considered warranted at this stage.

7.4. MAH's response to request no 4: IgA Nephropathy (IgAN)

Request to MAH:

A. The MAH is requested to provide literature references that are not readily accessible to the rapporteur in full-text format in English. The request concerns the following two publications:

- Fukuda Y, Namiki M, Taniguchi M, Takata F, Osaki K, Taro Y et al. A case of recurrence of IgA nephropathy induced by vaccination with the COVID- 19 vaccine. The Japanese Journal of Nephrology. 2022;64 (6-W):173

- Higashi T, Ko T, Nakamura K, Adachi M, Mukoyama M. A case of IgA nephropathy diagnosed after gross hematuria after SARS-CoV-2 vaccination. The Japanese Journal of Nephrology. 2022;64 (6-W):P-174.

B. In addition, the MAH is requested to provide English translation of the abstracts that were used as a source for cases number [redacted], [redacted] and [redacted], and that were published in:

- The 65th Annual Meeting of the Japanese Society of Nephrology published in The Japanese Journal of Nephrology, 2022; 64(3)

Response from MAH:

The MAH is submitting the requested articles in English with this response. In addition, the MAH is submitting with this response the missing table in section 16.4 Characterization of risks, corresponding for the classification of IgA Nephropathy as an Important Potential Risk. (Appendix 1)

Rapporteur assessment comment:

The MAH has submitted the requested material, including risk characterisation for PSUR section 16.4, which is acknowledged.

A. The case report of Fukuda Y et al concerns a 44-year-old man, diagnosed by biopsy with IgAN 4 years prior to a second dose of elasomeran. Intermittently reported in full remission by every 6-month check-ups. 2 month later no sign of remission and a 2nd biopsy confirmed relapse of the IgAN. Authors note that most cases of gross hematuria after COVID-19 vaccination were transient and improved. However, this patient experienced recurrence of highly active primary disease. Due to sparse information on other medications and MedHx, confounding cannot be excluded (causality Possible).

Higashi T reported on a 47-year old man with relapse of IgAN (diagnosed one year prior) with gross hematoria on days 1-6 after the second vaccination with elasomeran, followed by affected renal biochemistry and a renal biopsy on day 20 indicating IgAN. Due to sparse information on other medications and MedHx, confounding cannot be excluded (causality Possible).

The information provided in these two cases does not change our preliminary assessment.

B. The MAH has submitted a reprint of the article by Kento Ota et al (2022): Comparison of renal histopathology in three patients with gross hematuria after SARS-CoV-2 vaccination. CEN Case Rep. 2023 May;12(2):176-183. doi: 10.1007/s13730-022-00743-w. Epub 2022 Oct 11.

This article seems to be based on the meeting abstract first referenced in PBRER (The 65th Annual Meeting of the Japanese Society of Nephrology published in The Japanese Journal of Nephrology, 2022; 64(3)).

This paper present 3 cases of of IgA nephropathy with gross hematuria following SARS-CoV-2 messenger RNA (mRNA) vaccination. Only 1 case was related to the Moderna mRNA-1273 vaccine, while the other 2 cases regarded the Pfzer BNT162b2 vaccine.

The Moderna case (case 2) concerned a 22-year-old woman with no history of urinary abnormality, which may already have been considered in this PEBRER/PSUR.

Furthermore, this article referred to 18 additional literature cases (article table 2), including 8 with elasomeran (4 new and 4 flare cases) and 10 with the Pfizer vaccine (4 new and 6 flare cases). All but 3 first-dose events were related to the second dose. The rapporteur confirmed that, among these papers, all cases involving elasomeran and IgAN was already considered in the current PBRER/PSUR.

However, in the listing of cases Appendix 11.17b, the cases listed in the request ([redacted], [redacted] and [redacted]) are classified as WHO-UMC Causality Conditional "because the vaccine type was not specified".

Because the vaccine type is now specified (in the Ota paper) the MAH is requested to confirm the origin of these 3 cases ([redacted], [redacted] and [redacted]) and to reclassify their causality status accordingly. This request should be addressed in the next PSUR.

7.5. MAH's response to request no 5: Mechanical urticaria

Request to MAH:

A. The MAH stated that 363 literature articles were identified in the literature search, however only 161 articles are described by the MAH. This discrepancy should be clarified within the current procedure.

B. The MAH is, within this procedure, requested to provide the literature review again and to be clear in how many case reports concerning Spikvax and mechanical urticaria or dermatographism that were identified in the literature review.

C. The MAH is requested, within this procedure, to provide an overview of the co-occurrence of mechanical urticaria/dermatographism and chronic urticaria for all cases with reported mechanical urticaria/dermatographism. The MAH should discuss potential underreporting as cases reported as "urticaria" with a prolonged course of >6 weeks, may not have been updated as chronic urticaria in the reporting system.

Response from MAH:

A. The MAH identified the articles during literature review as follows: the search strategy implemented was broad and captured articles using the term "urticaria" in relation to the safety of mRNA-1273 (SPIKEVAX) or similar vaccines. This search yielded 363 articles. After review of abstracts and titles, 202 articles (mostly regarding skin manifestations following COVID-19 infection [without vaccination] or skin manifestations following vaccines other than mRNA COVID-19 vaccinations) were excluded. Thus, 161 articles with information describing skin manifestations (including urticaria) occurring after vaccination with an mRNA COVID-19 vaccine underwent full length review. These 161 articles mostly described generalized urticaria in relation to SPIKEVAX. Only five articles specifically described mechanical urticaria or dermatographism. Five case reports were generated from these articles. These 5 case reports were included in the mechanical urticaria case listings and were medically reviewed. These 5 articles are summarized in (B) below.

Rapporteur assessment comment:

Out of the in total 363 articles, 202 articles were excluded. The exclusion criteria are not entirely clear, but "mostly regarding skin manifestations following COVID-19 infection [without vaccination] or skin manifestations following vaccines other than mRNA COVID-19 vaccinations". Thus, 161 articles were identified with information describing skin manifestations (including urticaria) occurring after vaccination

with an mRNA COVID-19 vaccine.

The MAH has clarified the discrepancy in the numbers of publications retrieved and presented, issue resolved.

B. Cumulatively, 5 case reports have been identified in the literature concerning SPIKEVAX and mechanical urticaria or dermatographism. These 5 case reports identified in the literature describing SPIKEVAX and mechanical urticaria or dermatographism matched the 5 case reports captured in the MAH's Global Safety Data Base. The case report IDs, literature citations, and summaries for each case report are provided below:

[redacted]:

Wolfson AR, Freeman EE, Blumenthal KG. Urticaria 12 days after COVID-19 mRNA booster vaccination. JAMA. 2022;327(17):1702-3

This article presented a case report describing a 27-year-old female, with no medical history of atopy, urticaria, angioedema, or food/drug allergies, who experienced pruritic wheals on her face and bilateral, transient eyelid swelling 12 days after receiving a booster of SPIKEVAX. Over the next week a pruritic rash spread over neck, chest, trunk, and arms; each lesion faded without scarring within 24 hours. Application of pressure to her forearm in a circular motion using a pen cap elicited wheal and flare lesions.

[redacted]:

Strahan A, Ali R, Freeman E. Chronic spontaneous urticaria after COVID-19 primary vaccine series and boosters. Jaad Case Reports. 2022; 25:63–6.

This article presented a case report which describes a 24-year-old female, with no previous history of atopy or urticaria, who experienced urticaria (migratory, pruritic wheals with surrounding erythema and significant dermatographism) on her face, upper and lower extremities, chest, back, and abdomen 12 days after receiving the third dose of SPIKEVAX (Original). She experienced pruritus without rash after Dose 1 of SPIKEVAX (Original) which intensified after Dose 2 and persisted until booster. Signs and symptoms were adequately managed with oral antihistamine (fexofenadine).

[redacted]:

Amjad MA, Hamid Z, Ochieng P, Li S. COVID-19 Vaccine Booster-Induced Dermatographism. *Cureus*. 2022;14(7): e26566. Published 2022 Jul 5. doi:10.7759/cureus.26566

This article presented a case report which describes a 31-year-old male who experienced itching and raised wheals in his bilateral forearms, thighs, and ankles (for 1 week) which occurred 2 weeks after receiving a booster dose of SPIKEVAX. Clinical examination displayed a positive Darier sign (In less than one minute, wheal and flare lesions appeared on his right forearm after a gentle tongue depressor stimulation). Signs and symptoms were adequately managed with a prednisone taper and oral antihistamine (cetirizine).

[redacted]:

Drivenes J L, Bygum A. Chronic spontaneous urticaria after COVID-19 vaccination. The Journal of the Danish Medical Association. 2022;184(25): V71130.

This article presented a case report which describes a young woman who experienced severe recurrent outbreaks of urticaria for 2 months (both spontaneously and when touching skin) beginning 1 week after vaccination with the third dose of SPIKEVAX. Clinical examination showed diffuse urticarial dermatographism on extremities. The patient was diagnosed with chronic spontaneous urticaria and urticarial dermographism.

[redacted]:

Anvari S, Samarakoon U, Fu X, Jaggers J, Gonzalez-Estrada A, Chong HJ, et al. Urticaria and/or angioedema secondary to mRNA COVID-19 vaccines: Updates from a United States case registry. Allergy. 2022;00: 1-4

This article featured a Letter to the Editor which presented a study describing events of urticaria and angioedema which occurred after COVID-19 vaccination. A case report was created in Argus in response to a photograph with caption in Figure 1 of the article which provided an example of generalized urticaria and dermatographism following Dose 2 of SPIKEVAX (Original). No other information was reported.

During the PBRER 4 reporting period, the MAH observed that the pattern of events of mechanical urticaria presented following the bimodal distribution previously described for urticarial events in general. Events of mechanical urticaria frequently occurred in the post- vaccination window of 0-6 days and then again in the post-vaccination window of days 7 to 13; more often after Dose 3 of SPIKEVAX (Original). Four of the five articles presented above describe events occurring after Dose 3 within that 2-week post-vaccination window. The MAH will continue to monitor this pattern using routine post market safety surveillance.

The rapporteur cited 6 other references concerning dermatographism following SPIKEVAX administration.

Two of these articles described case reports ([redacted] and [redacted]) that were included in the PBRER 4 review:

Strahan A, Ali R, Freeman E. Chronic spontaneous urticaria after COVID-19 primary vaccine series and boosters. Jaad Case Reports. 2022; 25:63–6.

Amjad MA, Hamid Z, Ochieng P, Li S. COVID-19 Vaccine Booster-Induced Dermatographism. *Cureus*. 2022;14(7): e26566. Published 2022 Jul 5. doi:10.7759/cureus.26566

One reference was from a Moderna clinical trial:

Drivenes JL, Banerji A, Bygum A. Delayed onset urticaria and symptomatic dermographism following COVID-19 booster vaccination: A case series. *Clin Transl Allergy*. 2022;12(11): e12206. doi:10.1002/clt2.12206

One article was from AIMS Press, which is not fully indexed in Moderna's literature search databases, however this journal is being added to the Moderna's literature search list of journals. Case MOD-2023-726948 has been created for this article.

DOI: 10.3934/Allergy.2022003 – publ. 17 Feb 2022. Migratory dermatographic urticaria following COVID-19 vaccine booster in young adult male

This article presented a case study which illustrates a delayed, chronic, and spontaneous reaction to a booster of SPIKEVAX (Original). A male in his mid-20's with a medical history of spontaneous urticaria and family medical history of recurrent spontaneous urticaria, experienced mild urticaria on his face 1 week after receiving his booster dose. Eleven days after the booster the patient began experiencing a diffuse, spontaneous rash around his neck, upper back, inner groin, hands, and feet along with maculopapular wheels on his right elbow. The rash continued to spread globally and lasted approximately 90 minutes in each location before migrating. Dermatographia was noted on physical exam.

Two articles contained case reports ([redacted], [redacted]) that were created after the PBRER 4 reporting period and will be included in Moderna's post market safety surveillance and in PBRER 5.

Malcolm TR, Shah YB. Woman with pruritic rash and dermatographism. *J Am Coll Emerg Physicians Open*. 2022;3(2): e12709. Published 2022 Mar 24. doi:10.1002/emp2.12709

This article presented a case report ([redacted]) which describes a 34-year-old female who experienced diffuse urticaria and dermatographism ten days after receiving an unspecified dose of SPIKEVAX booster. The patient reported persistent symptoms at Day 23 despite low dose prednisone and oral antihistamine therapy. On Day 42, the patient was diagnosed with chronic spontaneous urticaria and prescribed omalizumab.

Please Note: *This article was made available to the MAH's literature repository (Read Cube) on 13 March 2023 as the MAH transitioned to an in-house service for literature review. This article has been reviewed and will be included in PBRER 5 (DLP 17 June 2023)*

Co M. Delayed Onset of Symptomatic Dermatographism following COVID-19 mRNA Booster. J Allergy Clin Immun. 2023;151(2): AB167.

This article presented a case series which included a case report ([redacted]) depicting an individual of unknown age and gender who experienced mechanical urticaria (dermatographism) at an unknown time following a booster with SPIKEVAX. No other information was reported.

Please Note: *The initial receipt date of this case report in Argus was 18 February 2023. The article was made available to the MAH's literature repository (Read Cube) on 27 February 2023. The article has been reviewed and will be included in PBRER 5 (DLP 17 June 2023).*

Rapporteur assessment comment:

The MAH has identified 5 case reports in the literature concerning SPIKEVAX and mechanical urticaria or dermatographism, and these have been captured in the MAH's Global Safety Data Base.

In addition, the MAH has considered the 6 references brought to attention by the assessor in the preliminary assessment report (not to be considered a complete list of references); of these, two were already captured by the MAH in the MAH's Global Safety Data Base.

Comments regarding the MAH retrieval of the remaining 4 publications:

The publication by Drivenes et al (doi:10.1002/clt2.12206) is claimed by the MAH to be a Moderna clinical trial, which is unexpected and not likely, as there is no such information in the paper/section on conflict of interest or funding sources. **The MAH should comment upon the paper by Drivenes et al (doi:10.1002/clt2.12206) in the next PSUR, both on the content regarding Spikevax and occurrence of urticaria-related events, in particular the events concerning chronic urticaria, and to explain the stated relationship to a Moderna clinical trial.**

In the case series by Drivenes, there are **11 described cases of dermatographism after Moderna booster**; 10 cases after 7-14 days after vaccination, and 1 case 21 days after vaccination.

The two papers by Maiella et al., (10.3934/Allergy.2022003) and Malcolm et al (doi:10.1002/emp2.12709), both of which were published in 2022, have not previously been identified by the MAH, which raises concern regarding the MAH literature retrieval procedures. It is noted that the MAH has not retrieved any other publication than the ones presented by the assessor in the preliminary assessment report (which was highlighted to be a non-complete list). **The MAH is requested to review their internal literature retrieval processes and to ensure that any publications published prior to the reporting interval, which have been missed in previous literature screenings, are included in relevant reviews in the next PSUR.**

From the abstract by Co (https://doi.org/10.1016/j.jaci.2022.12.521), the MAH mentions "A case report". However, from the abstract, it is evident that **11** patients had received the Moderna booster 1-2 weeks prior to onset of dermatographism.

Additional publications

It should be noted that there are additional publications concerning Spikevax and mechanical urticaria which have not been considered by the MAH.

Bianchi et al (doi: 10.1111/dth.15680) describe an italian case series where patients with delayed urticaria occurring at least 4 h after the **third dose** of mRNA COVID-19 vaccine were prospectively collected in January-February 2022. 23 patients developed urticaria from 2 to 21 days (mean latency time: 9.7 days) after the third dose of COVID19 mRNA vaccine **with marked dermographism** and intense itch. Of those, **21 patients** had received **Moderna** mRNA-1273 vaccine.

The MAH has observed that the pattern of events of mechanical urticaria presented following the bimodal distribution previously described for urticarial events in general. Events of mechanical urticaria frequently occurred in the post- vaccination window of 0-6 days and then again in the post-vaccination window of days 7 to 13; more often after Dose 3 of SPIKEVAX (Original). *These observations are agreed upon*. Also, in the publications not mentioned by the MAH, the pattern is similar. In the three case series by Drivenes et al, Co, Bianchi et al., dermatographism is observed to occur with a delayed onset of up to 21 days after the booster administration of Moderna.

The pattern of occurrence is similar to what has been observed for urticaria, and a similar pathomechanism is likely. The significant consistent pattern of occurrence with a delayed onset across different countries further strengthens the observation.

C The MAH appreciates the clarity of the request and has adjusted its review accordingly.

The MAH reviewed cases of mechanical urticaria/dermatographism through PBRER #4 to identify those cases where co-occurrence of chronic urticaria was reported (PT Urticaria chronic or PT Chronic spontaneous urticaria) and to identify those cases where chronic urticaria was not reported per se, however information in the report may suggest co- occurrence of chronic urticaria.

The MAH queried the Global Safety Data Base (GSDB), cumulatively (18 December 2020 - 17 December 2022) for valid case reports received from HCP, HA, consumers, and literature worldwide reported for elasomeran and Moderna's bivalent COVID-19 vaccines (SPIKEVAX Bivalent .214 [Original/BA.1] and SPIKEVAX Bivalent .222 [Original/BA.4/5]). The search strategy used to identify cases of mechanical urticaria included the MedDRA PT "Mechanical urticaria".

To assess potential underreporting of chronic urticaria in cases reported as "urticaria", the MAH identified cases for individual review by excluding those cases reporting co-occurring Urticaria chronic or Chronic spontaneous urticaria and selecting the remaining cases of co- occurring Urticaria for further review. Of the 466 reports of mechanical urticaria, 44 contained events of Urticaria chronic or Chronic spontaneous urticaria (subset chronic urticaria) and 53 contained events of urticaria without co-occurring Urticaria chronic or Chronic spontaneous (subset possible chronic urticaria).

The 44 cases (6 serious) in which chronic urticaria was captured involved 29 (66%) females and 15 (34%) males and originated predominantly from health authorities (37, 84%). The 53 cases (9 serious) in which possible chronic urticaria was identified involved 25 (47%) females and 28 (53%) males and similarly were predominantly from health authorities (45, 85%). No cases had a fatal outcome. In all reports except [redacted] (presented below), the criteria for seriousness were disability or medically significant without hospitalization or evidence of disability. Most reports contained minimal

information and lacked details such as medical history, concomitant medications and clinical course necessary to conduct a proper evaluation.

In the 44 reports of chronic urticaria, the majority of cases did not provide a time course to objectively quantify the duration of the urticaria. The classification of urticaria as chronic is based on the reported event. Of the 53 cases of possible chronic urticaria, 51 were taken to be chronic because urticaria was reported as ongoing at the time of the report (report date > 6 weeks beyond event date) rather than due to a quantitative time course reported. Based on such assumptions, the approximate duration of urticaria ranged from 2 months to 9 months. Two cases reported as urticaria specified a duration of urticaria as ongoing 6 months after dose 3 ([redacted]) and lasting >6 weeks after dose 3 ([redacted]). Both are presented further below.

By dose, 4 reports of possible chronic urticaria occurred after dose 1, 4 reports of chronic urticaria and 6 reports of possible chronic urticaria occurred after dose 2, 25 reports of chronic urticaria and 26 reports of possible chronic urticaria occurred after dose 3. There were 32 reports having no dose reported. The MAH notes the apparent prevalence towards the co-occurrence after dose 3, however the cases are poorly documented and small in number to draw further conclusions.

The MAH discusses the following reports due to their medical relevance.

[redacted] is a consumer report (subsequently medically confirmed) concerning a 56-year-old female with an extensive medical history including idiopathic chronic hives, dermatographism, angioedema, asthma, multiple allergies who was taking multiple medications (including cetirizine, fluticasone, triamcinolone, alprazolam, others) and who experienced same day non-serious mechanical urticaria and urticaria (covered in hives) following dose 1 mRNA-1273 with angioedema (medically signifcant) developing one month later. At the time of the report (~2.5 months later), chronic hives, angioedema and dermatographism had not resolved. Based on the temporal association, a causal association is possible, however the co-occurrence of events likely represents the spectrum of urticaria in a patient with a significant history of allergic and dermatologic conditions. No further conclusions can be drawn with regards to co-occurrence of the events.

[redacted] is a regulatory authority case from a consumer describing same day urticaria and dermographism in a male of an unknown age who received third dose of mRNA-1273. He had urticaria with no visible improvement for 6 weeks. Treatment included Antihistamine medication and avoidance of skin contact. The patient reported that the urticaria was still active 6 months after vaccination and itches and burns. No further information was provided. While there is a temporal association, the case is lacking important information for proper assessment including complete medical history, concomitant medications, diagnostic evaluation and details of clinical course. No further conclusions can be drawn with regards to co-occurrence of the events.

[redacted] is a regulatory authority report from a consumer concerning a 35-year- old male who experienced mechanical urticaria and urticaria approximately 10 days after dose 3 mRNA-1273. There was pronounced stinging nettles even with minimal touching which could occur all time of the day. still symptoms. Duration was reported as over 6 weeks and the events were reported as resolving. While there is a temporal association, the case is lacking important information for proper assessment including complete medical history, concomitant medications, diagnostic evaluation and details of clinical course. No further conclusions can be drawn with regards to co-occurrence of the events.

[redacted] is a health authority report of a 42-year-old female with no relevant medical history who experienced serious urticaria chronic, skin reaction, mechanical urticaria, chills, and diarrhoea 9 days after dose 3 as a booster of mRNA-1273 with previous vaccination schedule described

as only dose 2 mRNA-1273. Nine days after vaccination with dose 3, the patient went to the emergency room due to a skin rash interpreted as a "stage II allergic reaction to an unidentified allergen." Two days later the patient went back to ER for worsening symptoms with workup ultimately suggesting "allergic reaction of grade I on an unclear allergen" with a differential diagnosis of food (fish) poisoning. At the allergy assessment 1 month, 16 days after the onset, the clinical picture of the patient was interpreted as an associated urticaria to a red dermatography (urticaria factitia). She was prescribed high-dose antihistamine (desloratadine 5 mg 3x/day) for approximately one month. On a follow- up two months later, the patient had a "chronification of the urticaria."

***MAH Comment*:** While a causal association is possible based on the temporal association following booster dose 3, the events were more likely caused by the suspected food allergy.

[redacted] is a case from a series of a young woman who experienced mechanical urticaria and severe recurrent outbreaks of chronic spontaneous urticaria for 2 months (both spontaneously and when touching skin) beginning 1 week after vaccination with the third dose of SPIKEVAX (Original). Clinical examination showed diffuse urticarial dermatographism on extremities. The patient was diagnosed with chronic spontaneous urticaria and urticarial dermographism. No further information was provided for this case in the series report. While there is a temporal association, the case is lacking important information for proper assessment including complete medical history, concomitant medications, diagnostic evaluation and details of clinical course. No further conclusions can be drawn with regards to co-occurrence of the events.

[redacted] is a case report from a series which describes a 34-year-old female who experienced diffuse urticaria and dermatographism ten days after receiving an unspecified dose of SPIKEVAX booster. The patient reported persistent symptoms at Day 23 despite low dose prednisone and oral antihistamine therapy. On Day 42, the patient was diagnosed with chronic spontaneous urticaria and prescribed omalizumab. While there is a temporal association and a causal association is possible, no further conclusions can be drawn with regards to co-occurrence of the events.

[redacted] is a case report of a male in his mid-20s with a history of multiple allergies, spontaneous urticaria and family history of recurrent spontaneous urticaria, who experienced dermatographia and urticaria two weeks after receiving a booster dose of mRNA-1273. The patient did not have any immediate reactions to the first dose, second dose, or booster except for mild headache and arm. Eleven days post-booster, the patient began experiencing a diffuse, spontaneous rash around his neck, upper back, inner groin, hands, and feet along with maculopapular wheels on his right elbow. He denied changes to diet and exposure to environmental or food allergens in the previous six months. The patient was advised to begin oral cetirizine, which significantly decreased global eruptions; however, as cetirizine dose began to cease, spontaneous urticaria would continue to occur. Based on the temporal association, a causal association is possible, however the patient tolerated two doses of mRNA without similar reactions and given the patient's significant history of urticaria, it is possible that other causative agents may be involved.

Discussion

Cumulatively, there were a total of 466 cases of mechanical urticaria through PBRER #4. The MAH further evaluated these reports to characterize the co-occurrence of chronic urticaria and potential underreporting in cases where urticaria alone, without time course, was reported. Of the 466 cases of mechanical urticaria, 44 reported chronic urticaria and 53 were suggestive chronic urticaria. Most of the 97 reports were received from health authorities where follow-up with the original reporter is not possible due to privacy restrictions. Furthermore, reports transmitted from health authorities are received into the GSDB with prepopulated structured data fields such as event date and outcome.

In the 44 reports where chronic urticaria was reported as a co-occurring event with mechanical urticaria, a small number of reports did provide a duration > 6 weeks indicating chronic urticaria, however the provided information was insufficient to assess causality beyond a temporal association and precluded evaluation of co-occurrence.

In the 53 reports suggestive of chronic urticaria, only two included information describing urticaria > 6 weeks in duration and these lacked adequate information to make a proper assessment. The remaining 51 cases were also generally poor documented and suggestion of chronic urticaria was based on inference and assumption involving event date and case receipt date, and thus are insufficient to establish a diagnosis of chronic urticaria and to assess causality.

Review of 97 reports considered as mechanical urticaria with co-occurrence of chronic urticaria does not suggest underreporting of chronic urticaria. The MAH notes a prevalence of co-occurrence after dose 3, however the cases are uninformative, and are based on urticaria reported as chronic without a specified duration, or are assumed to be chronic. The MAH considers this review to provide insufficient evidence to characterize a compelling pattern of co-occurrence.

Rapporteur assessment comment:

The MAH has provided an adjusted review on the co-occurrence of mechiancal urticaria and chronic urticaria. Out of 466 reports, 44 contained events of Urticaria chronic or Chronic spontaneous urticaria (subset chronic urticaria) and 53 contained events of possible chronic urticaria (coded as urticaria but reported to be ongoing for >6 weeks).

Mechanical/inducible urticarias are commonly co-occurring in patients suffering from chronic urticaria; according to UpToDate, inducible urticarias are present in 20 to 30 percent of adults with chronic urticaria.

In the data regarding Spikevax, mechanical urticaria is co-reported with chronic urticaria in 97/466 reports (~21%); hence, a large proportion of cases with mechanical urticaria occurs as an entity on its own and not as part of an episode of chronic urticaria.

Rapporteur overall conclusion:

The MAH has presented responses to the requests for supplementary information regarding mechanical urticaria/dermatographism.

The literature review provided by the MAH is of poor quality; several relevant articles have not been presented, and only after being highlighted by the assessor in the preliminary assessment report, these publications were added to the MAHs database.

The pattern of occurrence of mechanical urticaria/dermatographism is highly similar to the pattern occurrence of urticaria. Both have primarily been reported after the booster administration and with a delayed onset of up to two weeks after administration.

In total, the MAH has identified 466 case reports of mechanical urticaria in the MAH Global safety database, and at least 50 cases have been identified from the scientific literature, showing a striking similarity in pattern of occurrence across reporters and countries.

The duration of the events varies from shorter duration up to treatment-requiring chronic urticaria.

In Eudravigilance, the ROR rose in the first quarter of 2022, (concurrent with the booster

administrations), and the ROR(-) shows a signal of disproportionate reporting at 7.85 (May 2023)

Notably, mechanical urticarias are likely underreported, as these are typically events of less severity, and also as the events "injection site urticaria" and "urticaria" are known to be associated with Spikevax.

In contrast to urticaria, the subgroup mechanical urticaria/dermatographism occurs only following a physical stimulus such as a scratch on the skin.

Urticaria is listed in the SmPC section 4.8, frequency Uncommon, whereas Mechanical urticaria is not listed.

Based on the totality of data, an association between Spikevax and mechanical urticaria is considered at least a reasonable possibility, and it is considered warranted to amend the product information to add the PT Mechanical urticaria. See section 3 for further details.

7.6. MAH's response to request no 6: Myocarditis

Request to MAH:

A. The MAH presented results from a case-control study which finds an increased risk of myocarditis for the 3rd dose compared with the 1st dose, but with a lower incidence than for 2nd dose. However, the PRAC rapporteur could not identify these results online (Ref 29. Epi-Phare. Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France Study based on data from the National Health Data System (SNDS).). The MAH is requested in the current procedure to point directly to where these study results can be found. The provided information will be taken into consideration for the update of the SmPC/PIL text when the PRAC rapporteur has been presented to the results in details.

B. The MAH is requested to comment on the suggested PI changes to the text concerning risk of myocarditis (please, see section 3 of this AR).

C. In the subpopulation analysis of children < 18 years, the MAH presented a 14-year-old male considered with BC level 2 myocarditis ([redacted]). This case was neither included in the present PSUR section of new information on myocarditis nor in the PSUR appendix 11.5 myocarditis/pericarditis. The MAH is requested to clarify this discrepancy in the current procedure and once more the MAH is requested to be thorough and precise in the presentation of data.

Response from MAH:

A. The MAH recognizes the discrepancy between the reference provided with the actual reference for this study. The appropriate reference is attached to this response:

Le Vu S, Bertrand M, Jabagi MJ, et al. Covid-19 messenger RNA vaccines and risk of myocarditis: effects of the third dose and the delay between doses. EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM. July 22, 2022. www.epi-phare.fr

B. The MAH will update the SmPC concerning the risk of myocarditis as recommended by the PRAC.

C. The MAH recognizes the oversight of providing information on this case of myocarditis in a 14-year-old in the current PBRER. Given that this is a regulatory report and the only term included in the report was "chest pain", the report would have not been included in the cases reporting myocarditis or pericarditis based on the search strategy implemented by the MAH, hence the case would had not been included in

the mentioned appendix. The case was identified during an additional evaluation of cases that the MAH has implemented within the subpopulation of adolescents 12 to 17 years old presenting any symptoms associated with myocarditis or pericarditis, including chest pain.

[redacted]**- (WWID:**[redacted]**)** concerns a 14-year-old male with no medical history reported, who experienced pyrexia and chest pain 1 day after mRNA-1273.222 as dose 4. Patient reportedly was admitted for complaints of chest pain, chest distress, suspected cardiogenic chest pain with pain index 8 points. Troponin value was slightly elevated on the first day and back to normal values afterward. CPK was elevated with other labs unremarkable. An EKG was performed and reported as abnormal but actual results were not provided. After one day patient was transferred to another hospital and discharged within 3 days with chest pain reported as resolved.

Company Assessment: According to the Brighton Collaboration case definition this case is considered Level 2. According to the CDC case definition this case is considered Probable, and according to the WHO causality assessment this case is considered possible. The report is lacking important information including medical history, concomitant medications, and actual EKG results.

Rapporteur assessment comment:

a) For the ref 29 (a matched case-control study which finds an increased risk of myocarditis for the 3rd dose compared with the 1st dose, but with a lower risk for the 3rd dose compared with the 2nd dose), the MAH recognizes the discrepancy between the reference provided with the actual reference for this study. The MAH provided an updated reference as follows: Le Vu S, Bertrand M, Jabagi MJ, et al. Covid-19 messenger RNA vaccines and risk of myocarditis: effects of the third dose and the delay between doses. EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM. July 22, 2022. www.epi-phare.fr

Furthermore, the MAH stated "The appropriate reference is attached to this response." The reference has not been identified by the PRAC rapporteur. However, a MS has provided a link to a French version: https://www.epi-phare.fr/rapports-detudes-et-publications/myocardite-rappel-vaccin-covid19/

This matched case-control study embedded in the French National Health Data System (SNDS) and several other data source (EPI-PHARE) of 4890 myocarditis cases and 10 times controls provides information on the risk of myocarditis in relation to dose, age and sex. The pattern in the results in relation to age and sex, as well as in relation to dose 1 and dose 2 are similar to what is already known, and also the results in relation to the type of mRNA vaccine. In relation to dose 3 the risk pattern shows an elevated risk higher than the risk associated with dose 1. The results also show that the risk of dose 3 (OR= 4.1, 95% CI 2.5-6.6) is lower than that associated with dose 2 (OR=19, 95% CI 14-25). When stratified by sex the risk pattern is consistent. For age 30+ the risk pattern is also consistent, for the 12-29-year-olds, there were not sufficient cases to estimate OR for dose 3. The results also indicated that when the time period between doses increased, the OR generally decreased. If the risk of myocarditis is driven by susceptibility in certain vaccinees, and those susceptible myocarditis cases that had myocarditis following dose 2, do not receive dose 3 (and an additional myocarditis), then this might have contributed to a lower risk associated with dose 3. However, this is not expected to explain the large difference in the risk associated with dose 2 and dose 3.

Based on these results from a large register-based study, where the results on known parameters (age, sex, type of mRNA vaccine, and dose 1/dose 2) are identical with the risk characterisation, the PRAC rapporteur suggests to revise the current SmPC wording in relation to dose, which currently states that the risk profile appears to be similar for the second and the third dose. Please see section 3. Recommendations.

b) The MAH suggested changes to the SmPC and PIL wording in the PI as highlighted in yellow below.

"SmPC text

There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax.

These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days after vaccination. They have been observed more in younger males, and more often after the second dose compared to the first dose (see section 4.8). The risk profile appears to be similar for the second and the third dose.

Available data indicate that most cases are mild and recipients tend to recover within a short time. Some cases require intensive care support and fatal cases have been observed. Data also indicate that the short term (≤3 months) course and outcome of myocarditis and pericarditis following vaccination is milder and less severe than myocarditis or pericarditis in general.

PIL text

These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days after vaccination. They have been observed more often in younger males, and more often after the second dose compared to the first dose.

Most cases of myocarditis and pericarditis are mild and individuals tend to recover within a short time. Some cases require intensive care support and fatal cases have been seen. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur."

Please see the final suggestion for PI wording in section 3. Recommendations.

c) The MAH recognizes a discrepancy in the reporting of the 14-year-old case of myocarditis in the subpopulation of children but not in the section of myocarditis. The MAH explains that terminology in the narrative is the root cause of this discrepancy. The MAH is reminded to be responsible for the pharmacovigilance system and make sure that this system captures relevant cases. A case of myocarditis in a 14-year-old is important to report in relevant settings. The MAH is reminded to make sure, that this myocarditis case is captured in future searches of myocarditis.

The MAH presented the case and was evaluated to be BC level 2. It was noted that the case lacked information concerning medical history, concomitant medications, and actual EKG results. This is endorsed.

7.7. MAH's response to request no 7: Single organ cutaneous vasculitis (SOCV)

Request to MAH: The MAH is requested within the current procedure to give full reference to and comment on any new articles (compared to PSUR#3) considered among the 47 publications cumulatively referred to.

Response from MAH:

As noted in PBRER #4, total of 47 literature articles were retrieved for the review period (see Appendix 2 for full list of references). It was further clarified that PBRER #3 and PBRER #4 each had 47 literature

articles retrieved which were different in each report. All 47 articles in PBRER #4 were new and different from the 47 articles identified in PBRER #3.

The PBRER # 4 literature search results were medically/scientifically reviewed. Most of these 47 articles were case reports presenting data on adverse cutaneous reactions or other conditions such as immune-mediated thrombotic thrombocytopenic purpura or thrombocytopenia. Review of these retrieved literature articles describe the occurrence of SOCV with COVID-19 vaccination but none of these provided compelling evidence of a causal association from mRNA vaccines.

Overall, a review of the literature for PBRER # 4 identified no articles with new and significant safety information.

Rapporteur assessment comment:

The rapporteur acknowledges the clarification and the MAH's evaluation of the 47 new articles on cutaneous reactions related to COVID-19 vaccination of which none provided new and significant safety information. This included all cases identified with SOCV.

Issue resolved. No further actions are required.

7.8. MAH's response to request no 8: RMP

Request to MAH:

A. The MAH is requested to provide an updated RMP according to the PRAC Rapporteur's comments on the safety specification.

B. In the pharmacovigilance plan, the MAH updated study milestones for studies mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901. As these changes were not previously agreed with the Rapporteur, the MAH is requested to provide a justification for the changes of milestones for each of these studies within this procedure.

C. Regarding the proposal to remove the missing information 'use in immunocompromised subjects' from the RMP, the MAH is requested to present (interim) data from additional pharmacovigilance activities addressing this safety concern (P304, P904 and P903). As the data from literature regarding safety was limited to one relevant epidemiological study, the MAH should also consider a comprehensive cumulative review of the literature. Moreover, if the evidence indeed supports the removal of this safety concern in the RMP, this should be reflected in the product information accordingly. Therefore, the MAH is also requested to propose an update of the wording in SmPC section 4.4 regarding the safety of Spikevax in immunocompromised individuals if considered applicable.

Response from MAH:

A. The MAH is submitting an updated RMP with this response. The current approved EU-RMP is version 6.5 (EMEA/H/C/005791/II/0097/G (grouped variation including extension of indication to include a 25 µg booster dose of Spikevax bivalent Original/Omicron BA.4-5 (12.5 µg elasomeran /12.5 µg davesomeran) in children aged 6 through 11 years of age) approved on 26/05/2023. The MAH has submitted two other EU-RMPs, RMP v6.7 on 18/04/2023, and this new revised version 7.0.

   The MAH would like to propose the integration of EU-RMP 6.5 with v6.7 and with this revised version 7.0, in order to harmonize all the available information for the elasomeran, elasomeran/ imelasomeran, and elasomeran/davesomeran vaccines.

Rapporteur assessment comment:

The MAH provided an updated RMP according to the assessment comments reflected in section 3. The changes made are acceptable. Furthermore, the MAH proposed to integrate RMP version 6.5 with 6.7 and the revised version 7.0. However, RMP version 6.7 is not yet approved and there are outstanding issues to be addressed in the ongoing procedure EMEA/H/C/005791/II/0104/G. Neverheless, the MAH's proposal to provide a consolidated version of the RMP to harmonize all the available information for the elasomeran, elasomeran/ imelasomeran, and elasomeran/davesomeran vaccines is acknowledged. Therefore, upon finalisation of procedure EMEA/H/C/005791/II/0104/G, the MAH is should submit a consolidated version of the RMP reflecting the agreed changes from the respective procedures for information.

Conclusion

The updated RMP version 7.0 is acceptable.

B. The MAH is providing below a justification for each changes in the mentioned above study milestones:

Final CSR date for the study mRNA-1273-P301 has been changed from 30-06-2023 to 19-12-2023.

The need to change the dates were pre-discussed with EMA PV contact lead and was endorsed to include it in PSUSA/00010897/202212 for evaluation. However, since Moderna realized that we were submitting variation EMEA/H/C/005791/II/0104/G before and the outcome of the PSUSA would come later than the need to submit the final CSR putting Moderna in non-compliance, we submitted also with the next regulatory opportunity. However, Moderna missed to add the rationale for asking an extended due date which is that, although the last subject las visit (LSLV) was performed as scheduled on December 22, 2022, it will take much longer than anticipated to obtain the data from the longer-term immunogenicity samples analysis. This delay to obtain the data is due to limited vendor capacity that arise with the emergence of new variants of concern over the past 1.5 years. This led to a massive increase in samples generation overwhelming their capacities to handle the immunogenicity-tests. As per protocol mRNA-1273-P301 (Section 4.4), "End of Study" is defined as "the final participant's final scheduled visit at Day 759 (Month 25) or Booster Dose 3 (BD-3), whichever is later. Since the End of study for P301 was Dec 22, 2022, and per EU CTR Regulation (EU) No 536/2014, "results of a clinical trial should be reported within one year from the end of the clinical trial conducted in adults, and 'end of a clinical trial' is defined as the last visit of the last subject, or at a later point in time as defined in the protocol.", the team proposes to request a change to the Final CSR due date under the RMP from June 30, 2023 to December 21, 2023.

Final CSR date for the study mRNA-1273-P205 has been changed from 31-12-2023 to 30-04-2024.

The need to change the dates were pre-discussed with EMA PV contact lead and was agreed to include it in PSUSA/00010897/202212 for evaluation. However, since Moderna realized that we were submitting the variation EMEA/H/C/005791/II/0104/G before and the outcome of the PSUSA would come later than the need to submit the final CSR putting Moderna in non- compliance, we submitted

also with the next regulatory opportunity. However, we missed to add the rationale for asking an extended due date which is that currently the date for the final CSR listed in the RMP is 31 Dec 2023. Given that we have added Part H (7th part of this study), we would like to accommodate the extra work of the additional data (study cleaning, immuno- testing, data analysis, writeup, etc) but also the same issue as above of having the immune testing handled with delay by our vendor. Ideally, for this study we would like 3 months delay with final CSR delivered by March 31, 2024.

Final CSR date for the study mRNA-1273-P304 has been changed from 31-01-2024 to 31-05-2024.

The need to change the dates were pre-discussed with EMA PV contact lead and was agreed to include it in PSUSA/00010897/202212 for evaluation. However, since Moderna realized that we were submitting the variation EMEA/H/C/005791/II/0104/G before and the outcome of the PSUSA would come later than the need to submit the final CSR putting Moderna in non- compliance, we submitted also with the next regulatory opportunity. However, we missed to add the rationale for asking an extended due date which is the same as that for Study P301 end of study CSR above. Last subject las visit (LSLV) for Study P304 was projected to be in May 2023 and as such the end of study CSR is proposed to be LSLV + 12 months (aligned with EU CTR Regulation (EU) No 536/2014) as there is a delay to obtain immunogenicity sample testing data due to our vendor limited.

Further details have been added to the study mRNA-1273-P901 and the dates for two interim reports have been changes as follows: from 14-06-2023 to 30-06-2023 and from 14- 12-2023 to 20-12-2023.

The need to change the interim report dates is to be in agreement with Amendment 5 of the protocol, which includes the creation of the interim reports 2 to 4 weeks following receipt of the report by the MAH from Kaiser Permanente. This provides sufficient time for the MAH to review the information received and provide comments to Kaiser for potential revision, if needed.

Rapporteur assessment comment:

The applicant submitted a rational for requesting extended due dates for studies mRNA- 1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901 upon request.

It appears that the request for extended timelines was pre-discussed with EMA and has been agreed.

The reasons for the delay are reduced laboratory capacities to handle immunogenicity testing, and amendments to study protocols that extend the end of study time and result in the processing of extra data.

The delays range from 6 and 16 days respectively for the two interim CSRs for study P901 to a 6 months delay for the final CSR for P301. For study P205, the applicant envisaged ideally a 3-month delay with due date March 31, 2024 which would have been covered by Regulation (EU) No 536/201, but finally requests one more month for laboratory capacity reasons, which is deemed acceptable. The delayed due dates for the final CSRs for studies P301 and P304 are covered by Regulation (EU) No 536/2014.

The justification given for each delayed time point is deemed acceptable.

The new time lines can be agreed upon.

Conclusion

The issue is solved.

C. As per request from the PRAC additional information is provided here to support the removal of "use in immunocompromised subjects" from the RMP as missing information. Additionally, the MAH is providing an updated SmPC with the proposed changes for updating the wording in SmPC section 4.4 regarding the safety of Spikevax in immunocompromised individuals.

Interim data from additional pharmacovigilance activities addressing this safety concern (P304, P904 and P903).

Interim Clinical Study Report for mRNA-1273-P304 - OPEN-LABEL PART A (PRIMARY SERIES) and PART B (BOOSTER DOSE) - Safety Results (31 March 2023)

Study mRNA-1273-P304 is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in solid organ transplant (SOT) recipients and healthy participants. This was a 2-part study. Part A of the study enrolled 214 SOT recipients to receive up to 3 doses of 100 µg mRNA-1273, and 20 healthy participants to receive 2 doses of 100 µg mRNA-1273 (the healthy participant group was intended as a comparator group for SOT in the assessment of the Cell Mediated Immune responses; the vaccine-induced antibody responses in the healthy participants were also described in comparison to the SOT group). In Part A, SOT participants who were unvaccinated and those who were previously vaccinated with 2 doses of mRNA-1273 were enrolled. The primary immunogenicity objective of Part A was to evaluate serum nAb responses obtained 28 days after the second or third dose of the study vaccine.

In Part B, a 100 µg BD was administered to participants at least 4 months from the last dose of a completed primary COVID-19 vaccination series. A 100 µg BD was selected for this study due to concern about reduced antibody responses associated with chronic immunosuppression in the SOT population and the potential immune escape associated with variants of concern. SOT participants enrolled in Part A were offered a fourth (booster) 100 µg dose of mRNA-1273 in Part B, and healthy participants enrolled in Part A were offered a third (booster) 100 µg dose of mRNA-1273 in Part B. Part B also enrolled SOT participants who completed primary vaccination series with an mRNA or non-mRNA COVID-19 vaccine outside of the study: SOT participants who previously received an mRNA COVID-19 primary series vaccination, with 3 doses, received a fourth (booster) 100 µg of mRNA-1273; and SOT participants who previously received a non-mRNA COVID-19 vaccine in combination with an mRNA COVID-19 vaccine or combination of mRNA-COVID-19 vaccines received a 100 µg booster dose of mRNA-1273.

The primary immunogenicity objective of Part B was to evaluate serum nAb responses against the SARS-CoV-2 ancestral strain with D614G mutation obtained 28 days after the BD.

The analyses presented in the P304 interim report dated 31 March 2023, is based on the results from a database lock date of 22 Nov 2022. Safety follow-up after vaccination includes a median of 292.0 days (range: 37 to 406 days) from Dose 3 in SOT participants in Part A and a median of 129.0 days (range: 10 to 181 days) from BD in SOT participants in Part B.

Summary of Safety Results

- Reactogenicity after the 3-dose primary series and BD in immunocompromised participants was similar to that which has been reported for mRNA-1273 in immunocompetent participants. This is also consistent with what has been reported in other clinical trials and post-authorization use of mRNA-1273 in the general population.
- Local and systemic solicited ARs were reported within 7 days after vaccination in 85% and 80% of SOT participants, respectively, after any injection. Systemic solicited ARs, chiefly fatigue,

headache, and myalgia, were reported in fewer kidney transplant participants compared to liver transplant participants, particularly after Dose 1, although a trend was evident at all doses; this was attributed to heavier immunosuppressant and anti-metabolite treatment in kidney transplant participants.

- Unsolicited treatment emergent adverse events (TEAEs) were reported in 42.1% of SOT participants through 28 days after vaccination after any injection and were considered related to vaccination by the Investigator in 21.5% of SOT participants. The most commonly reported vaccine related events included fatigue (12.6%), headache and myalgia (6.1%, each), and arthralgia (5.6%), which were also frequently reported symptoms of reactogenicity. Other unsolicited TEAEs were largely due to underlying disease or intercurrent illness or injury in SOT participants.
- Four cases of biopsy-proven organ rejection were reported during the study, all in SOT liver participants (one involved a kidney transplant in a prior liver transplant recipient). None of the cases were considered related to vaccination and all were due to changes in immunosuppressant medications.
- Through the data cutoff date, 4 SAEs in 3 SOT participants were assessed as related to study vaccination by the Investigator. Two SAEs (worsening anemia, angina) occurred in a kidney transplant recipient on Relative Days 10 and 11 after vaccination and were considered vaccine-related by the Investigator; the Sponsor considered the events more likely attributable to underlying disease. One SAE of vomiting was reported as a solicited AR and, per protocol, considered related to vaccine, although the event was not assessed as vaccine-related by the Investigator. One SAE of AIHA occurred 4 months after Dose 2 in a participant with a concurrent COVID-19 infection; AIHA was considered possibly related to vaccine by the Investigator due to the temporal relationship of the decline in hematocrit after vaccination, although the Sponsor considered the event more likely due to pre-existing anemia.
- One AESI of non-serious myocarditis was reported on Relative Day 1 after vaccination and was assessed as related to vaccine by the Investigator; the case was adjudicated by the CEAC as not meeting the CDC definition of myocarditis. One CEAC-adjudicated case of pericarditis occurred on Study Day 122 that was attributed to an underlying inflammatory process and was not considered vaccine related by the Investigator or Sponsor.
- Two fatal events (congestive heart failure and death of unknown cause) in participants with underlying comorbidities were reported and were not considered related to vaccination.
- Laboratory shifts did not show notable trends after vaccination with mRNA-1273; shifts noted were attributed to underlying disease or intercurrent medical processes.
- Shifts in vital signs were explained by underlying disease or intercurrent medical processes. Elevation of systolic or diastolic blood pressure was the most common vital sign change and, in most participants, reflected underlying hypertension.
- No mRNA-1273 vaccine-related safety concerns were identified during the study

Safety conclusion: The 3-dose primary series and BD of mRNA-1273 were well tolerated with an acceptable safety profile in immunocompromised post-transplant population.

mRNA-1273-P904: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe

Based on results from the P904 Interim Report #4 submitted at the end of March 2023, the proportion of persons with indicators of immunocompromised status ranged from 2.2% to 6.4% among Spikevax recipients (by dose), and 2.6% to 6.7% among the historical cohort (Table 1). In Denmark, Norway and Spain, the cohort of persons receiving the third dose of Spikevax had a higher proportion of immunocompromised persons than the other cohorts. In Denmark, the Spikevax cohorts and the historical cohort had similar proportions of persons with indicators of immunocompromised status (approximately 3%).

In the UK, the Spikevax cohorts had a lower proportion of persons with indicators of immunocompromised status compared to the historical cohort (ranging from 2.2% to 2.3% among the Spikevax cohort vs. 6.7% in the historical cohort).

Table 1. Summary of Persons with Immunocompromised Status by country and cohort, from P904 Interim Report #4

Country	Spikevax recipients first dose N (%)	Spikevax recipients second dose N (%)	Spikevax recipients third dose N (%)	Historical Cohort N (%)
Denmark	15,390 (2.7%)	15,282 (2.7%)	12,986 (3.0%)	152,239 (2.6%)
Norway	13,127 (2.4%)	11,838 (2.8%)	4,405 (6.4%)	154,110 (2.8%)
Spain	21,920 (3.5%)	20,388 (3.8%)	13,946 (6.1%)	181,277 (3.2%)
UK	5,266 (2.3%)	4,282 (2.2%)	1,227 (2.2%)	632,991 (6.7%)

Note: To date, signal detection analyses have not been conducted for subpopulations, such as persons with immunocompromised status, and thus, no results were available for the Interim Report #4. However, these analyses are expected to be included for the final analysis and report.

mRNA-1273-P903: Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity

Study mRNA-1273-P903 is a retrospective, observational cohort study which uses secondary, de-identified individual-level medical and pharmacy claims data provided by HealthVerity. The study aims to contextualize the risk of myocarditis, pericarditis and other adverse events of special interest. Analyses are ongoing for study, which includes components of active vaccine surveillance via a historically controlled comparator and signal refinement using a self-controlled risk interval design. Full details of applied methods and results available to date are available in study Interim Report #8 submitted in January 2023.

Based on the results from Interim report # 8, the study cohort included 664,640 immunocompromised (IC) adults who were vaccinated with at least 1 dose of Spikevax, of which 439,878 (66.2%) received a second dose with a median dosing interval of 28 days (IQR 28, 31 days). Additionally, there were 578 IC children with at least 1 dose of Spikevax. Of these 578 individuals, 403 (69.7%) had a second dose with a median dosing interval of 28 days (IQR 28, 33 days).

Immunocompromised Spikevax recipients were slightly older than the overall population of Spikevax recipients with a higher baseline prevalence of comorbidities. For adults, the most common comorbidities were cardiovascular disease (50.1% in immunocompromised vs 29.8% general population), hypertension (42.5% vs 25.3%), obesity (12.0% vs 7.2%), and diabetes (10.4% vs. 5.1%). For children a higher burden of comorbidities in the immunocompromised was also observed (e.g., lung disease [13.8% vs 5.8%], asthma [13.7% vs 5.6%], and obesity [10.6% vs 4.7%]).

Outcomes of interest included the following:

- Myocarditis
- Pericarditis
- Anosmia/Ageusia
- Anaphylaxis
- Chilblain-like Lesions
- Cerebral Venous Sinus Thrombosis
- Coagulation Disorders
- Erythema Multiforme
- Immune Thrombocytopenia
- Narcolepsy/Cataplexy
- Thrombosis with Thrombocytopenia
- Arrhythmia
- Bell's Palsy
- Single Organ Cutaneous Vasculitis
- Seizures/Convulsions
- Gestational Diabetes
- Preeclampsia
- Preterm Labor
- Spontaneous Abortion
- Stillbirth
- Acute Aseptic Arthritis
- Acute Disseminated Encephalomyelitis
- Acute Kidney Injury
- Acute Liver Injury
- Acute Myocardial Infarction
- Acute Respiratory Distress Syndrome
- Aseptic Meningitis
- Deep Vein Thrombosis
- Disseminated Intravascular Coagulation
- Encephalitis/Encephalomyelitis
- Glomerulonephritis
- Guillain-Barre Syndrome
- Heart Failure
- Ischemic Heart Disease
- Kawasaki Disease
- Meningoencephalitis
- Microangiopathy
- Multisystem Inflammatory Syndrome
- Pulmonary Embolism
- Stroke, Hemorrhagic
- Stroke, Non-Hemorrhagic

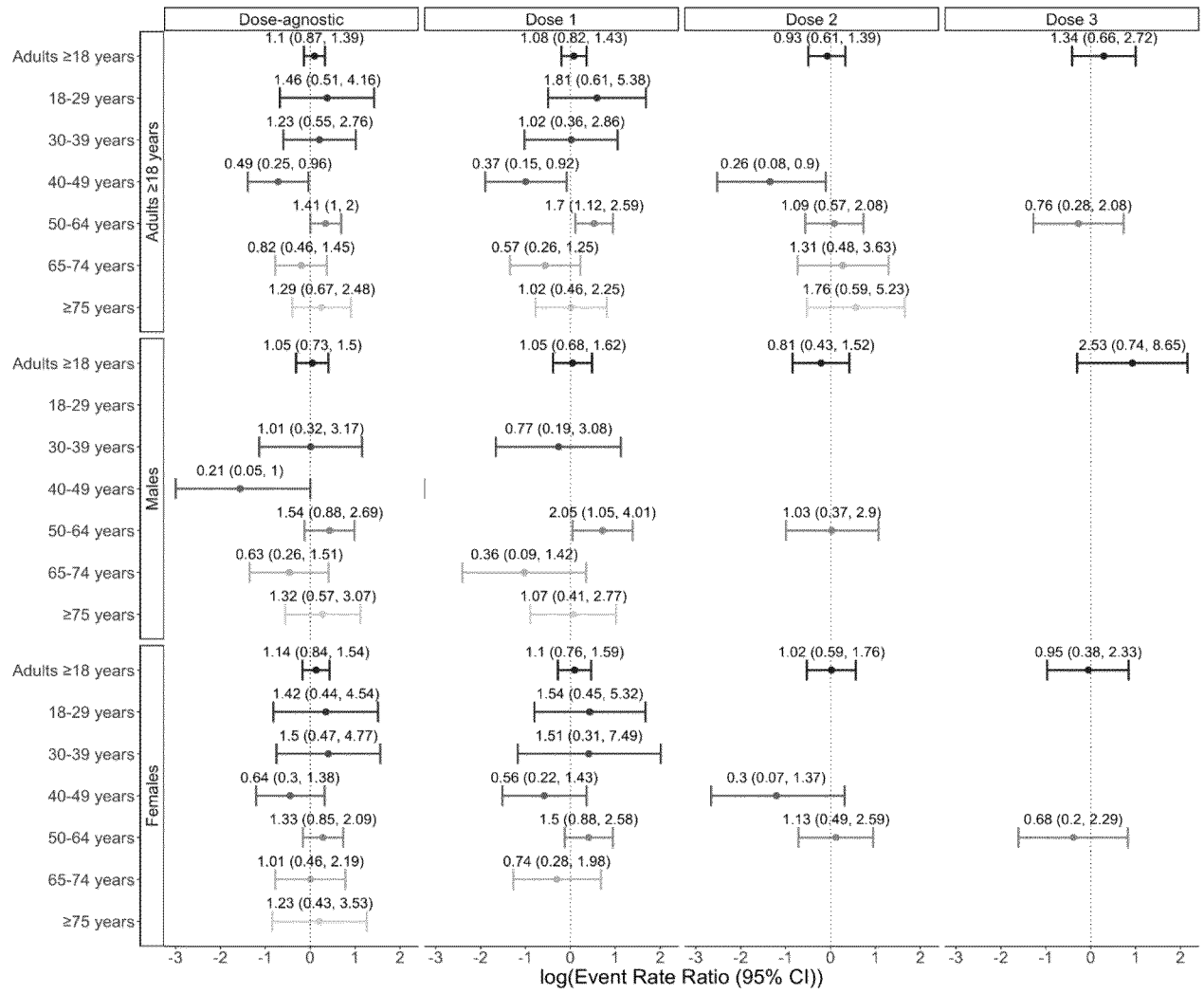
- Transverse Myelitis
- Type I Diabetes Mellitus

Per the study protocol, SCRI analysis were conducted for the AESI where the incidence rate ratio comparing individuals after vaccination is >1 with a lower bound of the 95% confidence interval >1 for observed to expected analysis vs a historical comparator. Analyses were performed only where >10 cases were observed.

For interim report #8, of the 43 pre-defined AESI, anosmia/ageusia, Chilblain-like lesions, and narcolepsy met the threshold for SCRI analysis in immunocompromised persons. Only anosmia/ageusia and Chilblain-like lesions had elevated rate ratios; all subgroup analyses for narcolepsy were consistent with the absence of association.

The results of SCRI for anosmia/ageusia among the IC adult population are shown in Figure 1. The event rate ratio (ERR)s was elevated in males 50-64 years of age, particularly following dose 1. Elevated ERR were not observed for other age/gender subgroups. Additional dose- agnostic sensitivity analysis removing the COVID-19 diagnosis censoring criteria included 818 adults. The increase in ERR was persistent in 50-64 years of age. Among the IC pediatric population, the ERR were not elevated in any of the age/gender subgroups, noting poor precision due to the small population size.

Figure 1. Event rate ratios for anosmia/ageusia among IC adults ≥ 18 years comparing risk versus control windows from SCRI analyses



*There were no estimates plotted for the specific age-strata that had infinite upper 95% confidence limits or <10 events

For Chilblain-like lesions, overall ERRs were elevated in dose-agnostic, dose 1 and dose 2 SCRI analysis, however subgroup analysis by age could not be performed due to low event counts excepting within individuals 50-64 years of age (ERR 1.41, 95% CI 0.47 - 4.23). The ERR following dose 2 (risk window = 8, control window = 2, ERR = 3.51, 95% CI 1.09 – 11.24) was higher compared to dose 1 (risk window = 15, control window = 8, ERR = 2.79, 95% CI 1.18 – 6.59), noting that both were imprecise. The ERRs were elevated in overall analyses including both males and females, however, the lower bound of 95% CI was > 1 only for subgroup analyses of males. Given low case counts, the precision of the estimate was poor with a wide 95% CI. Age-stratified and dose 3-specific analyses were not conducted given an insufficient number (<10) of cases. Also, as the number of case counts were < 10 in the pediatric population, the SCRI analysis was not conducted for IC children.

All AESI that met threshold for SCRI analysis in the IC population also met the threshold in the general population, and no new risks specific to immunocompromised persons were identified.

Final analyses including additional algorithm refinements and restriction of data to the closed claim environment will be completed for the final study report in June 2023.

Comprehensive Cumulative Review of Literature

Literature Search Methodology

A focused cumulative literature search and review was performed using PubMed of the National Library of Medicine since the IBD of Spikevax/Elasomeran through 30 April 2023. The search strategy was used to identify articles related to immunocompromised and Moderna COVID-19 vaccines included:

(((((immunocompromised[MeSH Terms])) OR (immunosuppressed[MeSH Terms])) AND (("mrna vaccines"[MeSH Terms] OR "2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "mRNA 1273"[All Fields] OR "mRNA 1273"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "mrna1273"[All Fields]) OR ("modernatx"[All Fields] OR "1273"[All Fields]) OR "1273"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "m 1273"[All Fields]) OR "m 1273"[All Fields] OR ("moderna"[All Fields] OR ("covid 19 vaccines"[MeSH Terms] OR ("covid 19"[All Fields] OR "vaccines"[All Fields]) OR "covid 19 vaccines"[All Fields] OR ("covid19"[All Fields] OR "vaccine"[All Fields]) OR "covid19 vaccine"[All Fields])) OR "moderna covid 19 vaccine"[All Fields] OR "moderna covid 19 vaccine"[All Fields] OR "moderna covid 19 vaccine"[All Fields] OR "Spikevax"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields] OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields] OR "elasomeran"[All Fields]) OR "CX-024414"[All Fields] OR "tak 919"[All Fields] OR "tak 919"[All Fields] OR ("2019 ncov vaccine mrna 1273"[MeSH Terms] OR ("2019 ncov"[All Fields]) OR (SARS-CoV-2 vaccination) OR "vaccine"[All Fields] OR "mRNA 1273"[All Fields]) OR "2019 ncov vaccine mrna 1273"[All Fields])) OR imelasomeran OR "Moderna vaccine"[All Fields] OR "Spikevax bivalent zero omicron"[All Fields] OR "Spikevax bivalent"[All Fields] AND

(2020/12/18:2023/04/31[Date - Publication] OR 2020/12/18:2023/04/30[Date - Create] OR 2020/12/18:2023/04/30[Date - Entry]))

Literature Findings

- The literature reviewed that extends the literature search from PBRER#4 did not identify any elasomeran immunization safety concerns for the IC population. This literature search, as outlined, yielded 579 articles. The articles were medically/scientifically reviewed to identify articles relevant to the safety and benefit/risk profile of Spikevax/Elasomeran in the context of the IC population. The title and abstracts were reviewed for these 579 retrieved hits and after exclusion of 402 articles that discussed COVID-19 disease or its impact on IC individuals, effect of the pandemic on the IC, therapeutic approaches for treatment of IC individuals, case reports/series, review articles and studies that did not include SPIKEVAX /Elasomeran and/or mRNA vaccines.
- The remaining 177 articles contained information regarding mRNA vaccine administration in the IC population. Most of these articles are discussed in the context of IC individuals with the possibility of lower immune response to the COVID-19 vaccine, the need for booster doses due to the waning immune response over time and the emergence of variants (Omicron) and subvariants, the effectiveness of the vaccine and risk factors for breakthrough COVID-19 and severe COVID-19 disease.
- The following is an overview of the literature search pointing out some of the many articles related to the IC population. For context, a recent article reviews in depth the various studies published in the IC population (Tan et al, 2023).
- Individuals who are immunocompromised because of primary or secondary immunodeficiencies are reported to have higher morbidity and mortality due to direct and indirect effects of COVID-19 infection especially those with co-morbidities (Delavari et al 2021). In individuals with primary immunodeficiency, the data from a limited number of patients receiving a mRNA vaccine have been found to develop an immune response except those with X-linked agammaglobulinemia who do not develop antibodies to vaccination (Shields et al 2022). The vaccinations did not demonstrate any increase in adverse events in this population. In individuals with secondary immunodeficiency (HIV), the subjects developed seroconversion similar to healthy controls. Full vaccination provides consistently improved seroconversion without increased adverse events. A booster dose appears to be beneficial (Kang et al 2022, Yin et al 2022).
- Individuals with unvaccinated cancer especially those with hematologic cancers who develop COVID-19 are reported to have more severe disease, hospitalizations and worse prognosis including death (Di Felice et al, 2022). Those patients with cancer and COVID-19 develop less evidence of immune protection than the normal population (Becerril-Gaitan et al 2022). This results in greater morbidity and mortality in addition to a delay in cancer treatment for those who survive. In 2022, numerous publications have demonstrated the benefits of mRNA vaccinations with limited serious adverse events (Becerril-Gaitan et al 2022, Corti et al 2022, Guven et al 2022, Sakuraba et al 2022, Javadinia et al 2022, Tang et al 2022, Yan et al 2022, Martins-Branco et al 2022, Yin et al 2022). In general, rates of seroconversion were reported to be 80% after two doses of vaccine and averages 90% in solid tumors but lower (70%) in individuals with hematologic cancers, especially those that are B-cell cancer. It was demonstrated to enhance with booster vaccines but is still lower for hematologic cancers (Mai et al 2022). While this population is still at risk of developing COVID-19 infection after vaccination, there is less morbidity and mortality with limited serious adverse events (Lee et al 2022).

- In addition to these findings, there were number of publications concerning patients with solid organ transplants and chronic kidney disease both of which are IC with greater morbidity and mortality (Williamson et al 2022, Cancarevic et al 2022). Both populations had lower seroconversion rates that were improved by a second vaccine and a booster vaccine (Manothummatha et al 2022, Shoar et al 2022, Li et al 2022, Chen et al 2021, Mehta et al 2022, Peiyao et al 2022). Finally, a recent study examined the role of a fourth dose of mRNA vaccine in enhancing responses to Omicron (Rescigno et al 2023). They found that the additional boosters enhance to both B and T-cell response.
- There is presently limited information concerning the pediatric IC population available in the published literature. However, a recent literature study found new safety signals in IC children (Morgans et al 2022). A recent report on the bivalent COVID-19 mRNA vaccine booster from a large VAERS database review of normal children aged 5-11 demonstrated no new safety issues (Hause et al 2023).

Summary

The large amount of literature demonstrates that for IC individuals, COVID-19 infection is related to significant morbidity and mortality. This most recent assessment of the literature concerning the use of SPIKEVAX is associated with less severe outcomes in COVID-19 infections and not associated with safety concerns in the IC population.

Conclusion

Overall, the published data from this literature search currently does not support a risk associated between IC individuals and SPIKEVAX. This literature review did not provide new substantive data that would impact the positive benefit-risk profile of the use of elasomeran (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5) for the IC subpopulation and they should no longer be treated as Missing Information.

Overall conclusion

In conclusion, the MAH considers there is sufficient justification for removing use in immunocompromised subjects as missing information from the RMP and proposes to continue monitoring use in immunocompromised subjects through routine surveillance and ongoing postauthorisation safety studies as applicable.

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Rapporteur assessment comment:

As requested, the MAH provided the following additional data to on the safety of Spikevax use in immunocompromised individuals: interim results from three ongoing additional PhV activities as well as a more comprehensive literature review.

Study mRNA-1273-P304

This is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of Spikevax in solid organ transplant (SOT) recipients and healthy participants. Comparison with healthy participants was primarily intended with regard to efficacy outcome measures.

Part A of the study enrolled 214 SOT patients to receive up to 3 doses of Spikevax. In Part B of the study, a 100µg booster-dose was administered to participants at least 4 months from the last dose of a completed primary COVID-19 vaccination series. The MAH provided interim results based on the latest interim report with a database lock date of 22 November 2022.

The reactogenicity profile among immunocompromised participants was similar to that of the general population. No significant new safety information was identified based on the description of serious adverse events and adverse events of special interest following use of Spikevax in SOT patients.

Study mRNA-1273-P904

This is an active surveillance study using secondary data to monitor real-world safety of Spikevax in **Europe**. Incidence rates of AESI are compared between vaccinated and unvaccinated cohorts, and analyses in subpopulations of interest, including in immunocompromised individuals, are to be performed. The MAH provided descriptive data from the recent interim report which was submitted for review in March 2023. A summary of the number of persons with immunocomporised status identified in the different databases was provided but no analyses have been conducted yet and these are expected to be included in the final study report.

Study mRNA-1273-P903

Similar to study p904, this is an active surveillance study using secondary data to monitor real-world safety of Spikevax in the **USA**. Incidence rates of AESI are compared between vaccinated and unvaccinated cohorts, and analyses in subpopulations of interest, including in immunocompromised individuals are performed. When a predefined threshold was met (incidence rate ratio comparing individuals after vaccination is >1 with a lower bound of the 95% confidence interval >1 for observed to expected analysis vs a historical comparator), self-controlled risk interval (SCRI) analyses were performed as signal refinement of the specific AESI. Of the 43 pre-defined AESIs, anosmia/ageusia, Chilblain-like lesions, and narcolepsy met the threshold for SCRI analysis in immunocompromised persons.

Elevated rates in from the observed-expected analyses for narcolepsy were not confirmed in the SCRI analyles, refuting an association of Spikevax and this AESI among immunocompromised persons.

For anosmia/ageusia, the event rate ratio (ERR) was elevated in males 50-64 years of age, particularly following dose 1 (ERR 2.05, 95% CI 1.05 – 4.01). However, elevated ERRs were not observed for other age/gender subgroups.

For Chilbain-like lesions, the overall ERR was elevated among adults in the dose-agnostic analysis (ERR 2.12, 95% CI 1.08 – 4.15). Dose- and gender-specific analyses were imprecise due to low event counts.

Importantly, elevated rates of anosmia/ageusia and chilblain-like lesions were also observed for the general, non-immunocompromised population in previous interim reports for this study. This triggered cumulative reviews, further sensitivity analyses and a discussion of the limitations of the analyses which hamper meaningful interpretation of the findings (EMEA/H/C/005791/MEA/003.8). Based on this, it was concluded that there is insufficient evidence to conclude upon causal associations.

It is agreed that no new risks specific to immunocompromised persons were identified in the provided analyses.

Literature review

Most articles identified by the MAH primarily concern the effectiveness of Spikevax vaccination in immunocompromised individuals. These are not relevant for the evaluation of whether the gaps in knowledge regarding the **safety** of Spikevax when used in immunocompromised individuals have been sufficiently addressed to remove this area of missing information from the list of safety concerns. While the benefit of effective immunisation may be higher in immunocompromised individuals, given the increased risk for severe COVID-19 infection, as suggested by many literature articles, this is not considered an argument that the safety concern has been adequately addressed in the context of risk management planning. However, relevant safety data were identified in two publications, as summarised

below.

- Kang et al performed a systematic review and meta-analysis (including observational studies and RCTs) to evaluate the immunogenicity and safety of COVID-19 vaccines among people living with HIV (PLWH). They found that there was no significant difference in risks of total adverse events between PLWH and healthy controls after the first (RR = 0.86, 95%CI 0.67–1.10) and the second (RR = 0.88, 95%CI 0.68–1.14) dose. The pooled incidence rates of adverse events in PLWH were close to results from previous studies in healthy populations. Of note, no details regarding COVID-19 vaccination type or brand were available.
- Javadinia et al performed a systematic review and meta-analysis of studies on the efficacy and safety of COVID-19 vaccines in patients with malignancy. While the heterogenity of safety assessments between studies regarding frequency and severity of adverse events limited ability to perform a meta-analysis, the authors summarised that most side effects reported in the included studies were mild and conclude that COVID-19 vaccines are safe in this population.

Of note, no details regarding COVID-19 vaccination type or brand were available in these articles. A number of studies referenced in several of the meta-analyses reported a comparable safety profile between immunocompromised patients and the general population following vaccination with the Comirnaty COVID-19 mRNA vaccine.

Conclusion

The MAH's response is acknowledged. Overall, the PRAC Rapporteur considers that there is sufficient evidence to conclude that the gaps in knowledge regarding the safety of Spikevax when used in immunocompromised individuals have been adequately filled and can no longer be considered an area of missing information. Removal of 'use in immunocompromised subjects' from the RMP is endorsed.

Regardless of the removal of the safety concern in the RMP, continued monitoring through routine pharmacovigilance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904 is warranted, as proposed by the MAH.

Regarding the effectiveness in immunocompromised subjects, the studies P304 and P901 are ongoing and will remain in the pharmacovigilance plan.

Updates of the PI

Removal of this area of missing information requires changes to the PI, and the MAH proposed the following changes to SmPC section 4.4:

Immunocompromised individuals

Post-authorisation safety information, including supporting literature information, indicate that ~~T~~the ~~efficacy and~~ safety of Spikevax ~~has not been assessed~~ in immunocompromised individuals, including those receiving immunosuppressant therapy **is not different than in the general population**. The efficacy of Spikevax may be lower in immunocompromised individuals.

The recommendation to consider a third dose in severely immunocompromised individuals (see section 4.2) is based on **post-marketing information as well as** limited serological evidence with patients who are immunocompromised after solid organ transplantation.

These changes are not accepted as information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk. As risks specific to immunocompromised individuals have been refuted, a warning is no longer considered required (refer to section 3).

8. Comments from Member States

8.1. MS#1

We thank the rapporteur for this PSUR assessment. We have some comments, and suggestions for rephrasing of the SmPC 4.4 and PIL for myocarditis and pericarditis.

Based on the data presented by the MAH, we agree that COVID-19 vaccine associated myocarditis in most cases have a favorable prognosis. Some studies indicate a more benign course of in comparison to "classic" myocarditis, however, other studies demonstrate little or no difference. Most of the studies comparing the two are small and some kind of selection bias is possible. It is also not clear how tx. Studies comparing the two types of myocarditis have been adjusted for confounders. Vaccine associated myocarditis are generally seen in young men with no other baseline risk factors which in part could explain the benign course and good prognosis. The current information regarding differences between the two types of myocarditis is therefore considered sufficient. We agree that no long term (beyond 3 month) data is available and the long-term prognosis for now is not known.

As we consider myocarditis a serious condition, even if the course and prognosis are favorable, we are not in favor of describing the conditions as "mild". We therefore propose the following change to the proposed SmPC update:

SmPC section 4.4 Special warnings and precautions for use

Myocarditis and pericarditis

There is an increased risk for myocarditis and pericarditis following vaccination with Spikevax.

These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often **in younger males, and more often** after the second dose compared to the first dose~~, and more often in younger males~~ (see section 4.8). The risk profile appears to be similar for the second and the third dose.

Available data **indicate that most cases** ~~**are mild and**~~ **tend to recover within a short time. Some cases required intensive care support and fatal cases have been observed. Data also indicate**~~suggest~~ that the **short term (≤3 months)** course **and outcome** of myocarditis and pericarditis following vaccination ~~**is milder and less severe than**~~~~not different from~~ is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Package Leaflet

2. What you need to know before you are given Spikevax

(...)

There is an increased risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) after vaccination with Spikevax (see section 4).

These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often **in younger males, and more often** after the second

dose compared to the first dose~~, and more often in younger males~~.

Most cases of myocarditis and pericarditis ~~are mild and individuals~~ tend to recover within a short time. Some cases required intensive care support and fatal cases have been seen.

Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before you are given Spikevax.

Amenorrhoea

MS#1 does not support closing the signal "amenorrhoea". As almost 2 years have passed since the vaccination started, we are still receiving cases of long term (18 months) loss of menstruation from patients and from health care professionals for mRNA-vaccines.

Also, taking into consideration there are ongoing research into this topic, it is considered that closing the issue is premature.

O/E-analysis:

The Rapporteur points to an O/E-analysis which showed a lower number of observed cases vs expected cases (a rate ratio of below 0.10). The analysis utilizes spontaneous reports (ICSRs) coded with "amenorrhea" as a numerator. Therefore, the O/E-analysis is of less relevance, as it is hampered by the fact that the majority of reports regarding menstrual disturbances and amenorrhea are received from patients and therefore not coded with "amenorrhea". Amenorrhea is a medical term, not considered well-known amongst laymen. (Terms such as "menstruation delayed" and "lack of menstruation" is what one would expect them to report, which would be coded with the PT "Menstruation delayed". Of note, in Vigibase there is approximately the same amount of ICSRs coded with "menstruation delayed" as "amenorrhoea" for COVID-19 vaccine active ingredients, which supports this view.). Including "menstruation delayed" is not a solution either, since this term is lacking a clear definition. O/E-analysis is therefore not a valuable tool in the assessment of this signal. Additionally, the study used to calculate the incidence background rate dates from the 1970's and therefore likely doesn't reflect the current situation.

Given the massive and rapid rollout of the vaccination it must be kept in mind that the ideal study with a non-vaccinated control group is probably not feasible.

Question 2 of the updated signal AR of amenorrhea (EPITT 19781) stated that there was a "need to evaluate ways in which more information can be obtained from epidemiological or clinical studies on the topic of menstrual disorders, including amenorrhoea. The MAH should outline which possibilities have been considered".

We acknowledge the limitations in using registerbased data sources and performing clinical trials. However, the MAH should investigate the possibility to measure a possible effect of Spikevax of menstrual disturbances in women using an app.

Positive rechallenge cases of amenorrhea:

We do not agree with the PRAC Rapporteurs conclusion on some of the cases. Case [redacted] (F/52 Y): the PRAC Rapporteur states that at TTO of 0-1 is difficult to interpret when amenorrhea is defined as a lack of menstruation for 3 months.

The first day where the period is delayed is the start of the reaction, this could occur with a TTO of 1 day. This would be considered a secondary amenorrhea if the duration of the reaction (ie missing period) is more than 3 months. Therefore a TTO of 0-1 days of amenorrhea is plausible. Additionally, we do not agree with the conclusion to categorize some of the cases as "unassessable" with the justification that the case is lacking information on menstrual cycle. We do not agree that this level of detail is necessary to assess causality according to the WHO-UMC causality system.

It is agreed that the level of information in many cases is limited. This does not however make the case unassessable. The population vaccinated is representative of the general population ie is generally healthy. Information on medical history is not necessarily relevant.

Cardiac arrhythmia

The conclusion regarding cardiac arrythmias is in general endorsed.

Of note, in the P203 adolescent trial (age 12<18 years), with approximately 3000 participants, - the TEAE "Sinus bradycardia" was reported in 8 patients in the vaccine arm vs 1 in the placebo. As younger patients are known to react stronger to the vaccine, focusing on adolescents is important.

In addition to the RSI from the PRAC Rapporteur, we also consider that the MAH should review all cases of arrhythmia with a positive rechallenge.

Rapporteur assessment comment:

The comments from MS#1 is appreciated.

Myocarditis and pericarditis

MS#1 argues that the available data is not sufficient to support the refrasing of the comparison between "classic" myocarditis and vaccine induced myocarditis. Furthermore, MS#1 is not in favour of describing myocarditis cases as mild since it is a serious condition. MS#1 suggested changes to the wording in SmPC section 4.4 and PIL in section 2 accordingly. Please see the final suggestion for wording in section 3. Recommendations.

Amenorrhea

The input concerning ammenorhea is appreciated. The PRAC Rapporteur agrees with the limitations of the O/E analysis pointed out by MS#1. However, despite the limitations, there is no evidence that would suggest that the number of cases reporting amerhorrea following Spikevax vaccination is higher than expected.

The input from MS#1 concerning time to onset is acknowledged. It demonstrates that the definition of TTO in the case reports of ammenorhea can be a subject of interpretation and, given that the cases are reported from several sources, including consumers, it is unclear whether the same definition was applied across all the reports.

With regards to the causality of case reports of amenorrhea, the PRAC Rapporteur maintains the position that, given the high background incidence and multifactorial aetiology of menstrual disorders, medical history, especially history of previous menstrual cycles is important for the assessment of causality.

MS#1 suggested that a potential effect of Spikevax in the menstrual disorders could be measured by an

app. MS#1 did not elaborate on a potential design of such a study, and hence it is difficult to comment on its feasibility and any potential benefits.

Cardiac arrhythmia

The rapporteur agrees to the comment regarding cardiac arrhythmia.

Based on results from the clinical trial P203, the MAH is requested in future PSURs to specifically report on arrhythmia cases in vaccinees <18 years in the relevant subpopulation analysis.

In addition, the MAH is requested in the next PSUR to review and present all cumulative cases of arrhythmia with a positive rechallenge including an individually justified WHO-UMC causality categorization.

8.2. MS #2

MS#2 endorses the Rapporteur assessment report and supports the proposed update of section 4.4 of the SmPC to amend a warning regarding myocarditis and pericarditis.

Of note, the data presented by the MAH and requested in the RSI no 6 are available, in French, here : https://www.epi-phare.fr/rapports-detudes-et-publications/myocardite-rappel-vaccin-covid19/

Moreover, MS#2 would like to inform PRAC members regarding cases of "hearing loss" in France.

Hearing loss

MS#2 agrees with the conclusion of the Rapporteur about that risk.

Moreover, the national cross-sectional audiogram-based study, presented in the last PSUSA (PSUSA/00010898/202206) was published in April 2023: https://europepmc.org/article/med/37071555.

In this study, all suspected Sudden Sensorineural Hearing Loss (SSNHL) cases following mRNA COVID-19 vaccination between January 2021 and February 2022 were included. They were retrospectively reviewed based on a comprehensive audiological and medical evaluation by ENT. The aim is to assess the relationship between SSNHL and exposure to mRNA COVID-19 vaccines and to estimate the reporting rates (Rr) of SSNHL after mRNA vaccination per 1,000,000 doses (primary outcome).

Over the study period, 22,690,889 doses of Elasomeran (Moderna mRNA-1273) were administered in France. The Reporting Rates (RR) of mRNA vaccine-induced SSNHL cases were calculated per 1,000,000 injections. Clinical classification was made according to patient history, unilaterality or bilaterality of the hearing loss, its degree, and recovery after a minimum 3-month follow-up.

A total of 29 cases of Elasomeran-induced SSNHL cases were included.

For these Elasomeran-induced SSNHL cases, the delay onset was ≤21 days for 26 (90%) cases whose median (range) delay onset was 8 (1-21) days. Women were concerned in 15 (52%) cases. The median (range) age was 47 (33-81) years, and 21 (72%) patients were in the 30-64 years age class. A total of 9 (31%) patients had a medical history, it was otoneurologic in 4 (14%) cases. The vaccination rank was known for 27 cases, the first injection was involved in 13 (45%) cases. Symptomatic corticotherapy was prescribed in 16 (55%) cases. SSNHL was unilateral in 18 (62%) cases. Detailed audiometric thresholds were available in 20 (69%) cases, with SSNHL being measured as mild to moderately severe in 10 (50%) cases, and as profound in 8 (40%) cases. Tinnitus was associated with SSNHL in 10 (34%) cases and vertigo in 12 (41%) cases. Total recovery was observed in 8 (28%) cases while hearing aid fitting was

required in 7 (24%) cases (Table 1). A rank effect was found in favor of the first injection (p<0.036). No sex effect or laterality of hearing loss effect was found. Case follow-up identified 3 cases of positive rechallenge (Table 2).

The total RR was estimated at 1.67/1,00,0000 doses for Elasomeran.

The conclusion is that episodes of SSNHL after COVID-19 mRNA vaccines are very rare adverse events that do not call into question the benefits of mRNA vaccines but deserve to be known given the potentially disabling impact of sudden deafness. It is, therefore, essential to properly characterize any post-injection SSNHL, especially in the case of a positive rechallenge, to provide appropriate individualized recommendations.

In France, the national pharmacovigilance survey about hearing loss following vaccination against COVID-19 with RNAm vaccines is still ongoing.

Rapporteur assessment comment:

The PRAC Rapporteur appreciates the endorsement from the MS#2 and the input provided regarding the topic of 'hearing loss'. The MS#2 also confirmed that a MAH referenced study is available in French. Please see the assessment in AR section 7.6.

The MS#2 summarised the results of a recently finalised retrospective study by Thai-Van et al. (2023)* who analysed reports of sudden sensineuronal hearing loss (SSHL) from the French Pharmacovgilance Spontaenous Reports Database. Based on the 29 reports of SSHL for Spikevax received between Jan-2022 and Feb-2023, the authors estimated the reporting rates of SSHL to 1.67/1,000,000 injections. The study did not include a control group of non-vaccinated individuals, but given the background incidence of the event in general population (11-77/100,000 persons-year- see section 2.5.2 in this AR), the results from Thai-Van et al. (2023) do not indicate overreporting of SSHL in the recipients of Spikevax.

Among the 29 reports identified for Spikevax, 3 had positive rechallenge. Limited information was provided on these 3 cases in the paper, but they concerned 45F, 71M and 41F. If these cases were to be assessed as WHO-probable due to positive rechallenge, the total number of WHO-probable cases of SSHL would be 4, which the PRAC Raporteur does not consider sufficient to establish a causal association between hearing loss and Spikevax, given limited evidence from other sources (clinical trials, published literature, the MAH's global safety database). Thus, the PRAC Rapporteur maintains the opinion that routine PV monitoring is considered sufficient given the level of evidence available on the topic.

*Thai-Van H, Valnet-Rabier MB, Anciaux M, et al. Is there a safety signal generation for sudden sensorial hearing loss following mRNA COVID-19 vaccination: nationwide post-marketing surveillance using the French Pharmacovigilance Spontaneous Reporting Database. JMIR Public Health and Surveillance. 2023 Apr. DOI: 10.2196/45263. PMID: 37071555.

8.3. MS #3

We fully endorse the PRAC rapporteur assessment, and have no further comments.

Rapporteur assessment comment:

The MS comment of full endorsement is appreciated.

8.4. MS #4

We fully endorse the PRAC rapporteur assessment, and have further comments.

We appreciate the thorough assessment of data for this PSUR.

We would like to suggest a minor change in the proposed wording for the warning of myocarditis and pericarditis in section 4.4. We feel that the current wording as it is now may be confusing since they refer to mild cases and fatal cases in the same paragraph. This may be solved rephrasing it as follow:
"Available data **indicate that most cases are mild and tend to recover within a short time. However, some cases require intensive care support and fatal cases have been observed. Data also indicate**~~suggest~~ that the **short term (≤3months**) course **and outcome** of myocarditis and pericarditis following vaccination **is milder and less severe than**~~not different from~~ myocarditis or pericarditis in general."

Rapporteur assessment comment:

The MS comment is appreciated. The MS suggests minor changes to the proposed wording in SmPC section 4.4. Please see the final suggestion for wording in section 3. Recommendations.

FOURTH PERIODIC SAFETY UPDATE REPORT

for

ACTIVE SUBSTANCES: Elasomeran (SPIKEVAX [COVID-19 Vaccine, mRNA-1273]), Elasomeran/imelasomeran (SPIKEVAX Bivalent.214 Original/BA.1, mRNA-1273.214) and Elasomeran/davesomeran (SPIKEVAX Bivalent.222 Original/BA.4/5, mRNA-1273.222)

ATC CODE: J07BX03

MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Product	Date of Authorization (*Underline Harmonized EU Birth Date)*	Marketing Authorization Holder
Elasomeran and (COVID-19 mRNA Vaccine [nucleoside modified])	06 Jan 2021	Moderna Biotech Spain, S.L.
Elasomeran/imelasomeran	12 Aug 2022	
Elasomeran/davesomeran	31 Aug 2022	

AUTHORIZATION PROCEDURE in the EU: Centralized

INTERNATIONAL BIRTH DATE (IBD): 18 Dec 2020

EUROPEAN UNION REFERENCE DATE (EURD): 18 Dec 2020

INTERVAL COVERED BY THIS REPORT:
from 19 Jun 2022 to **17 Dec 2022**
DATE OF THIS REPORT:
16 Feb 2023

OTHER INFORMATION:

Elasomeran (Previously COVID-19 Vaccine Moderna), Bivalents Elasomeran/imelasomeran and Elasomeran/devasomeran.

MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:

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DATE:

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EXECUTIVE SUMMARY

This Fourth Periodic Safety Update Report (PSUR) on SPIKEVAX® (elasomeran or mRNA-1273, formerly known as Moderna's COVID-19 mRNA Vaccine), SPIKEVAX Bivalent.214 Original/BA.1 (elasomeran/imelasomeran; mRNA-1273.214) booster, and SPIKEVAX Bivalent 222 Original/BA.4/5 (elasomeran/davesomeran; mRNA-1273.222) booster was compiled for regulatory authorities in the Periodic Benefit-Risk Evaluation Report (PBRER) format detailed in the European Medicines Agency (EMA) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E2C guidelines (Good Pharmacovigilance Practice guideline Module VII PSURs, 2012 and ICH-E2C(R2) and Consideration on Core Requirements for PSURs of COVID19 Vaccines (core PSUR19 guidance [EMA/362988/2021 08 Jul 2021]). This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran based on review of cumulative safety information with a focus on new safety information from available worldwide data sources received during the reporting period. The reporting period for this PBRER#4 is from 19 Jun 2022 to 17 Dec 2022. Currently, the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates. The three previous PBRERs (PBRER#1, PBRER#2 and PBRER#3) submitted included single International Nonproprietary Name elasomeran, however, beginning with this PBRER#4, bivalent forms; elasomeran/imelasomeran, and elasomeran/davesomeran will also be included.

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" with the Anatomical Therapeutic Chemical (ATC) code: J07BX03.

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; severe acute respiratory syndrome [SARS-CoV-2]). Elasomeran/imelasomeran active substance is mRNA encoding the prefusion stabilized spike glycoprotein of original SARS-CoV-2 embedded in lipid nanoparticles (elasomeran) and mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 Omicron variant (B.1.1.529) embedded in LNPs (imelasomeran). Elasomeran/davesomeran active substance is mRNA encoding the prefusion stabilized spike glycoprotein of original SARS-CoV-2 embedded in LNPs (elasomeran) and mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 Omicron lineages BA.4 and BA.5 (Omicron variants B.1.1.529.4

and B.1.1.529.5) embedded in LNPs (davesomeran). As per Company Core Data Sheet (CCDS) (v15.0, dated 15 Nov 2022), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. Elasomeran/imelasomeran and elasomeran/davesomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

During this reporting period, ModernaTx, Inc. was in pharmacovigilance agreement with co-sponsors: GlaxoSmithKline plc (GSK), Sanofi S.A., the Division of Microbiology and Infectious Diseases (DMID)/National Institute of Allergy and Infectious Diseases (NIAID), National Cancer Institute (NCI), University of California, Los Angeles (UCLA), South Africa Medical Research Council (SAMRC), Merck, Sharp and Dohme (MSD), University of Southampton, Moffitt Cancer Center, and Takeda Pharmaceutical Company The agreements began on 16 Dec 2021 (GSK), 21 Feb 2020 (Sanofi and DMID/NIAID), May 2020 (NCI), 15 Mar 2022 (UCLA), 14 Apr 2022 (SAMRC), 02 Dec 2021 (MSD), 08 Feb 2022 (University of Southampton), 29 Sep 2021 (Moffitt Cancer Center), and 29 Oct 2020 (Takeda). The entities agreed to share all the relevant safety data from trials 20-0003, 21-0002, 21-0012, 22-0004 (DMID/NIAID sponsored), 217670-ZOSTER-091 (GSK sponsored), QHD00028 (Sanofi sponsored), 000115 (NCI Sponsored), COVID-19 Version 2.0 (UCLA sponsored), mRNA-1273-P508 (SAMRC sponsored), V110-911-00 and V503-076-00 (MSD sponsored), RHM MED1781 (University of Southampton sponsored), MCC 21536 (Moffitt Cancer Center sponsored), and TAK-919-1501 (Takeda sponsored).

Elasomeran, is formulated as a dispersion for injection to be supplied in multidose vial and dispersion for injection in pre-filled syringe and is administered intramuscularly (IM). Elasomeran/imelasomeran and elasomeran/davesomeran are formulated as a dispersion for injection to be supplied in multidose vial and single use pre-filled syringe (only for elasomeran/imelasomeran).

- Elasomeran 0.20 mg/mL dispersion for injection

Elasomeran is supplied as a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each. One dose (0.5 mL) contains 100 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran 0.10 mg/mL dispersion for injection and pre-filled syringe

Elasomeran is supplied as a multidose vial that contains 5 doses of 0.5 mL each or a maximum of 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). One dose (0.25 mL) contains 25 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 ml. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/imelasomeran is supplied as a multidose 2.5 mL vial (blue flip-off cap) that contains 5 doses of 0.5 mL each and a multidose 5 ml vial containing 10 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/imelasomeran 25 µg/25 µg dispersion for injection and pre-filled syringe

Elasomeran/imelasomeran is supplied as a single dose vial which contains 1 dose of 0.5 mL. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 mL, for single use only. One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/davesomeran is supplied as a multidose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of davesomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

Following are the dosages of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran:

Elasomeran posology for primary series, a third dose in severely immunocompromised and booster doses is provided in Table 1.1 below.

Table 1.1 Dosages and description for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran

Elasomeran: 0.20 mg/mL concentration	*Primary series*	*Individuals 12 years of age and older* Elasomeran is administered as a course of 2 (two) 100 µg doses (0.5 mL each).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 through 11 years of age Elasomeran is administered as a course of 2 (two) 50 µg doses (0.25 mL each, containing 50 µg mRNA, which is half of the primary dose for individuals 12 years and older).	
	Third dose in severely immunocompromised	*Individuals 12 years of age and older* Elasomeran is administered as course of one dose of 0.5 mL, containing 100 µg mRNA.	A third dose may be given at least 28 days after the second dose
		Children 6 through 11 years of age Elasomeran is administered as course of one dose of 0.25 mL, containing 50 µg mRNA	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran 0.25 mL, containing 50 µg mRNA	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series
Elasomeran 0.10 mg/mL concentration and 50 µg dispersion for injection in pre-filled syringe	*Primary series**	*Children 6 years through 11 years of age* Elasomeran is administered as a course of 2 (two) 50 µg doses (0.5 mL each,	It is recommended to administer the second dose 28 days after the first dose.

		containing 50 µg mRNA).	
		Children 6 months through 5 years of age Elasomeran is administered as a course of 2 (two) 25 µg doses (0.25 mL each, containing 25 µg mRNA each, which is half of the primary dose for children 6 years through 11 years of age).	
	Third dose in severely immunocompromised†	*Children 6 years through 11 years of age* Elasomeran is administered as a course of one dose of 0.5 mL, containing 50 µg mRNA	A third dose may be given at least 28 days after the second dose
		Children 6 months through 5 years of age Elasomeran is administered as a course of one (one) dose of 0.25 mL, containing 25 µg mRNA	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran, 0.5 mL, containing 50 µg mRNA	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series
Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 6 years through 11 years of age* Dose is administered as one dose of 0.25 mL containing 12.5 ug of elasomeran and 12.5 ug of imelasomeran.	There should be an interval of at least 3 months between administration of elasomeran/imelasomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/imelasomeran

		Individuals 12 years of age and older Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of imelsasomeran	is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.
Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 12 years of age and older* Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of davesomeran	There should be an interval of at least 3 months between administration of elasomeran/davesomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/davesomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

*For primary series for individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.
†For the third dose in severely immunocompromised patients 12 years of age and older, the 0.2 mg/mL strength vial should be used.
‡ For details on the primary vaccination course for ages 12 and above, the 0.2 mg/mL strength vial should be used.

Elasomeran/imelasomeran and elasomeran/davesomeran may be used to boost adults who have received a primary series with elasomeran, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine.

Cumulatively, 52,530 subjects have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA -1273.617.2, mRNA-1273.529), and participants exposed to mRNA-1273 in conjunction to mRNA-1283(including its variants mRNA-1283.211), in the mRNA clinical development program sponsored by ModernaTx, Inc. Out of the 52,530 subjects, 42,434 subjects were exposed to mRNA-1273 primary series. The total count of 52,530 represents unique subjects (Subjects enrolled in both trials P301 and P201 (Part C)/P205, or in both P204 and P306 are only counted once in total). Out of the 52,530 subjects, 42,434 subjects were exposed to mRNA-1273 primary series and the remaining 10,096 subjects were exposed to either mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA-1273.617.2, or mRNA-1273.529.

Cumulatively, 17,020 subjects were exposed to mRNA-1273 in clinical trials (CTs) sponsored by licensing partners. Out of 17,020 subjects, 1,280 subjects were exposed to mRNA-1273 in CTs sponsored by DMID, 1,534 subjects from a CT sponsored by GSK, 204 subjects from a CT sponsored by Sanofi, 17 subjects from a CT sponsored by NCI, 19 subjects from a CT sponsored by UCLA, 12,340 subjects from a CT sponsored by SAMRC, 931 subjects from CTs sponsored by MSD, 209 subjects from a CT sponsored by University of Southampton, 336 subjects from a CT sponsored by Moffitt Cancer Center, and 150 subjects were exposed to mRNA-1273 from a CT sponsored by Takeda. Cumulatively, 1,566 subjects were enrolled in investigator-initiated trials.

The International Birth date of elasomeran is 18 Dec 2020. The product is currently authorized in 48 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelosomeran was granted by the Medicines and Healthcare products Regulatory Agency for use in the United Kingdom (UK) on 12 Aug 2022. Elasomeran/davesomeran was granted Emergency Use Authorization (EUA) status by Food and Drug administration on 31 Aug 2022.

Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations (e.g., immunocompromised) and/or as a booster dose, including authorization for two bivalent vaccines (elasomeran/imelosomeran and elasomeran/davesomeran continue to expand.

Cumulatively, at the end of the reporting period, 17 Dec 2022, a total of 1,315,589,716 doses of elasomeran were delivered to 91 countries and an estimated total of 772,908,958 doses of elasomeran had been administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered.

The cumulative evidence on the safety and efficacy for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran fully supports the indication as described in the Reference Safety Information (RSI), authorized as a suspension for injection for active immunizations to prevent COVID 19 caused by SARS-CoV-2 in individuals 6 months of age and older. Clinical trial data

and the results of the post-authorization non interventional studies conducted to date support the positive safety and efficacy profile of mRNA-1273. The ongoing review of ModernaTx, Inc.'s Global Safety Database supports the current listed adverse events (AEs).

The following safety-related actions related to marketing experience were taken by ModernaTx, Inc.:

During the reporting period, the marketing authorization holder (MAH) conducted a signal evaluation of the potential signal of medication errors due to product confusion and/or product underdosing. The signal evaluation included a cumulative review of the MAH safety database with a data lock point (DLP) of 04 Oct 2022. Analysis of the data showed that medications error reports had been received at a higher proportion for individuals vaccinated with one of the authorized Spikevax bivalent vaccines (relative to elasomeran original). Based on the findings of the safety evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a Potential Risk (Not Important) and was classified as a Priority 1 Urgent (emerging) Safety Issue. A communication letter was distributed to those countries where Spikevax bivalents was authorized, and additional informational material regarding dosing information was posted on the ModernaTx, Inc. website for easy access by providers and consumers. The MAH will continue to monitor events for potential medication errors related to product confusion and/or product underdose using routine pharmacovigilance surveillance.

During the reporting period, requests related to the topics Immunoglobulin A (IgA) Nephropathy, Heavy menstrual bleeding (re-evaluation), Myocarditis/Pericarditis (re-evaluation), Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran), Capillary Leak Syndrome (Re-evaluation), Amenorrhea (re-evaluation) and Pemphigus and pemphigoid were received from Health Authorities (HAs) or regulatory bodies; as such, these were all considered as validated signals. Of these 7 signals, 2 signals, Amenorrhea (re-evaluation) and Pemphigus and pemphigoid were ongoing at the DLP of the reporting period, 3 signals were closed and refuted and one signal, Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) was categorized as a Potential Risk (not important) during the reporting period. Lastly the signal of Capillary Leak Syndrome (Re-evaluation), which was closed as a refuted Signal before the reporting period of this PBRER, but not presented in PBRER#3, is presented here for completeness.

During the reporting period, the important identified risk of 'Anaphylaxis' was removed and reclassified as an identified risk (not important). While anaphylaxis, remains as an identified risk for the product, as with any other biological, it does not have a considerable impact on the benefit-risk balance of the vaccine.

The important identified and potential risks as per Risk Management Plan version 6.3 dated 15 Dec 2022 are:

Important identified risks:

- Myocarditis
- Pericarditis

Important potential risk:

- Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

At the beginning of the reporting period, the RSI for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran was CCDS (v13, dated 03 Jun 2022). During the reporting period, Section 4.4 (Myocarditis details were deleted) and Section 4.8 (inclusion of Urticaria) of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran CCDS v13.0 (dated 03 Jun 2022) and Section 4.1 (indication to include till 6 months of age and bivalent data), Section 4.2 (Posology updated), Section 4.4 (Updated myocarditis text per Pharmacovigilance recommendations) and Section 4.8 (Added pediatric data per EMA approval of European Medicines Evaluation Agency. Added bivalent BA.1 data per EMA of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran CCDS v14 (dated 18 Jul 2022) were updated. The RSI for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in effect at the end of the reporting period (DLP 17 Dec 2022) and used for this report is the CCDS v15.0 (dated 15 Nov 2022).

Examination of the data contained within this report further supports the conclusion that the overall benefit-risk balance for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran continues to be positive and remains unchanged.

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LIST OF ABBREVIATIONS

Acronym	Definition
ADE	Antibody Dependent Enhancement
ADHD	Attention Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI/ID	Autoimmune and Inflammatory Disorders
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
BI-RADS	Breast Imaging-Reporting and Data System
BNP	Brain Natriuretic Peptides
BRAO	Branch Retinal Artery Occlusion
BRVO	Branch retinal Vein Occlusion
CAD	Coronary Artery disease
CCDS	Company Core Data Sheet
CD	Case Definition
CDC	Center for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukaemia
CLS	Capillary Leak Syndrome
cMRI	Cardiac Magnetic Resonance Imaging
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
COVE	Corona Virus Efficacy

Acronym	Definition
COVID-19	Coronavirus Disease
CRAO	Central Retinal Artery Occlusion
CRP	C-Reactive Protein
CRVO	Central Retinal Vein Occlusion
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Clinical Trial
CU	Chronic Urticaria
CVST	Central Venous Sinus Thrombosis
DART	Developmental and Reproductive Toxicity
DLP	Data Lock Point
DM	Diabetes Mellitus
DMID	Division of Microbiology and Infectious Diseases
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECDC	European Center for Disease Prevention and Control
ECG	Electrocardiogram
EEA	European Economic Area
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMEA	Europe, Middle East, and Africa
EPITT	European Pharmacovigilance Issues Tracking Tool
ERR	Event Rate Ratio
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EUA	Emergency Use Authorization
EVDAS	EudraVigilance Data Analysis System
FDA	Food and Drug Administration
FVFP	First Visit First Patient
GA	Gestational Age
GBS	Guillain-Barre Syndrome

Acronym	Definition
GHS	Gutenberg Health Study
GISAID	Global Initiative on Sharing Avian Influenza Data
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GSDB	Global Safety Database
GSK	Glaxo SmithKline
GVP	Good Pharmacovigilance Practices
HA	Health Authorities
HCP	Healthcare Care Professional
HHV	Human Herpesvirus
HIT	Heparin-Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLT	High Level Term
HMB	Heavy Menstrual Bleeding
HNL	Histiocytic Necrotizing Lymphadenitis
IBD	International Birth Date
ICH	International Council on Harmonization
ICMR	Indian Council of Medical Research
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
ID	Inflammatory disease
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IM	Intramuscular
INN	International Nonproprietary Name
IQR	Interquartile range

Acronym	Definition
IR6	Interim Report 6
IRR	Incidence Rate Ratio
ISRR	Immunization Stress-Related Response
IST	Internal Safety Team
ITP	Immune Thrombocytopenia
IVIg	Intravenous Immunoglobulin
KFD	Kikuchi-Fujimoto Disease
LGE	Late Gadolinium Enhancement
LLOQ	Lower Limit of Quantification
LNP	Lipid Nanoparticle
LV	Left ventricular
LVEF	Left Ventricular Ejection Fraction
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MFS	Miller Fisher syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MHX	Medical history
MI	Myocardial infarction
MIS	Multisystem Inflammatory Syndrome
MIS-A	Multisystem Inflammatory Syndrome in Adults
MIS-C	Multisystem Inflammatory Syndrome in Children
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MSD	Merck, Sharp and Dohme
MSSR	Monthly Safety Summary Report
NAM	National Academy of Medicine
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases

Acronym	Definition
NICU	Neonatal Intensive Care Unit
NIS	Non-Interventional Study
NOC	Notice of Compliance
NOS	Not Otherwise Specified
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
O/E	Observed Expected
OR	Odds Ratio
PAN	Polyarteritis Nodosa
PASS	Post-Authorization Safety Studies
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase Chain Reaction
PD1	Programmed Cell Death 1
PDL1	Programmed Cell Death Ligand 1
PDV	Program Data Vector
PIL	Patient Information Leaflet
PMD	Pharmaceutical and Medical Devices
PMS	Post-marketing Surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PSSF	Product Signaling Strategy Form
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
PT	Preferred Term
PTS	Post-thrombotic syndrome
PVA	Pharmacovigilance agreement
QR	Quick response
RAs	Regulatory Authorities
RLU	Relative luminescence units
RMP	Risk Management Plan
RNA	Ribonucleic acid

Acronym	Definition
ROR	Rate of Return
RR	Risk Ratios
RSI	Reference Safety Information
RSV	Respiratory syncytial virus
RTQ	Response to Query
SAE	Serious Adverse Event
SAMRC	South Africa Medical Research Council
SARS	Severe Acute Respiratory Syndrome
SARs-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SCLS	Systemic Capillary Leak Syndrome
SCRI	Self-controlled risk interval
SD	Standard Deviation
SIR	Standardized Incidence Ratio
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SNHL	Sensorineural Hearing Loss
SOC	System Organ Class
SOCV	Single Organ Cutaneous Vasculitis
SRMT	Safety and Risk Management Team
SRR	Seroresponse Rates
SSNHL	Sudden Sensorineural Hearing Loss
TEAE	Treatment-Emergent Adverse Event
TFQ	Targeted follow-up questionnaire
TGA	Therapeutic Goods Administration
TTO	Time to Onset
TTP	Thrombotic Thrombocytopenic Purpura
TTS	Thrombosis with Thrombocytopenia Syndrome
UCLA	University of California, Los Angeles

Acronym	Definition
ULOQ	Upper Limit of Quantification
UMC	Uppsala Monitoring Center
UK	United Kingdom
URI	Upper Respiratory Infection
US/USA	United States/United States of America
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VIPIT	Vaccine-induced prothrombotic immune thrombocytopenia
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VOC	Variants of Concern
VOI	Variant of Interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WAO	World Allergy Organization
WHO	World Health Organization

1 INTRODUCTION

This Fourth Periodic Safety Update Report (PSUR) on SPIKEVAX® (elasomeran or mRNA-1273, formerly known as Moderna's COVID-19 mRNA Vaccine), SPIKEVAX Bivalent.214 Original/BA.1 (elasomeran/imelasomeran; mRNA-1273.214) booster, and SPIKEVAX Bivalent.222 Original/BA.4/5 (elasomeran/davesomeran; mRNA-1273.222) booster was compiled for regulatory authorities in the Periodic Benefit-Risk Evaluation Report (PBRER) format detailed in the European Medicines Agency (EMA) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E2C guidelines (Good Pharmacovigilance Practice guideline Module VII PSURs, 2012 and ICH-E2C(R2) and Consideration on Core Requirements for PSURs of COVID-19 Vaccines (core PSUR19 guidance [EMA/362988/2021 08 Jul 2021]). This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran based on review of cumulative safety information with a focus on new safety information from available worldwide data sources received during the reporting period. The reporting period for this PBRER#4 is from 19 Jun 2022 to 17 Dec 2022. Currently, the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates. The three previous PBRERs (PBRER#1, PBRER#2 and PBRER#3) submitted included single International Nonproprietary Name (INN) elasomeran, however, beginning with this PBRER#4, bivalent forms; elasomeran/imelasomeran, and elasomeran/davesomeran will also be included.

The international birth date (IBD) of elasomeran is 18 Dec 2020, the date of the first marketing approval in any country in the world. The product is currently authorized in 48 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First authorization approval for elasomeran/imelosomeran was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom (UK) on 12 Aug 2022, and elasomeran/davesomeran was granted Emergency Use Authorization (EUA) status by US Food and Drug Administration (US FDA) on 31 Aug 2022.

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has Anatomical Therapeutic Chemical (ATC) code: J07BX03.

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; SARS-CoV-2). As per Company Core Data Sheet

(CCDS) (v15.0, dated 15 Nov 2022), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. Elasomeran/imelasomeran and elasomeran/davesomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

Elasomeran is Single-stranded, 5'-capped messenger Ribonucleic acid (RNA) (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the full-length Spike protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S-protein into a prefusion conformation (S-2P). The elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1 monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). Imelasomeran contains mRNA, 5'-capped, encoding a full length, codon-optimized prefusion stabilized conformation variant (K983P and V984P) of the SARS-CoV-2 spike (S) glycoprotein (Omicron variant, B.1.1.529). Davesomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

Elasomeran, is formulated as a dispersion for injection to be supplied in multidose vial and dispersion for injection in pre-filled syringe and is administered intramuscularly (IM). Elasomeran/imelasomeran and elasomeran/davesomeran are formulated as dispersion for injection to be supplied in multidose vial and single use pre-filled syringe (for elasomeran/imelasomeran).

- Elasomeran 0.20 mg/mL dispersion for injection

Elasomeran is supplied as a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each. One dose (0.5 mL) contains 100 μg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 50 μg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran 0.10 mg/mL dispersion for injection and pre-filled syringe

Elasomeran is supplied as a multidose vial that contains 5 doses of 0.5 mL each or a maximum of 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 μg of elasomeran, a COVID-19 mRNA

Vaccine (embedded in LNPs). One dose (0.25 mL) contains 25 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 ml. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/davesomeran is supplied as a multidose 2.5 mL vial (blue flip-off cap) that contains 5 doses of 0.5 mL each and a multidose 5 ml vial containing 10 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/imelasomeran 25 µg/25 µg dispersion for injection and pre-filled syringe

Elasomeran/davesomeran is supplied as a single use pre-filled syringe which contains 1 dose of 0.5 mL. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). It has also been supplied as single use pre-filled syringe that contains 1 dose of 0.5 mL, for single use only. One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of imelasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection

Elasomeran/davesomeran is supplied as a multidose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of davesomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

Following are the dosages of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran:

Elasomeran posology for primary series, a third dose in severely immunocompromised and booster doses are provided in the below Table 1.1.

Table 1.1 Dosages and description for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran

Elasomeran 0.20 mg/mL concentration	*Primary series*	*Individuals 12 years of age and older* Elasomeran is administered as a course of 2 (two) 100 µg doses (0.5 mL each).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 through 11 years of age Elasomeran is administered as a	

		course of 2 (two) 50 µg doses (0.25 mL each, containing 50 µg mRNA, which is half of the primary dose for individuals 12 years and older).	
	Third dose in severely immunocompromised	*Individuals 12 years of age and older* Elasomeran is administered as course of one dose of 0.5 mL, containing 100 µg mRNA.	A third dose may be given at least 28 days after the second dose.
		Children 6 through 11 years of age Elasomeran is administered as course of one dose of 0.25 mL, containing 50 µg mRNA	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran 0.25 mL, containing 50 µg mRNA	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Elasomeran 0.10 mg/mL concentration and 50 µg dispersion for injection in pre-filled syringe	*Primary series*[*]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of 2 (two) 50 µg doses (0.5 mL each, containing 50 µg mRNA).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age Elasomeran is administered as a course of 2 (two) 25 µg doses (0.25 mL each, containing 25 µg mRNA each, which is half of the primary dose for children 6 years through 11 years of age).	
	Third dose in severely immunocompromised[†]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of one dose of 0.5 mL, containing 50 µg mRNA.	A third dose may be given at least 28 days after the second dose.

		Children 6 months through 5 years of age Elasomeran is administered as a course of one (one) dose of 0.25 mL, containing 25 µg mRNA.	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran, 0.5 mL, containing 50 µg mRNA.	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 6 years through 11 years of age* Dose is administered as one dose of 0.25 mL containing 12.5 ug of elasomeran and 12.5 ug of imelasomeran.	There should be an interval of at least 3 months between administration of elasomeran/imelasomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/imelasomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.
		Individuals 12 years of age and older Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of imelsasomeran.	
Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 12 years of age and older* Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of davesomeran.	There should be an interval of at least 3 months between administration of elasomeran/davesomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/davesomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

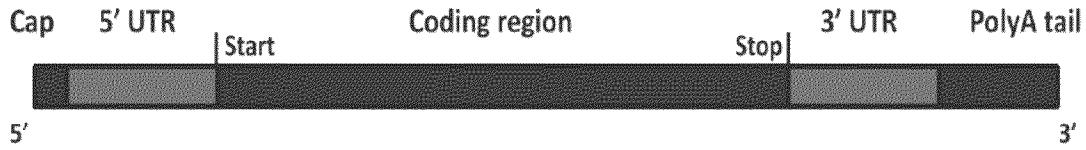
*For primary series for individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.
†For the third dose in severely immunocompromised patients 12 years of age and older, the 0.2 mg/mL strength vial should be used.
‡ For details on the primary vaccination course for ages 12 and above, the 0.2 mg/mL strength vial should be used.

Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran may be used to boost adults who have received a primary series with elasomeran, or a primary series comprised of another

mRNA vaccine or adenoviral vector vaccine.

The mRNA drug substance in mRNA-1273 is chemically similar to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs [1] [2]. This nucleoside is included in mRNA-1273 drug substance in place of the normal uridine base to minimize the indiscriminate recognition of the mRNA-1273 by pathogen-associated molecular pattern receptors (e.g., toll-like receptors) [3]. The cap structure used in the mRNA is identical to the natural mammalian Cap one structure [4,5] and is presented in Figure 1-1 below.

Figure 1-1 mRNA 1273 COVID-19 Vaccine Cap 1 mRNA structure



Abbreviations: mRNA, messenger RNA; PolyA, polyadenylated; UTR, untranslated region.

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, contain mRNA encapsulated in LNPs. The mRNA encodes for the full length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the spike protein and is immunogenic against the Wuhan-Hu-1 (D614) isolate and all key emerging variants tested, including B.1.1.7, B.1.351, BA.1 (Omicron variant B.1.1.529), BA.2, BA.4, and BA.5 (Omicron variants B.1.1.529.4 and B.1.1.529.5). After IM injection, cells at the injection site and the associated draining lymph nodes take up the LNP, effectively delivering the mRNA sequence into cells for translation into viral protein. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The expressed, membrane-bound spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralizing antibodies, which may contribute to protection against COVID-19.

A modified, variant-matched bivalent COVID-19 mRNA vaccine has been developed that contains equal amounts of two mRNAs that encode for the Spike protein of the ancestral SARS-CoV-2 (Wuhan-Hu-1) and an antigenically divergent variant of concern (elasomeran/imelasomeran), each

encapsulated into individual LNPs, and co-formulated into a single drug product (Spikevax bivalent). After delivery, both mRNAs are delivered to cells in the body where the two distinct spike protomers, each of which represents one of the three components of the spike trimer, are expressed. After expression these spike protomers assemble into the spike trimer and both homotrimers as well heterotrimers (mixed protomers from the Wuhan spike and the Variant spike), form. The inclusion of both the original and the variant spikes in the vaccine are intended to broaden immunity.

Below are the target variants for the various mRNA-1273 vaccines used in the clinical development program (See Table 1.2).

Table 1.2 Variants and WHO labels for mRNA-1273

Suffix	Variants
mRNA-1273.351	Beta
mRNA-1273.617.2	Delta
mRNA-1273.211	Bivalent: 1:1 ratio of prototype and beta (.351)
mRNA-1273.213	Bivalent: 1:1 ratio of beta (.351) and delta (.617)
mRNA-1273.214	Bivalent: 1:1 ratio of prototype and omicron BA.1 (.529)
mRNA-1273.222	Bivalent: 2 mRNAs: CS-023314 and CX-034476
mRNA-1273.529	Omicron BA.1

Note: The original 1273 vaccine, targeting the Wuhan strain is referred to as prototype.

The expressed Spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

Further details on mechanism of action, indications, pharmaceutical forms, and instructions for use are presented in the CCDS for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran (current v15 dated 15 Nov 2022) in Appendix 1.

2 WORLDWIDE MARKETING APPROVAL STATUS

The International Birth date of elasomeran is 18 Dec 2020. The product is currently authorized in 48 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelosomeran was granted by

the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by Food and Drug administration on 31 Aug 2022.

Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations (eg, immunocompromised) and/or as a booster dose, including authorization for two bivalent vaccines (elasomeran/imelosomeran and elasomeran/davesomeran) continue to expand.

Cumulative information on marketing authorizations in all countries and approval dates are provided in Appendix 11.1.

Table 2.1 Worldwide Marketing Authorizations

List of Authorizations	Link to Table
Use in adults aged 18 years and older (primary series)	Table 20.5
Use in adolescents aged 12 to < 18 years (primary series),	Table 20.6
Use in for ages 6 to <12-year-old pediatrics indication (primary series)	Table 20.7
Use in 6 months to < 6-year-old indication (pediatrics)	Table 20.8
Use as a booster indication in adults (50 ug)	Table 20.9
Use as a booster indication in adolescents (50 ug)	Table 20.10
Third dose in immunocompromised patients	Table 20.11
Elasomeran/imelasomeran booster indication for adults aged 18 years and older	Table 20.12
Elasomeran/imelasomeran booster indication for adolescents aged 12 to <18 years	Table 20.13
Elasomeran/imelasomeran booster indication for the 6 years to <12-year-old (pediatrics)	Table 20.14
Elasomeran/davesomeran booster indication for adults aged 18 years and older	Table 20.15
Elasomeran/davesomeran booster indication for use in adolescents aged 12 to <18 years of age	Table 20.16
Elasomeran/davesomeran booster indication for the 6 years to <12-year-old (pediatrics)	Table 20.17
Elasomeran/davesomeran booster indication for the 6 months to <6-year-old	Table 20.18

3 ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting period, the following safety-related actions were taken by ModernaTx, Inc.:

During the month of Sep 2022, ModernaTx, Inc. became aware of reports of medication errors that were indicating the occurrence of product confusion and product underdosing related to the administration of the bivalent vaccines, elasomeran/imelasomeran and elasomeran/davesomeran. Reports of accidental underdosing of the Spikevax bivalent booster vaccines, indicated that a 0.25 mL dose (equivalent to 25 µg) was administered instead of 0.5 mL (50 µg). In most cases, underdosing was due to dose confusion since the booster dose volume for the original monovalent elasomeran vaccine used earlier in 2022 was 0.25 mL (equivalent to 50 µg).

The marketing authorization holder (MAH) conducted a signal evaluation of the potential signal of medication errors due to product confusion and/or product underdosing. The signal evaluation included a cumulative review of the MAH safety database with a data lock point (DLP) of 04 Oct 2022. Analysis of the data showed that medication error reports had been received at a higher proportion for individuals vaccinated with one of the authorized Spikevax bivalent vaccines (relative to elasomeran original).

Based on the findings of the safety assessment evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a Potential Risk (Not Important) and was classified as a Priority 1 Urgent (emerging) Safety Issue[1].

A communication letter was distributed to those countries where Spikevax bivalent was authorized, and additional informational material regarding dosing information was posted on the ModernaTx, Inc. website for easy access by providers and consumers.

The MAH will continue to monitor events for potential medication errors related to product confusion and/or product underdose using routine pharmacovigilance surveillance.

4 CHANGES TO REFERENCE SAFETY INFORMATION

The Reference Safety Information (RSI) for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in effect at the end of the reporting period (DLP 17 Dec 2022) and used for this report is the CCDS v15.0 (dated 15 Nov 2022). This CCDS was used to assess listedness

[1] Issues which have a significant impact on the product's benefit-risk profile, and which require the most rapid communication and implementation) and that risk minimization measures needed to be implemented in agreement with the respective health authorities in the countries where the bivalent vaccines had been authorized.

of adverse reactions (ARs), risks in risk sections, and to support benefit-risk evaluation in this report. The RSI contains a complete review of the safety profile for the product. This document is provided in Appendix 1.

During this reporting period, the RSI (CCDS) was updated from v13.0 (dated 03 Jun 2022) to v14.0 (dated 18 Jul 2022) and then to v15.0 (dated 15 Nov 2022). The safety-related changes are summarized below in Table 4.1.

Table 4.1 CCDS safety-related changes during the reporting period

Version	Date	Summary of changes
14.0	18 Jul 2022	**Section 4.4, myocarditis:** Deleted last paragraph in line with EMEA/H/C/005791/II/57 (Adolescent booster). **Section 4.8, Table 1:** Added "acute and delayed urticaria" to Skin and subcutaneous tissue disorders SOC. Deleted "includes urticaria" from Immune system disorders SOC and adjusted related footnote.
15.0	15 Nov 2022	**Section 4.1**: Updated the indication to lower and include till 6 months of age and also add bivalent indication. **Section 4.2:** Posology updated to address all possible dosing methods across strength and vaccination type, including bivalents. Added infant and young children site for injection per EMA approval. **Section 4.4:** Updated myocarditis text per Pharmacovigilance recommendations. **Section 4.8:** Added little peds data per EMA approval of EMEA. Added bivalent BA.1 data per EMA.

EMA=European Medicines Agency, EMEA=Europe, Middle East, and Africa, SOC=System Organ Class

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Exposure in Clinical Trials

5.1.1 Cumulative exposure in clinical trials

Cumulatively, 52,530 subjects have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA-1273.617.2, mRNA-1273.529), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its variants mRNA-1283.211), in the mRNA clinical development program sponsored by ModernaTx, Inc. Out of the 52,530 subjects, 42,434 subjects were exposed to mRNA-1273 primary series. The total count of 52,530 represents unique subjects (Subjects enrolled in both trials P301 and P201 (Part C)/P205 or in both P204 and P306 and are only counted once in total).

Estimates of cumulative subject exposure, based upon actual exposure data from completed CTs and the enrolment/randomization schemes for ongoing trials is provided in Table 5.1. Further details on cumulative subject exposure categorized by age, gender, racial group and ethnicity is provided in Table 5.2, Table 5.3, Table 5.4 and Table 5.5, respectively.

Table 5.1 Estimated Cumulative Subject Exposure from Clinical Trials

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P201	Placebo	42[a]
mRNA-1273-P201	mRNA-1273	558[a]
mRNA-1273-P201	mRNA-1273 Booster	344
mRNA-1273-P201	mRNA-1273.351 Booster	40
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	20
mRNA-1273-P203	Placebo	1,144[a]
mRNA-1273-P203	mRNA-1273 100 ug	2,582[a]
mRNA-1273-P203	mRNA-1273 50 ug	52[a]
mRNA-1273-P203	EUA+mRNA-1273 Booster	154[a]
mRNA-1273-P203	Primary series+mRNA-1273 Booster	1,427
mRNA-1273-P204	Placebo	885[a]
mRNA-1273-P204	mRNA-1273	11,030[a]
mRNA-1273-P204	mRNA-1273 10 ug Booster	217
mRNA-1273-P204	mRNA-1273 25 ug Booster	2,886
mRNA-1273-P204	mRNA-1273 50 ug Booster	1
mRNA-1273-P204	mRNA-1273.214 10 ug Booster	2,309
mRNA-1273-P204	mRNA-1273.214 25 ug Booster	236
mRNA-1273-P204	mRNA-1273.214 50 ug Booster	1
mRNA-1273-P205	mRNA-1273 Booster	687[a]
mRNA-1273-P205	mRNA-1273.211 Booster	759[a]
mRNA-1273-P205	mRNA-1273.211	135[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
	Booster+mRNA-1273.214 Booster	
mRNA-1273-P205	mRNA-1273.213 Booster	954[a]
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	511[a]
mRNA-1273-P205	mRNA-1273.529 Booster	508[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	1,157[a]
mRNA-1273-P206	mRNA-1273.214	12[a]
mRNA-1273-P301	Placebo	2,513[a]
mRNA-1273-P301	mRNA-1273	27,833[a]
mRNA-1273-P301	mRNA-1273 Booster	19,609
mRNA-1273-P304	mRNA-1273	81[a]
mRNA-1273-P304	EUA+mRNA-1273	71[a]
mRNA-1273-P304	EUA+mRNA-1273 Booster	82[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	87
mRNA-1273-P305	Overall (Trial is still Blinded)	3,548[a]
mRNA-1273-P306	mRNA-1273.214	188[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	5[a]
mRNA-1283-P101	mRNA-1273	22[a]
mRNA-1283-P201	Overall (Trial is still Blinded)	543[a]
mRNA-CRID-001	mRNA-1273	58[a]

[a]=These numbers were counted to get the total for each study.

Table 5.2 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Age[a]

Age Range	mRNA-1273									mRNA-128		mRNA-CRID	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	
<2 years	0	0	2,828	0	12	0	0	0	166	0	0	0	**2,881**[b]
2 to <6 years	0	0	4,244	0	0	0	0	0	561	0	0	0	**4,333**[b]
6 to <12 years	0	0	4,843	0	0	0	0	0	0	0	0	0	**4,843**
12 to <16 years	0	2,936	0	0	0	0	0	0	0	0	0	0	**2,936**
16 to <18 years	0	996	0	0	0	0	0	1	0	0	0	0	**997**
18 to <65 years	508	0	0	3,858	0	22,826	184	2,350	0	27	447	55	**27,257**[b]
65 to <75 years	128	0	0	1,033	0	6,121	43	1,117	0	0	76	3	**7,692**[b]
75 to <85 years	21	0	0	235	0	1,309	7	75	0	0	16	0	**1,482**[b]
>=85 years	3	0	0	22	0	90	0	5	0	0	4	0	**109**[b]
Missing	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Total	**660**	**3,932**	**11,915**	**5,148**	**12**	**30,346**	**234**	**3,548**	**727**	**27**	**543**	**58**	**52,530**[b]

[a]=Data from ongoing and completed trials till 17 Dec 2022.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.

Table 5.3 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Sex[a]

Sex	mRNA-1273									mRNA-1283		mRNA-CRID	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	
Male	238	2,018	6,050	2,405	7	15,974	124	1,757	380	18	198	21	**26,875**[b]
Female	422	1,914	5,865	2,743	5	14,372	110	1791	347	9	345	37	**25,655**[b]
Missing	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Total	**660**	**3,932**	**11,915**	**5,148**	**12**	**30,346**	**234**	**3,548**	**727**	**27**	**543**	**58**	**52,530**[b]

[a] =Data from ongoing trials and completed trials till 17 Dec 2022.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.

Table 5.4 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Racial Group[a]

Race	mRNA-1273									mRNA-1283		mRNA-CRID	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	
White	626	3,268	8,713	4,352	8	24,034	160	3347	560	19	436	49	**41,715**[b]
Black or African American	16	166	760	389	3	3096	39	12	65	1	70	7	**4,300**[b]
Asian	7	228	843	207	1	1395	13	92	31	1	21	2	**2,641**[b]
American Indian or Alaska Native	4	20	43	25	0	234	2	0	1	0	3	0	**309**[b]

Race	mRNA-1273									mRNA-1283		mRNA-CRID	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	
Native Hawaiian or Other Pacific Islander	1	3	13	10	0	68	0	0	2	0	1	0	**87[b]**
Multiple	2	177	1236	69	0	638	3	56	61	1	6	0	**2,137[b]**
Other	4	40	207	63	0	593	9	17	2	0	1	0	**876[b]**
Not Reported	0	22	76	23	0	171	6	20	4	5	5	0	**310[b]**
Unknown	0	8	24	10	0	117	2	3	1	0	0	0	**154[b]**
Missing	0	0	0	0	0	0	0	1	0	0	0	0	**1**
Total	**660**	**3932**	**11915**	**5148**	**12**	**30346**	**234**	**3548**	**727**	**27**	**543**	**58**	**52,530[b]**

[a]=Data from ongoing and completed trials till 17 Dec 2022.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.

Table 5.5 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Ethnicity[a]

Ethnicity	mRNA-1273									mRNA-1283		mRNA-CRID	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	
Hispanic or Latino	48	483	1,888	672	3	6,229	22	0	83	9	67	15	**8,863[b]**
Not Hispanic or Latino	610	3,413	9,918	4,433	9	23,839	210	0	640	17	470	43	**39,675[b]**
Not Reported	1	32	81	32	0	188	2	0	2	1	6	0	**320[b]**
Unknown	1	4	28	11	0	90	0	0	2	0	0	0	**124[b]**

Ethnicity	mRNA-1273									mRNA-1283		mRNA-CRID	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	
Missing	0	0	0	0	0	0	0	3,548	0	0	0	0	**3,548**
Total	**660**	**3,932**	**11,915**	**5,148**	**12**	**30,346**	**234**	**3,548**	**727**	**27**	**543**	**58**	**52,530**[b]

[a]=Data from ongoing and completed trials till 17 Dec 2022.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.

5.1.2 Interval exposure in clinical trials

As requested by the Pharmacovigilance Risk Assessment Committee (PRAC), information pertaining to interval exposure in CTs has been added in this section.

During the reporting period, 2,663 subjects have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mrNA-1273.222, mRNA-1273.617.2, mRNA-1273.529) or placebo in the mRNA clinical development program sponsored by ModernaTx, Inc.

Further details on the clinical exposure during the reporting period is in Table 5.6.

Table 5.6 Estimated Subject Exposure from Clinical Trials during reporting period

Study ID	Vaccine Type	Total Subject Exposure during the reporting period
mRNA-1273-P201	Placebo	0[a]
mRNA-1273-P201	mRNA-1273	0[a]
mRNA-1273-P201	mRNA-1273 Booster	0
mRNA-1273-P201	mRNA-1273.351 Booster	0
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	0
mRNA-1273-P203	Placebo	0[a]
mRNA-1273-P203	mRNA-1273 100ug	0[a]
mRNA-1273-P203	mRNA-1273 50ug	48[a]

Study ID	Vaccine Type	Total Subject Exposure during the reporting period
mRNA-1273-P203	EUA+mRNA-1273 Booster	102[a]
mRNA-1273-P203	Primary series+mRNA-1273 Booster	40
mRNA-1273-P204	Placebo	0[a]
mRNA-1273-P204	mRNA-1273	1,082[a]
mRNA-1273-P204	mRNA-1273 10ug Booster	42
mRNA-1273-P204	mRNA-1273 25ug Booster	719
mRNA-1273-P204	mRNA-1273 50ug Booster	1
mRNA-1273-P204	mRNA-1273.214 10ug Booster	2,309
mRNA-1273-P204	mRNA-1273.214 25ug Booster	236
mRNA-1273-P204	mRNA-1273.214 50ug Booster	1
mRNA-1273-P205	mRNA-1273 Booster	0[a]
mRNA-1273-P205	mRNA-1273.211 Booster	0[a]
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	102[a]
mRNA-1273-P205	mRNA-1273.213 Booster	0[a]
mRNA-1273-P205	mRNA-1273.214 Booster	0[a]
mRNA-1273-P205	mRNA-1273.222 Booster	511[a]
mRNA-1273-P205	mRNA-1273.529 Booster	0[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	0[a]
mRNA-1273-P206	mRNA-1273.214	12[a]

Study ID	Vaccine Type	Total Subject Exposure during the reporting period
mRNA-1273-P301	Placebo	0[a]
mRNA-1273-P301	mRNA-1273	0[a]
mRNA-1273-P301	mRNA-1273 Booster	0
mRNA-1273-P304	mRNA-1273	0[a]
mRNA-1273-P304	EUA+mRNA-1273	0[a]
mRNA-1273-P304	EUA+mRNA-1273 Booster	21[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	13
mRNA-1273-P305	Overall (Trial is still Blinded)	0[a]
mRNA-1273-P306	mRNA-1273.214	188[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	0[a]
mRNA-1283-P101	mRNA-1273	0[a]
mRNA-1283-P201	Overall (Trial is still Blinded)	0[a]
mRNA-CRID-001	mRNA-1273	58[a]

[a]=To have the total for each study, these numbers were counted

5.2 Exposure from Marketing Experience

5.2.1 Cumulative Patient Exposure from Marketing Experience

Cumulatively, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries (a proportion of doses distributed have been subsequently donated via either bilateral agreements or collaborative efforts such as COVAX). Some countries rely on the assessment of the World Health Organization (WHO) rather than holding a country level approval. Therefore, the countries that have received elasomeran (91) exceed the number of countries where elasomeran has been approved (48 countries/regions or unions/areas). North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed (Table 5.8). Cumulatively, 208,489,076 (13.4%) doses had been distributed in lower-and middle-income countries.

A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the United Kingdom, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered (Table 5.9).

ModernaTx, Inc. internally tracks the number of doses of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran globally. Prior to Jul 2022, ModernaTx, Inc. estimated global doses administered based on review of health authority websites where estimates were posted. More recently, a large number of countries to which ModernaTx, Inc. distributed elasomeran, and elasomeran/imelasomeran and elasomeran/davesomeran did not publicly post data on doses administered with a lag time that was suitable to mandatory monthly safety reporting schedules required in some countries. Because there was concern that the approach of reviewing health authority websites was not sustainable with potentially progressive data degradation, the methods for estimation of administered doses were changed. Review of recent safety reports showed that the proportion of doses distributed globally that had been administered varied from 53% to 59% of the doses distributed. Based on this, the MAH estimated administered doses as 55% of country specific doses distributed plus an estimate of doses donated to COVAX. [Since Sep 2021, the number of donated doses distributed were estimated as 15% of the total distributed doses. Furthermore, a conservative estimate of 25% of the donated doses, were assumed to be administered]. The change in process to estimate administered doses was implemented from

Jul 2022, after the previous PBRER report on Jun 2022. In this PBRER, doses administered in the review period are defined as the difference between the previous PBRER (PBRER#03) and the current PBRER (PBRER#04). Given this change in process, the region-specific interval administered doses are questionably interpretable and hence not presented in this report.

Table 5.7 Total doses distributed and administered for elasomeran andelasomeran/imelasomeran and elasomeran/davesomeran[a]

	Cumulative				Interval	
Region	**Distributed**	**%[a]**	**Administered**	**%[a]**	**Distributed**	**%[a]**
Total	**1,553,749,469**	**100.0**	**912,827,813**	**100.0**	**299,417,683**	**100.0**
North America	**631,787,740**	**40.7**	**347,483,257**	**38.1**	**114,869,440**	**38.4**
US	571,787,750	36.8	314,483,263	34.5	100,826,690	33.7
All Europe	**450,792,773**	**29.0**	**247,936,025**	**27.2**	**116,323,473**	**38.8**
European Economic Area	386,448,843	24.9	212,546,864	23.3	91,040,843	30.4
Asia	**326,051,716**	**21.0**	**179,328,444**	**19.6**	**47,233,330**	**15.8**
Middle East	**61,485,250**	**4.0**	**33,816,888**	**3.7**	**3,983,550**	**1.3**
Latin America	**32,461,600**	**2.1**	**17,853,880**	**2.0**	**11,871,410**	**4.0**
Oceania	**26,176,600**	**1.7**	**14,397,130**	**1.6**	**4,120,400**	**1.4**
Africa	**24,993,790**	**1.6**	**13,746,585**	**1.5**	**1,016,080**	**0.3**
International donations	-	-	**58,265,605**	**6.4**	-	-

[a]=The doses distributed and administered in US, European Economic Area are not mutually exclusive of North America, All Europe respectively. Therefore, their proportions are not included in the total number of doses.

Table 5.8 Doses distributed and administered for elasomeran[a]

	Cumulative				Interval	
Region	**Distributed**	**%[a]**	**Administered**	**%[a]**	**Distributed**	**%[a]**
Total	**1,315,589,716**	**100.0**	**772,908,958**	**100.0**	**63,269,010**	**100.0**
North America	**553,351,210**	**42.1**	**304,343,166**	**39.4**	**36,432,910**	**57.6**
US	505,350,070	38.4	277,942,539	36.0	34,389,010	54.4
All Europe	**340,925,400**	**25.9**	**187,508,970**	**24.3**	**7,956,700**	**12.6**
European Economic Area	301,338,500	22.9	165,736,175	21.4	5,930,500	9.4
Asia	**282,128,566**	**21.4**	**155,170,711**	**20.1**	**3,310,180**	**5.2**

Region	Cumulative				Interval	
	Distributed	%[a]	Administered	%[a]	Distributed	%[a]
Middle East	**22,660,640**	**1.7**	**12,463,352**	**1.6**	**16,50,400**	**2.6**
Latin America	**60,485,300**	**4.6**	**33,266,915**	**4.3**	**11,381,940**	**18.0**
Oceania	**23,676,600**	**1.8**	**13,022,130**	**1.7**	**1,620,400**	**2.6**
Africa	**32,362,000**	**2.5**	**17,799,100**	**2.3**	**916,480**	**1.4**
International donations	-	-	**49,334,614**	**6.4**	-	-

[a]=The doses distributed and administered in US, European Economic Area are not mutually exclusive of North America, All Europe respectively. Therefore, their proportions are not included in the total number of doses

Table 5.9 Spikevax bivalent doses distributed and estimated bivalent doses administered as of 17 Dec 2022[a]

Region	Product 214				Product 222			
	Distributed	%[a]	Administered	%[a]	Distributed	%[a]	Administered	%[a]
Total	**127,413,973**	**100.0**	**70,077,685**	**100.0**	**110,745,780**	**100.0**	**60,910,179**	**100.0**
North America	**10,521,450**	**8.3**	**5,786,798**	**8.3**	**67,915,080**	**61.3**	**37,353,294**	**61.3**
US	21,600	0.0	11,880	0.0	66,416,080	60.0	36,528,844	60.0
All Europe	**82,625,473**	**64.8**	**45,444,010**	**64.8**	**27,241,900**	**24.6**	**14,983,045**	**24.6**
European Economic Area	57,868,443	45.4	31,827,644	45.4	27,241,900	24.6	14,983,045	24.6
Asia	**29,334,350**	**23.0**	**16,133,893**	**23.0**	**14,588,800**	**13.2**	**8,023,840**	**13.2**
Latin America	**999,950**	**0.8**	**549,973**	**0.8**	-	-	-	-
Africa	**99,600**	**0.1**	**54,780**	**0.1**	-	-	-	-
Oceania	**2,500,000**	**2.0**	**1,375,000**	**2.0**	-	-	-	-
Middle East	**1,333,150**	**1.0**	**733,233**	**1.0**	**1,000,000**	**0.9**	**550,000**	**0.9**

North America: Canada and US
Europe: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Ukraine, Switzerland, UK
Asia: Bangladesh, Bhutan, Cambodia, Indonesia, Japan, Kyrgyzstan, Nepal, Pakistan, Philippines, Singapore, Taiwan, Tajikistan, Thailand, Turkmenistan, Uzbekistan, Vietnam, South Korea
Middle East: Israel, Kuwait, Qatar, Saudi Arabia, United Arab Emirates, Palestine
Latin America: Argentina, Bolivia, Chile, Colombia, Dominica, Grenada, Haiti, Mexico, Paraguay, Peru, St. Lucia, St. Vincent and the Grenadines

Oceania: Australia, Fiji, Vanuatu
Africa: Angola, Benin, Botswana, Brunei Darussalam, Burkina Faso, Central African Republic, Democratic Republic of Congo, Egypt, Guinea, Kenya, Nigeria, Rwanda, Sao Tome and Principe, Tanzania, Tunisia, Uganda, Zambia
[a]=The doses distributed and administered in US, European Economic Area are not mutually exclusive of North America, All Europe respectively. Therefore, their proportions are not included in the total number of doses.

Summaries of ModernaTx, Inc. distribution administered by country and distribution by lots/batches are included in Appendix 11.2.

Demographic characteristics of US recipients of all COVID-19 vaccine products for primary series are shown in Figure 5-1, data for booster doses are shown in Figure 5-2 and data for Bivalents are shown in Figure 5-3. Because product specific demographic data (age, gender, and race/ethnicity) are not published by Center for Disease Control and Prevention (CDC) or international public HAs, figures presented in this section consider vaccinations targeting SARS-CoV-2 as a class. The proportion of vaccines administered was highest for those 50-64 years of age, female gender, and white race.

Figure 5-1 Characteristics of US Recipients of All COVID-19 Vaccine Products for Primary Series by Age, Sex, and Race/Ethnicity

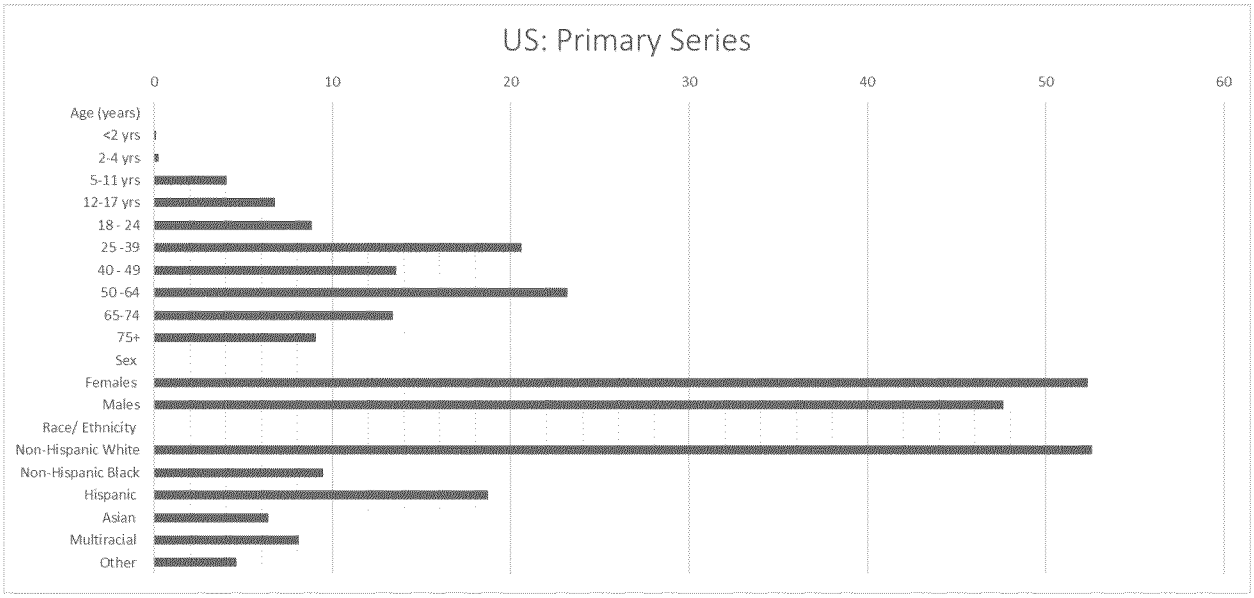


Figure 5-2 Characteristics of US Recipients of All COVID-19 Vaccine Products, Booster Doses, by Age, Sex, and Race/Ethnicity

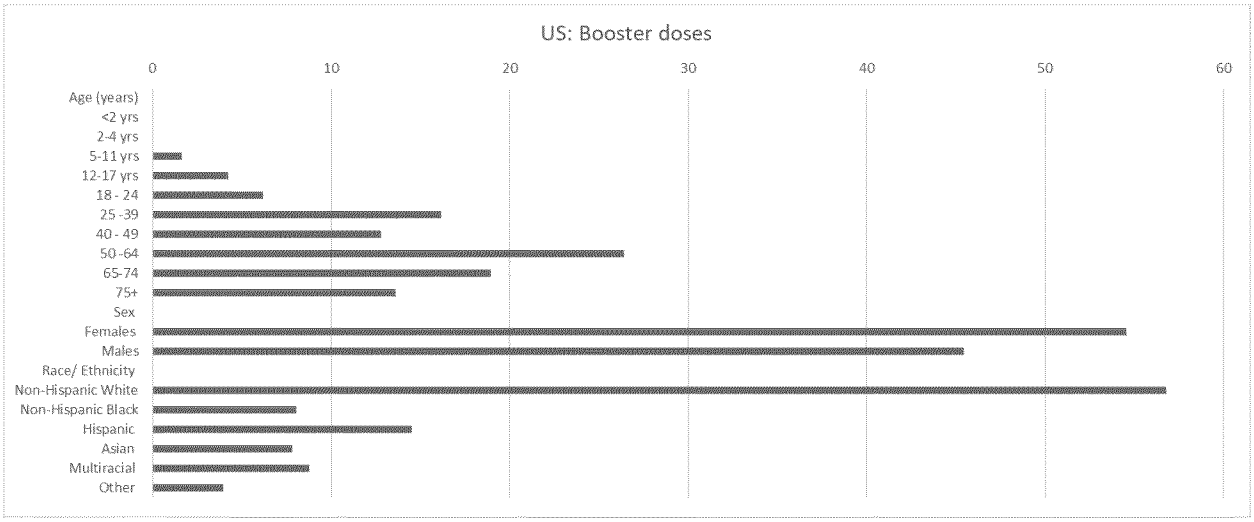
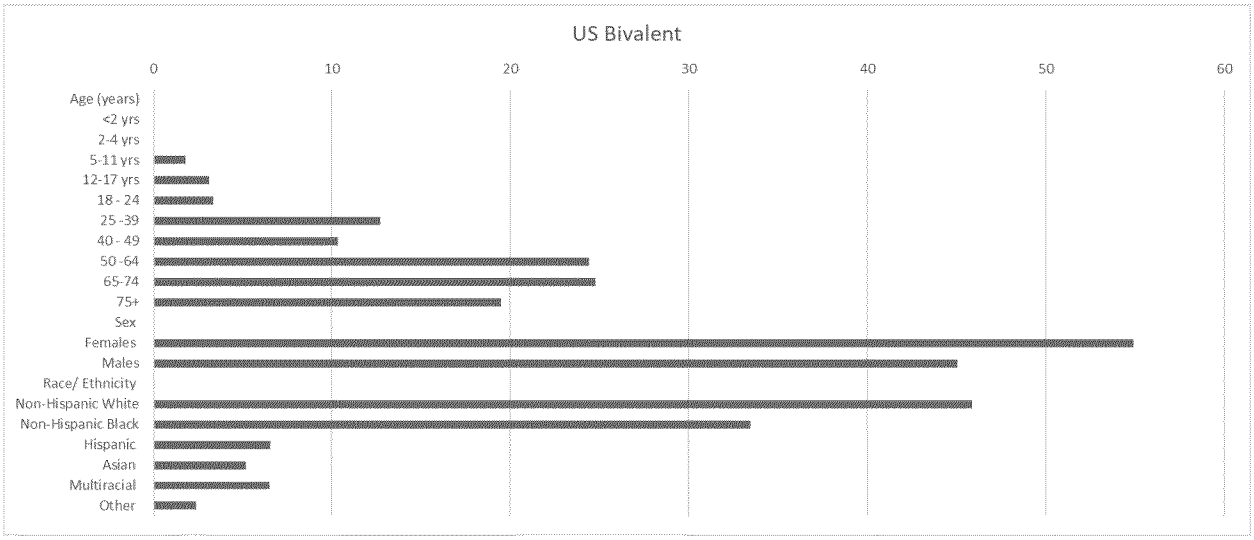


Figure 5-3 Characteristics of US Recipients of All COVID-19 Vaccine Products, elasomeran/davesomeran, by Age, Sex, and Race/Ethnicity



Available demographic characteristics of vaccine recipients (primary series boosters and bivalents) are shown for the European Economic Area (EEA) (Figure 5-4, Figure 5-5, Figure 5-6 and Figure 5-7) and Canada (Figure 5-8, Figure 5-9 and Figure 5-10). In the EEA, the highest proportion of vaccinated individuals were among 25-49 years of age for primary series and 60 years and older for booster doses. In Canada, the highest proportion of vaccinated individuals were among 18-29 years for primary series and 60-69 years for booster doses. Information on distribution by

gender was not published by European Center for Disease Prevention and Control (ECDC) at the time that the data were accessed (https://vaccinetracker.ecdc.europa.eu /public/extensions/COVID-19/vaccine-tracker.html accessed 19 Jun 2022).

Figure 5-4 EEA Recipients of All COVID-19 Vaccine Products for Primary Series by Age

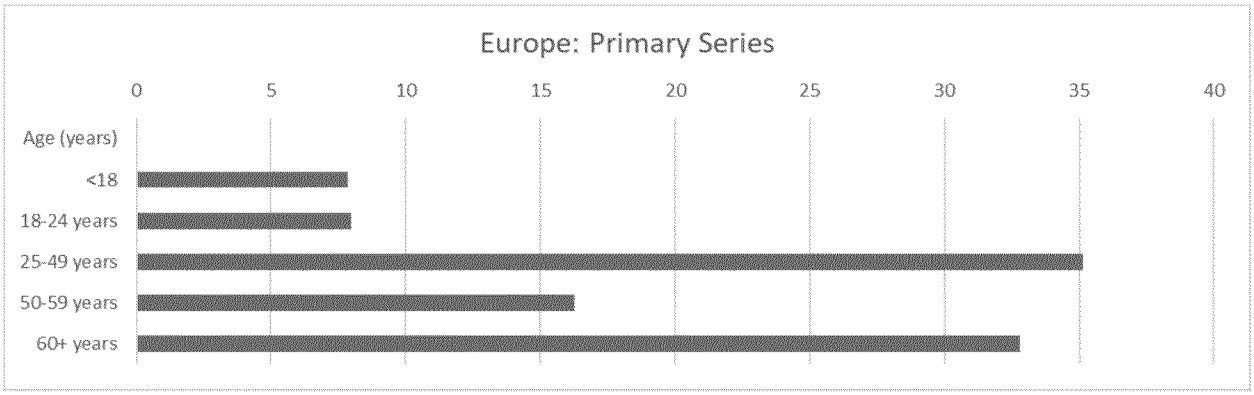


Figure 5-5 EEA Recipients of All COVID-19 Vaccine Products for First Booster by Age

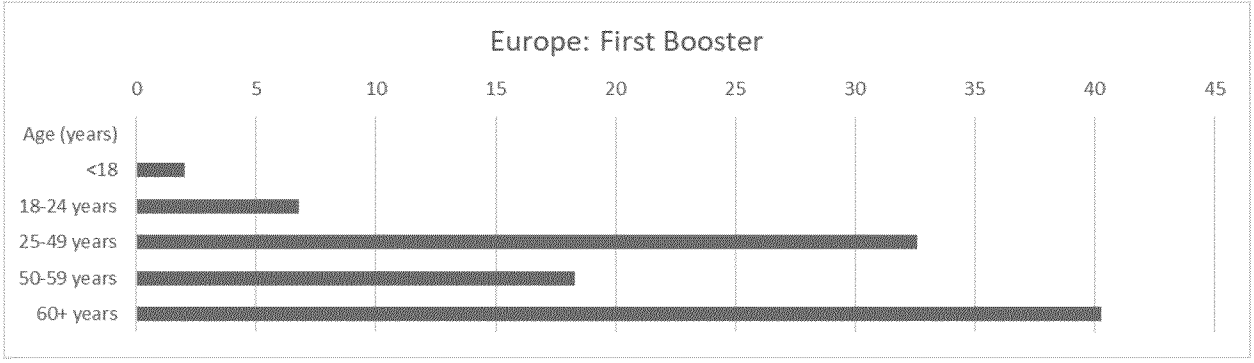


Figure 5-6 EEA Recipients of All COVID-19 Vaccine Products for Second Booster by Age

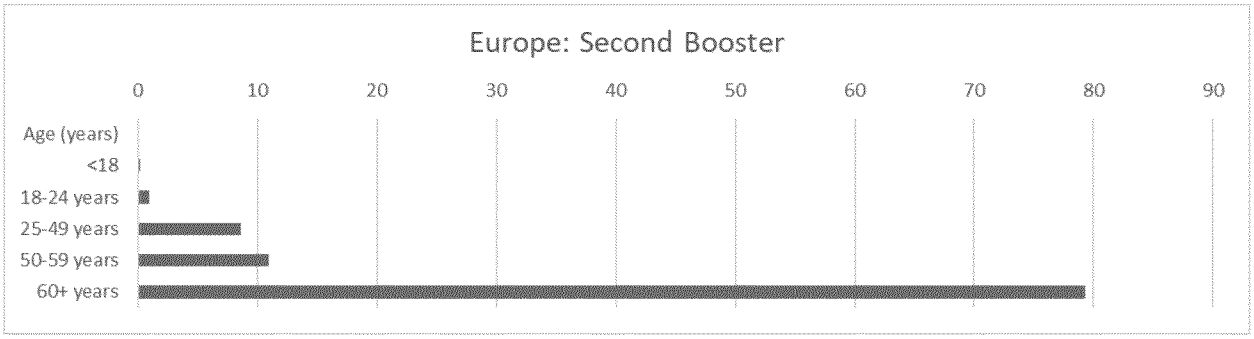


Figure 5-7 EEA Recipients of All COVID-19 Vaccine Products for Third Booster by Age

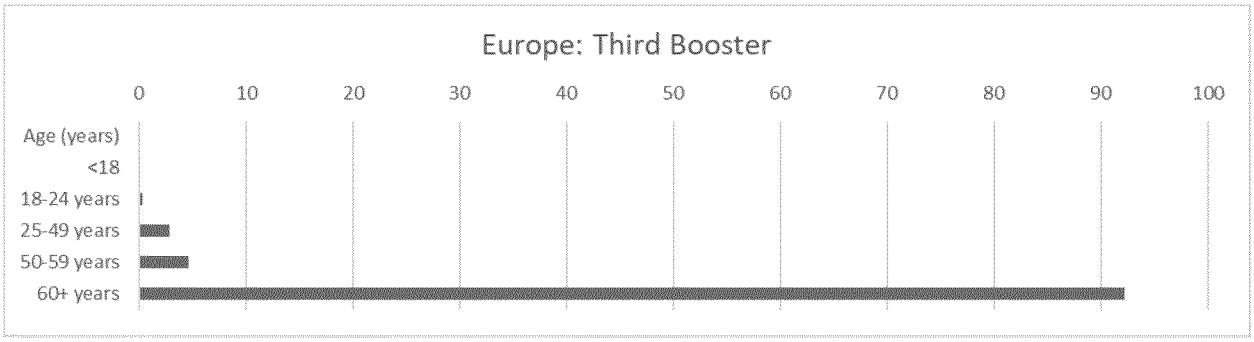


Figure 5-8 Canadian Recipients of All COVID-19 Vaccine Products for Primary Series by Age and Sex

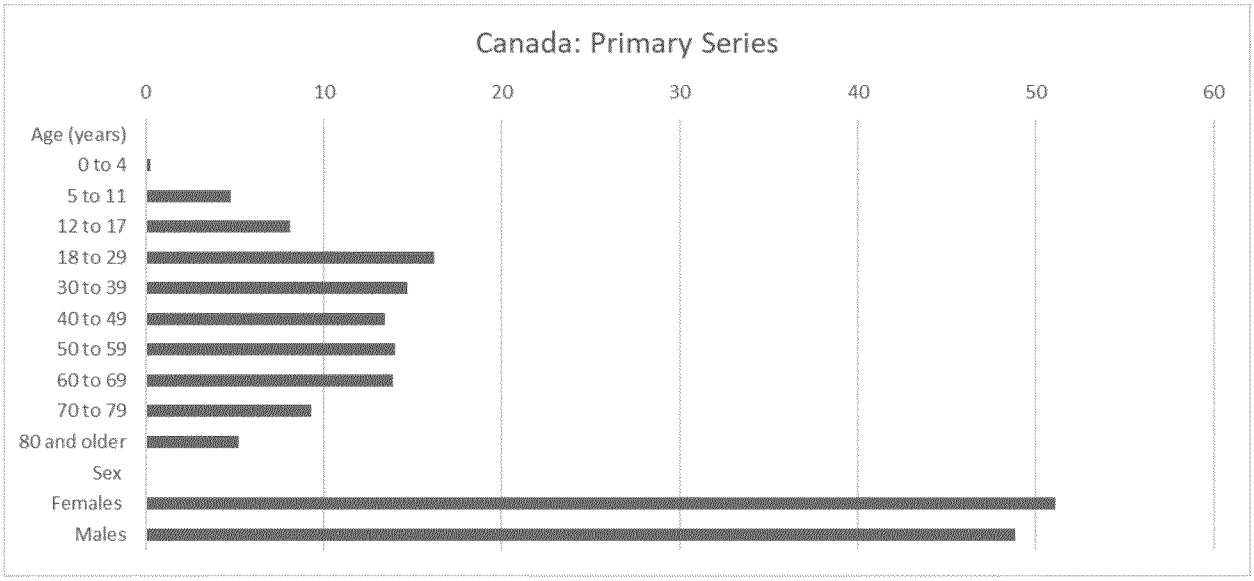


Figure 5-9 Canadian Recipients of All COVID-19 Vaccine Products for First Booster by Age and Sex

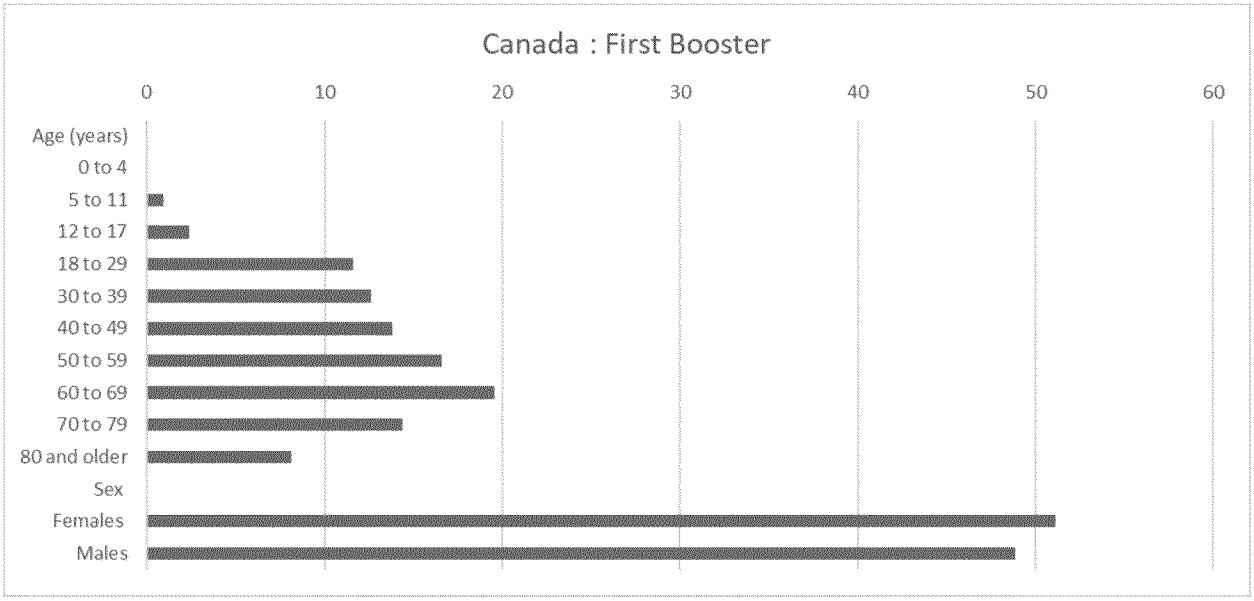
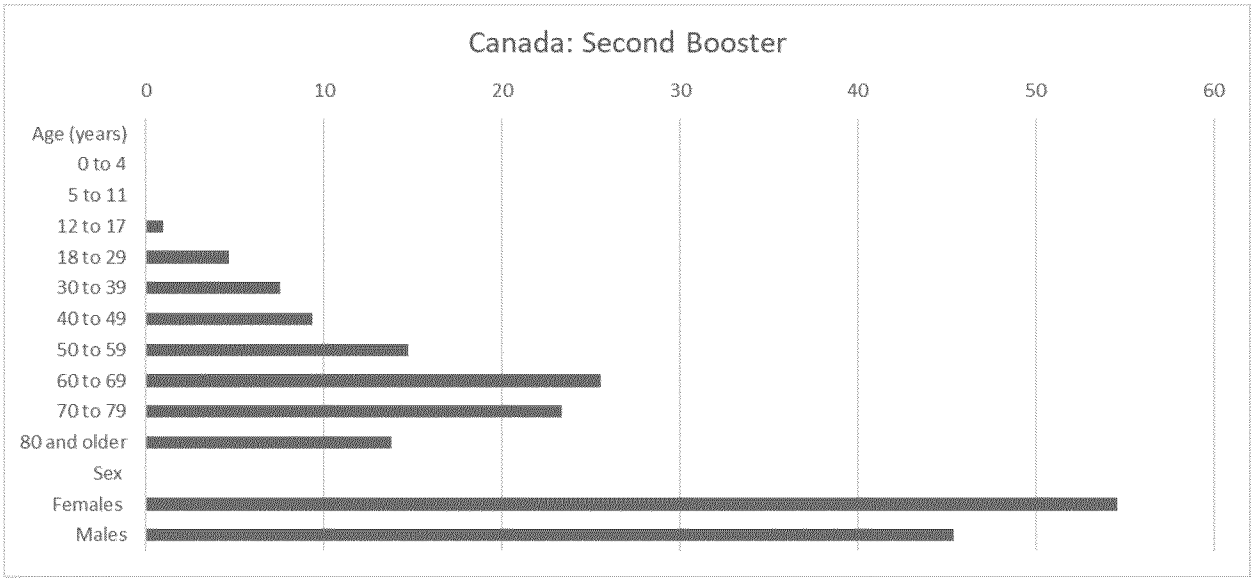


Figure 5-10 Canadian Recipients of All COVID-19 Vaccine Products for Second Booster by Age and Sex



5.2.2 Interval Patient Exposure from Marketing Experience

In this reporting period (19 Jun 2022 to 17 Dec 2022), a total of 63,269,010 doses of elasomeran had been delivered and an estimated total of 110,037,791 doses had been administered. North America, Europe, and Latin America accounted for approximately 88% of elasomeran doses distributed (Table 5.7). During this reporting period, 12,622,400 (20%) elasomeran doses had been distributed in lower- and middle-income countries.

5.2.3 Traceability

Batch monitoring is performed using distribution data derived from the ModernaTx, Inc. supply chain and US manufacturing records. Patient level exposure for the EU is presented below by age. Subpopulation data across gender, race and ethnicity are not presently available.

As part of the EU Risk Management Plan (RMP) and Summary of Product Characteristics (SmPC), instructions have been provided with our product for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability. ModernaTx, Inc. has also developed Traceability and Vaccination Reminder cards.

The card is accessible electronically and though a Quick response (QR) code, on the applicant's website. The Traceability and Vaccination Reminder cards contain the following elements:

- Placeholder space for name of vaccine;
- Vaccine brand name and manufacturer name;
- Placeholder space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine.
- QR code that links to a website with additional information on product use; and
- Adverse event reporting information.

The vaccine carton labeling also contains a scannable 2D barcode that provides the batch/lot number and expiry date. In addition, ModernaTx, Inc. also provides stickers (two stickers per dose, containing printed batch/lot information, product identification, and 2D bar code) that encodes a unique identifier [serial number]) either in cartons or to be shipped along with each shipment, in the countries where this is required.

6 DATA IN SUMMARY TABULATIONS

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 was used for the coding of adverse events (AEs)/adverse drug reactions (ADRs) presented in this report. The line listings and summary tabulations are first arranged alphabetically by primary MedDRA System Organ Class (SOC) and then by the Preferred Term (PT).

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative (18 Dec 2020 to 17 Dec 2022) summary tabulation of Serious Adverse Events (SAEs) from Company-sponsored CTs is provided in Appendix 2. The SAEs presented in this summary tabulation were derived from Company-sponsored interventional CTs. Inclusion requirement parameters for the incorporation of data from Company-sponsored CTs are that the SAE occurred during active treatment, the SAE originated from a clinical study with mRNA-1273, the event was assessed as serious, and the active treatment was mRNA-1273 or placebo.

6.3 Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

A cumulative (18 Dec 2020 to 17 Dec 2022) and interval (19 Jun 2022 to 17 Dec 2022) summary tabulation of ADRs (serious and non-serious) is provided in Appendix 3. The ADRs presented in this tabulation were derived from spontaneous sources (healthcare professionals [HCPs], consumers, scientific literature, and regulatory authorities [RAs]) as well as serious ADRs from non-interventional studies and non-interventional solicited sources.

7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS IN THE REPORTING INTERVAL

7.1 Completed Clinical Trials

There was one ModernaTx, Inc. sponsored CT which was completed during the reporting period.

Study Protocol Number: mRNA-1273-P201

Study Title: A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older.

Clinical Study report was finalized on 22 Aug 2022.

Summary:

Part A was the Blinded Phase, was a randomized, observer-blind, and placebo-controlled study, and evaluated the safety, reactogenicity, and immunogenicity of two dose levels (50 μg and 100 μg) of mRNA-1273 vaccine, each administered as two doses 28 days apart, in adult participants at least 18 years of age, grouped into two cohorts (≥ 18 to < 55 years old and ≥ 55 years old). Following authorization of a COVID-19 vaccine under EUA, the study was amended to provide transition to Part B, the Open-label Interventional Phase.

Part B was designed to offer participants who received placebo in Part A of the study. This was an option to receive two injections of open-label mRNA-1273 (100 μg) and participants who received one or two doses of 50 μg or 100 μg mRNA-1273 in Part A of this study the option to receive a single booster dose of 50 μg mRNA-1273.

Part C: A proof-of-concept, was the open-label interventional part of the study to evaluate a single booster dose of mRNA-1273.351 (50 μg or 20 μg) or mRNA-1273/mRNA-1273.351 mixture (50 μg total). Part C was prompted by the need to proactively prepare for vaccination strategies that induce broader protection against variants of concern such as the SARS-CoV-2 Beta (B.1.351) variant.

The mRNA-1273-P201 Primary Analysis (Day 57) clinical study report (CSR), dated 22 Aug 2022, provides the primary analysis of safety and immunogenicity data through Day 57 of Part A (database lock 05 Nov 2020) and includes a complete description of the study investigational plan and methodology. The mRNA-1273-P201 CSR Addendum 1 (End of Part A), dated 13 Aug 2021, provides updated safety and immunogenicity data through the Program Data Vector (database lock 10 Jun 2021). The mRNA-1273-P201 CSR Addendum 2 (Part B), dated 24 May 2022, provides safety and immunogenicity results for Part B (database lock 23 Nov 2021). The mRNA-1273-P201 CSR Addendum 3 (Part C) dated 22 Aug 2022 provides safety and immunogenicity results for Part C (database lock 23 Nov 2021) and is considered the last study report for P201 marking the completion of the study.

Study Conclusions: All booster vaccines demonstrated no unexpected reactogenicity or safety results. Findings were similar to those of Part A and Part B, thereby further supporting the acceptable benefit-risk profile of the booster vaccination with monovalent and bivalent variant vaccines.

7.2 Ongoing Clinical Trials

There was a total of 11 ModernaTx, Inc. sponsored CTs ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P305, mRNA-1283-P101, mRNA-1283-P201, mRNA-1273-P206, mRNA-1273-P306, and mRNA-CRID-001), during the current reporting period. Of these 11 ongoing CTs, three trials (Protocol mRNA-1283-P101, Protocol mRNA-1283-P201 and Protocol mRNA-CRID-001) included an additional mRNA-1273 treatment arm. Cumulative exposure split by studies has been presented in Table 7.1.

There was no clinically important information that arose from ongoing CT during the reporting period.

Table 7.1 Summary of Cumulative Subject Exposure by Study

Study ID	Total subjects exposed
mRNA-1273-P203	3,932
mRNA-1273-P204	11,915
mRNA-1273-P205	5,148
mRNA-1273-P206	12
mRNA-1273-P301	30,346
mRNA-1273-P304	234
mRNA-1273-P305	3,548
mRNA-1273-P306	727
mRNA-1283-P101	27
mRNA-1283-P201	543
mRNA-CRID-001	58

Refer to Appendix 5 for further details of all the ongoing and completed studies during the reporting period.

7.3 Long-term Follow-up

Patients completing CTs mRNA-1273-P101 (Division of Microbiology and Infectious Diseases [DMID] 20-0003), mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P903, and mRNA-1273-P904 are followed up for long-term safety. The clinical development program has a safety follow-up period of 12 months in all the above listed studies except in the Phase 3 study mRNA-1273-P301 where subjects will be followed up for 24 months.

In the Phase 3 Study mRNA-1273-P301, the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) which is 183 days (range: 1 to 218 days), or approximately 6 months. The follow-up time is through Day 209 for the Phase 1 study mRNA-1273-P101 (DMID 20-0003) and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.

As of the DLP of this PBRER, there have been no significant safety findings in the ongoing studies nor in the completed studies mRNA-1273-P201 and mRNA-1273-P101 (DMID 20-0003) studies, which are being assessed to characterize the long-term safety of mRNA-1273/mRNA-1273.214/mRNA-1273.222.

7.4 Other Therapeutic Use of Medicinal Product

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran have not been investigated for any other therapeutic use during the reporting period.

7.5 New Safety Data Related to Fixed Combination Therapies

This section is not applicable as elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran are monotherapies and are not marketed as a combination drug.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

The following non-interventional studies were ongoing during the reporting period:

mRNA-1273-P902

Title: Moderna mRNA-1273 Observational Pregnancy Outcome Study

Status: Enrolment for this prospective pregnancy registry began in Oct 2021. Although data collection is ongoing and remains a commitment, enrolment has proceeded slowly, and the study

has been replaced in the EU-RMP by ongoing study mRNA-1273-P905 and planned study mRNA-1273-P919, a US administrative claims-based study of pregnancy safety. It is expected that study mRNA-1273-P902 will be terminated upon approval of the study protocol and initiation of data management for study mRNA-1273-P919. At this time, no safety findings have yet been identified.

mRNA-1273-P903

Title: Post-marketing safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity.

Status: This is a retrospective observational cohort study which uses secondary, de-identified individual level medical and pharmacy claims data provided by HealthVerity. Analyzes are ongoing for study, which includes components of active vaccine surveillance via a historically controlled comparator and signal refinement using a SCRI design. The main results of preliminary signal refinement analyzes discussed in Interim Report#7 (Oct 2022) are presented here. The final report will be prepared by 30 Jun 2023.

Results:

There were 140,122,236 individuals identified in the HealthVerity database at any time between 01 Dec 2017 and 10 Dec 2020. Of these individuals, 108.8 million were enrolled in a health plan providing information on enrolment during the same time frame. We excluded 134,778 individuals will missing information on sex, 6,096 individuals with missing information on age, and 15,157,248 individuals without continuous enrolment for at least 365 days at any time during the study period before sampling 50,015,708 individuals to mirror the distribution of the 2019 US census age and sex distribution. Of these individuals, 38,686,912 were at least 18 years of age and 11,328,796 were under 18 years of age.

To form the pre-COVID and COVID era cohorts, 50,015,708 individuals meeting study entry criteria were sampled to mirror the distribution of the 2019 US census age and sex distribution. Of these individuals, 38,686,912 were at least 18 years of age and 11,328,796 were under 18 years of age. Among the historical comparator populations, there were 908,741 and 894,045 immunocompromised adults and 33,640 and 35,011 immunocompromised pediatric individuals in the pre-COVID and COVID eras, respectively. Among females of childbearing age (12-55 years) in the historical populations, after applying study inclusion criteria, there were 91,122 and 65,519 pregnant women in the pre-COVID and COVID eras, respectively. Within the

pre-COVID comparator population, 3,104,556 adults and 1,570,161 pediatric individuals were vaccinated for influenza.

There were 22,589,594 adults and 119,401 pediatric patients vaccinated with elasomeran who met study entry criteria through 25 Apr 2022. Among these individuals, 64.3% of adults and 55.6% of pediatric patients received a second dose. Among individuals who received a second dose, 23.9% of adults and 26.6% of pediatric patients also received a third dose. There were 622,568 immunocompromised adults who were vaccinated with elasomeran, of which 65.8% received a second dose; 35.7% of immunocompromised adults with a second dose also received a third dose. Slightly more immunocompromised adults received a non- elasomeran COVID-19 vaccine during follow-up than the general population (2.1% vs. 1.6%). There were 33,639 pregnant women 12-55 years who received elasomeran and met study entry criteria to be included in the pregnancy-specific analyzes, and 61% received a second dose of elasomeran. Of these, 4.1% also received a third dose.

Table 8.1 indicates the specific populations by Adverse Events of Special Interest (AESI) that met the threshold for both signal refinement (observed expected [O/E] analyzes) and signal evaluation (SCRI analyzes) in this interim report.

Table 8.1 Adverse Events of Special Interest meeting thresholds for signal refinement and evaluation

AESI	Met Threshold for Observed versus Expected Analysis[a]	Met Threshold for Self-Controlled Risk Interval Analysis[b]
Anosmia/Ageusia	Both Adults + Pediatrics	Both Adults + Pediatrics
Anaphylaxis	Both Adults + Pediatrics	Both Adults + Pediatrics
Chilblain-like Lesions	Both Adults + Pediatrics	Both Adults + Pediatrics
Cerebral Venous Sinus Thrombosis	Adults	Adults
Coagulation Disorders	Pediatrics	Pediatrics
Erythema Multiforme	Both Adults + Pediatrics	Both Adults + Pediatrics
Immune Thrombocytopenia[c]	-	-
Narcolepsy/Cataplexy	Adults	Adults

AESI	Met Threshold for Observed versus Expected Analysis[a]	Met Threshold for Self-Controlled Risk Interval Analysis[b]
Thrombosis with Thrombocytopenia	Pediatrics	Pediatrics
Arrhythmia	Pediatrics	Pediatrics
Bell's Palsy	Pediatrics	-
Single Organ Cutaneous Vasculitis	Both Adults + Pediatrics	Both Adults + Pediatrics
Seizures/Convulsions	Pediatrics	Pediatrics
Gestational Diabetes	-	-
Preeclampsia	-	-
Preterm Labor	-	-
Spontaneous Abortion	-	-
Stillbirth	-	-
Acute Aseptic Arthritis	Adults	-
Acute Disseminated Encephalomyelitis	-	-
Acute Kidney Injury	Pediatrics	Pediatrics
Acute Liver Injury	-	-
Acute Myocardial Infarction	Pediatrics	-
Acute Respiratory Distress Syndrome	Pediatrics	Pediatrics
Aseptic Meningitis	-	-
Deep Vein Thrombosis	Pediatrics	
Disseminated Intravascular Coagulation	-	-
Encephalitis/Encephalomyelitis	-	-

AESI	Met Threshold for Observed versus Expected Analysis[a]	Met Threshold for Self-Controlled Risk Interval Analysis[b]
Glomerulonephritis	-	-
Guillain-Barre Syndrome	Adults	-
Heart Failure	-	-
Ischemic Heart Disease	Pediatrics	-
Kawasaki Disease	Adults	-
Meningoencephalitis	-	-
Microangiopathy	-	-
Multisystem Inflammatory Syndrome	-	-
Pulmonary Embolism	Pediatrics	-
Stroke, Hemorrhagic	-	-
Stroke, Non-Hemorrhagic	-	-
Transverse Myelitis	-	-
Type I Diabetes Mellitus	Pediatrics	Pediatrics

[a] Overall crude incidence rate ratio (IRR) is ≥2 with an event count ≥5; crude incidence rate ratio is ≥2 with an event count ≥5 in any subgroup.

[b] Lower bound of 95% confidence interval (CI) for observed cases is greater than the estimated number of expected cases; or the lower bound of the observed to expected ratio is >1.

[c] Immune thrombocytopenia met the threshold for observed versus expected and SCRI analyzes in Interim Report 6 (IR6, thus SCRI analyzes were performed for this report despite Immune thrombocytopenia (ITP) no longer meeting those thresholds for the current report.

Myocarditis

Interpretation of analyzes of myocarditis is similar to that shared in Interim Report 6 (IR6), where 1,636 cases of myocarditis were identified using claims through 25 Apr 2022; most (68.9%) cases occurred after the second dose of elasomeran. Dose-agnostic, dose 1 and dose 2-specific SCRI analyzes produced findings comparable to the previous interim report, where the event rate ratio (ERR) was greater following the second dose compared to the first dose among adults overall and

among both males and females 18-29 years. Event rate ratios following dose 3 were attenuated compared to IR6.

Consistent with IR6, there was not a sufficient number of myocarditis events among the pediatric population to conduct SCRI analyzes.

Pericarditis

Interpretation of analyzes of pericarditis has also not changed substantially from IR6, where 3,175 cases of pericarditis occurred through 25 Apr 2022; most (69%) cases were identified after the second dose of elasomeran. Observed ERRs were largely consistent with IR6 following dose-agnostic, dose 1, and dose 2-specific SCRI analyzes, where the ERR was greater following the second dose compared to the first dose among adults overall and among both males and females 18-29 years. The ERR for young adult females was increased, however this was estimated from only 6 events in the risk (n=4) and control (n=2) windows. Unlike IR6, in both the adult population and males overall, a slight attenuation in the ERR was observed in dose 3 analyzes compared to dose 2 in the current analyzes.

Consistent with IR6, there was not a sufficient number of pericarditis events among the pediatric population to conduct SCRI analyzes.

Other AESIs

In the current interim report, anosmia/ageusia, anaphylaxis, arrhythmia, chilblain-like lesions, cerebral venous sinus thrombosis, coagulation disorders, erythema multiforme, narcolepsy/cataplexy, seizures/convulsions, single organ cutaneous vasculitis, and thrombosis with thrombocytopenia met pre-specified thresholds for execution of SCRI analyzes in at least one subgroup. Results from the signal detection (unadjusted historical IRR comparison) and preliminary refinement (O/E) stages of analyzes were similar to those presented in the last interim report, with the exception of immune thrombocytopenia which no longer met the threshold for O/E analyzes and Bell's palsy which no longer met the threshold for SCRI analyzes. Given the results of IR6, SCRI analyzes were conducted for immune thrombocytopenia regardless, however insufficient case counts were available to support SCRI for Bell's palsy.

Anosmia, ageusia

There were 18,721 cases observed among adults through 25 Apr 2022, compared to 16,202 in IR6. Among adults (overall ERR 1.04, 95% CI 0.89–1.22), dose 3 ERRs were elevated among males 18-29 years and ≥75 years, noting that these estimates were imprecise. Dose 3 results among other age and sex strata were largely consistent with the dose-agnostic and dose 1 or 2 specific analyzes.

SCRI analyzes among pediatric patients were conducted for previous interim reports and will be included in the final report.

Anaphylaxis

There were 4,764 cases observed among adults through 25 Apr 2022, compared to 3,781 in IR6. Following dose-agnostic SCRI analyzes, increased risks were observed among all adult and females age strata. Similar findings were seen following dose 1-specific results. Following dose 2 and dose 3-specific analyzes, increased risks were observed among several age and sex strata, although generally attenuated compared to dose-agnostic and dose 1 estimates.

Among pediatric patients, there were 35 cases, compared to 30 in IR6. Results of dose-agnostic SCRI analysis among the pediatric population were generally consistent with IR6, except among pediatric patients and female pediatrics overall where elevated ERRs were newly observed. This is consistent with the known safety profile of elasomeran.

Arrhythmia

Among adults, neither signal refinement nor evaluation were conducted as there were no increased rates of arrhythmia observed after any dose of elasomeran compared to historical rates.

There were 155 cases observed among pediatric patients, compared to 121 in IR6. Results from signal refinement in IR6 newly met the threshold for SCRI analyzes, for which increased risk of arrhythmia was observed in dose-agnostic, dose 1 and dose 2 SCRI analyzes among male pediatric patients, albeit among a small number of patients producing imprecise estimates. Dose 3 SCRI were not performed because the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report.

Bell's palsy

There were 7,927 cases observed among adults through 25 Apr 2022, compared to 6,341 in IR6. Rates of Bell's palsy were not elevated following any dose of elasomeran among adults.

There were 14 cases observed among pediatric patients, compared to 12 in IR6. Results from signal refinement in IR6 newly met the threshold for SCRI analyzes for Bell's palsy, however the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report. Bell's palsy will continue to be monitored for IR8 as cases accrue.

Chilblain-like lesions

There were 1,353 cases observed among adults through 25 Apr 2022, compared to 969 in IR6. Compared to IR5, results from dose-agnostic and dose 1 and 2-specific analyzes were slightly

attenuated, though increased risk was still observed across multiple age and sex subgroups. With the exception of overall females and females 40-64 years, no elevated ERRs were observed in dose 3 SCRI analyzes.

Cases will continue to be monitored among the pediatric population with SCRI analyzes expected to be included in the final report.

Cerebral venous sinus thrombosis

There were 360 cases observed among adults through 25 Apr 2022, compared to 272 in IR6. Results of SCRI analyzes of Central Venous Sinus Thrombosis (CVST) were consistent with IR6 with elevated ERRs observed among adults ≥75 years. There were only 14 events in the dose 3-specific analysis to draw meaningful conclusions. Results from two sensitivity analyzes requiring claims for imaging 14 days before or after the CVST event and applying a washout period for CVST utilizing all available data resulted in no observed increased risk in any subgroup.

Only 2 cases observed among pediatric patients through 25 Apr 2022, consistent with IR6.

Coagulation disorders

Among adults, there were 112,178 cases observed through 25 Apr 2022, compared to 87,962 in IR6. Consistent with IR6, the rates of coagulation disorders following elasomeran vaccination were not elevated after any dose.

Among pediatric patients, 56 cases were observed, compared to 44 in IR6. Dose-agnostic and dose 1-specific SCRI analyzes resulted in elevated ERRs among overall pediatric and female pediatric patients, which were attenuated when compared to IR6. Clinician review of the specific events included within the composite definition of coagulation disorders in IR6 suggested that the observed events may be reflective of erroneous lab values secondary to other diagnoses or medications or of unclear clinical significance, leading to an overestimation in the risk of clinically relevant coagulation disorders. Dose 3 SCRI were not performed because the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report.

Erythema multiforme

There were 1,239 cases observed among adults through 25 Apr 2022, compared to 1,023 in IR6. Newly reported SCRI analyzes among adults resulted in elevated ERRs among young women 30-39 years in dose-agnostic, dose 1, and dose 2-specific analyzes. Older males had elevated ERRs in dose 2-specific analyzes, while elevated ERRs were observed among young adults aged

18-29 years in dose 3-specific analyzes, although both estimates may be imprecise due to low sample size.

There were 38 cases observed among pediatric patients, compared to 29 in IR6. Consistent with IR6, there was no elevated risk of erythema multiforme in the dose-agnostic analysis. There was not a sufficient number of events (≥10) to perform dose specific SCRI analyzes for this report.

Immune thrombocytopenia

There were 3,474 cases observed among adults through 25 Apr 2022, compared to 2,765 in IR6. Consistent with IR6, ERRs were attenuated, and slightly elevated, in the dose-agnostic and dose specific analyzes across age and sex subgroups. Additional sensitivity analysis excluding all cases using all prior available data resulted in elevated ERRs only among adults 50-64 years, which was not previously observed.

Among pediatric patients, there were 5 cases through 25 Apr 2022, compared to 4 in IR6. Results from signal refinement in IR6 met the threshold for SCRI analyzes for ITP among pediatrics <12 years, however the minimum threshold for SCRI analyzes (≥10 cases) was not met in this report. Immune thrombocytopenia will continue to be monitored for IR8 as cases accrue.

Narcolepsy/cataplexy

There were 3,207 cases observed among adults through 25 Apr 2022, compared to 2,555 in IR6. SCRI analyzes were largely consistent with IR6, identifying an increased risk of narcolepsy/cataplexy among adults ≥75 years. Among immunocompromised adults, an elevated ERR in the dose-agnostic SCRI was newly observed among males 50-64 years, although among only 2 events in the control window. Sensitivity analyzes requiring a washout of narcolepsy/cataplexy utilizing all available data resulted in slightly elevated ERRs that were attenuated when compared to the primary analyzes.

Among pediatric patients, neither signal refinement nor evaluation were conducted as there were no increased rates of narcolepsy/cataplexy observed after any dose of elasomeran compared to historical rates.

Seizures/convulsions

There were 51,673 cases observed among adults through 25 Apr 2022, compared to 41,356 in IR6. Among adults, neither signal refinement nor evaluation were conducted as there were no increased rates of seizures/convulsions observed after any dose of elasomeran compared to historical rates.

There were 184 cases observed among pediatric patients, compared to 151 in IR6. Newly included dose-agnostic and dose 1-specific SCRI analyzes found an increased risk of seizures/convulsions among pediatrics overall and within several age and sex-specific strata. Elevated ERRs were observed following dose 2, however there is greater uncertainty around these estimates given there were only 11 events. There was insufficient sample size to conduct dose 3-specific SCRI analyzes in the pediatric population.

Single organ cutaneous vasculitis

There were 3,141 cases observed among adults through 25 Apr 2022, compared to 2,517 in IR6. Newly included SCRI analyzes resulted in elevated ERRs within dose-agnostic, dose 1, and dose 2-specific SCRI analyzes among adults 18-29 years. Within the dose 3-specific analysis, an increased risk of single organ cutaneous vasculitis was observed among adults aged 50-64 years, though estimates may be imprecise given the sample size.

There were 9 cases observed among pediatric patients, compared to 8 in IR6. Consistent with IR6, Single Organ Cutaneous Vasculitis (SOCV) met the threshold for SCRI analyzes, however there were insufficient sample sizes to conduct SCRI analyzes among pediatric patients. SOCV will continue to be monitored within the pediatric population as events accrue.

Thrombosis with thrombocytopenia

There were 112,663 cases observed among adults through 25 Apr 2022, compared to 88,357 in IR6. Among adults, neither signal refinement nor evaluation were conducted as there were no increased rates of thrombosis with thrombocytopenia observed after any dose of elasomeran compared to historical rates.

In pediatric patients, 59 cases were observed, compared to 47 in IR6. Consistent with IR6, no increased risk of thrombosis with thrombocytopenia was observed in dose-agnostic and dose 1 SCRI analyzes. Due to insufficient sample size, dose 2 and 3-specific SCRI analyzes were not included in this report but will continue to be monitored.

AESI for which SCRI analyzes have not yet been performed

The AESI that met thresholds for observed versus expected analyzes from the last interim report consistently met those thresholds with the updated data in this interim report, with the exception of immune thrombocytopenia. Additionally, following preliminary, unadjusted signal detection, thresholds for O/E analyzes were met in at least 1 adult or pediatric population comparison for the following AESI: acute aseptic arthritis, acute respiratory distress syndrome (ARDS), and acute myocardial infarction. Acute respiratory distress syndrome and type 1 diabetes both had higher

than expected observed events in their respective risk windows following elasomeran vaccination among pediatric patients, newly meeting the threshold for self-controlled analyzes. Protocol annexes describing the approach for these self-controlled analyzes will be submitted, with the results from those analyzes reported in the next interim report.

Discussion

Interim results of this post-marketing safety study describe the absolute and relative incidence rates of 43 pre-specified AESI among adult and pediatric patients across three time-specific cohorts (pre-COVID, COVID era, and post-EUA elasomeran vaccination era).

Consistent with the previous interim report, AESI with elevated incidence rates among adults with at least 1 dose of elasomeran were identified for anaphylaxis, anosmia/ageusia, cerebral venous sinus thrombosis, chilblain-like lesions, erythema multiforme, immune thrombocytopenia, myocarditis, pericarditis, and narcolepsy/cataplexy. Sensitivity analyzes for narcolepsy/cataplexy and ITP resulted in slightly elevated ERRs that were attenuated compared to primary analyzes, and sensitivity analyzes for CVST resulted in no elevated ERRs. Results from the self-controlled analysis for arrhythmia, SOCV, and seizures/convulsions are newly included in this interim report. Within the adult population, no AESI newly met the threshold for self-controlled analyzes.

Among pediatric patients, elevated rates among those who received at least one dose of the elasomeran vaccine was consistent with IR6. Interpretation of these analyses should consider that all use as of the DLP was off-label administration of adult dosage in the United States. Unlike IR6, acute kidney injury met the threshold for SCRI analyzes as part of this report, similar to IR5 where these estimates were first reported, and are expected to be included in the final report. Upon further refinement via O/E analysis, ARDS and type 1 diabetes mellitus (DM) met the criteria for a self-controlled analysis. A protocol annex will be submitted detailing the approach to further evaluate these potential findings. Results from the self-controlled analysis for ARDS and type 1 DM in pediatric patients will be presented in IR8.

Results evaluating the risk of pregnancy-related AESI (gestational diabetes, preeclampsia, preterm labor, spontaneous abortion, and stillbirth) found no elevated risks, consistent with IR6 after all doses of elasomeran.

Additional analyzes in forthcoming reports will characterize and refine the observed signals. The subsequent IR8 will include results for additional SCRI analyzes identified in this report.

mRNA-1273-P904

Title: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of Spikevax in Europe.

Summary: A preliminary screening stage analyzes for selected databases in this observational study using large administrative databases in Denmark, Norway, Italy, Spain and the UK was presented in Interim Report 3 on 30 Sep 2022. the number of eligible elasomeran recipients with at least one dose of elasomeran was 563,998 in Denmark, 428,779 in Italy, 532,797 in Norway, and 587,436 in Spain.

Rates of several AESIs were lower than expected in Italy, subject to further investigation and quality control.

Results of the signal detection, available from the Italy/ARS database, identified the following AESIs as fulfilling pre-specified criteria for additional signal evaluation based on at least one analysis performed: Diabetes type 1, (Idiopathic) Thrombocytopenia , Microangiopathy, Heart failure, Stress-induced cardiomyopathy, Coronary artery disease (CAD), Arrhythmia, Myocarditis, Pericarditis, Cerebrovascular disease, Deep vein thrombosis, Splanchnic vein thrombosis, Coagulation disorders, Acute liver injury, Acute kidney injury, Generalized convulsions, ARDS, Anaphylaxis, and Death of any cause. No signal evaluation was undertaken, and signal detection was not conducted in other databases.

The results reported here should be considered preliminary and are not interpretable as indicative of any changes to the current benefit-risk profile of elasomeran. Results inclusive of all participating countries and all study objectives will be presented and interpreted in the Final Study Report.

mRNA-1273-P905

Title: Monitoring safety of Spikevax in pregnancy: an observational study using routinely collected health data in five European countries.

Summary: For this observational cohort study carried using large administrative databases in Denmark, Norway, Italy, Spain and the UK, with feasibility counts were described in the Sep 2022 interim study update. At this time, no safety findings have yet been identified given the early stage of the study.

mRNA-1273-P911

Title: Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA).

Summary: The overarching goal of this study is to characterize presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (elasomeran). A first interim feasibility report was completed 31 Oct 2022. At this time, no safety findings have yet been identified given the early stage of the study.

In addition, the following studies are planned as of the DLP of this PBRER. No safety findings have yet been identified given the early stage of these studies:

mRNA-1273-P910

Title: Natural History of Vaccine-Associated Myocarditis

Summary: The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and Spikevax bivalent vaccination. A statistical analysis plan is currently in development.

mRNA-1273-P915

Title: Survey on acute phase safety for persons with underlying diseases with high risk

Status: The overarching goal of this post-marketing surveillance (PMS) activity to confirm the incidence of hypersensitivity reactions including shock and anaphylaxis observed after vaccination with this drug and to explore risk factors in persons with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A protocol is currently under review.

mRNA-1273-P916

Title: Survey on Shock and Anaphylaxis for Persons with Underlying Diseases with High Risk

Status: The overarching goal of this PMS activity is to identify the incidence of specified AEs in the acute phase observed after vaccination in subjects with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A protocol is currently under review.

mRNA-1273-P917

Title: Survey on non-acute phase safety for persons with underlying diseases

Status: The overarching goal of this PMS activity is to identify hypotheses for the safety evaluation of this product by confirming the occurrence status of non-acute hospitalization-associated serious events observed after vaccination in persons with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A protocol is currently under review.

mRNA-1273-P918

Title: General Use Results Survey: Spikevax Intramuscular Injection (Previously COVID-19 Vaccine Moderna Intramuscular Injection) During the Early Phase of Treatment With Novel Corona Vaccine, Follow-up of Key Survey Participants.

Summary: The overarching goal of this PMS activity is to follow-up subjects who are vaccinated early after the marketing approval of this product in Japan for 11 months from the day after the day following the last day of the last vaccination with this drug as the primary immunization (the last day of the observation period in the health status investigation of preceding vaccinees) to 12 months after the last vaccination with this drug as the primary immunization, and to collect information on SAEs observed during the follow-up period and COVID-19.

mRNA-1273-P919

Title: An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to SPIKEVAX During Pregnancy

Status: This observational PMS study will evaluate the risk of adverse pregnancy and infant outcomes following maternal exposure to elasomeran during pregnancy. A statistical analysis plan is currently under review.

mRNA-1273-P920

Title: Post-marketing safety of an Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine in the United States

Status: The overarching aim of this study is to characterize the safety of the Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine as used in routine clinical practice. A statistical analysis plan is currently under review.

mRNA-1273-P921

Title: Evaluation of Post-marketing safety of Spikevax (elasomeran) in the Kingdom of Saudi Arabia

Status: The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and Spikevax bivalent vaccination. A protocol is currently under review.

mRNA-1273-P923

Title: Post-marketing safety of Spikevax vaccine in South Korea

Status: The overarching aim of the study is to characterize the safety of the elasomeran vaccine (primary series and booster) as used in the routine clinical practice in Korea. A protocol is currently in development for a retrospective database study supporting this aim.

mRNA-1273-P924

Title: Post-marketing Surveillance: Use-Result Surveillance with Spikevax Bivalent.

Status: This PMS activity aims to evaluate safety of elasomeran elasomeran/imelasomeran (SARS-CoV-2 mRNA vaccine)] and elasomeran/davesomeran in Korea. A protocol has been recently approved for execution of the survey.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other Clinical Trials

9.1.1 Investigator-sponsored Studies

The following Investigator-sponsored Study was completed during the reporting period:

Short Title: RADAVA

Title: A prospective study of rheumatoid arthritis disease activity and immunogenicity following COVID-19 vaccination.

Summary: For this study, enrolment has been completed, first patient first visit dated 30 Mar 2021 and planned final report date is 30 Jun 2022. Total no of subjects enrolled were 107. No AEs were reported. No significant safety findings have been identified for the above study during the reporting period of this PBRER.

The following Investigator-sponsored Studies were ongoing during the reporting period:

Short Title: Vaccine in chronic lymphocytic leukaemia (CLL)

Title: Vaccine responsiveness in patients with CLL.

Summary: For this study enrolment has been completed, first patient first visit dated 01 Sep 2020 and planned final report date is Sep 2022. Total no of subjects enrolled were 36. No AEs were reported. No significant safety findings have been identified for the above study during the reporting period of this PBRER.

Short tittle: N/A

Title: A Phase 2 trial of the safety and immunogenicity of the COVID-19 vaccine in participants with hematologic malignancies and various regimens of immunosuppression, and in participants with solid tumors on Programmed Cell Death Ligand (PD1/PDL1) inhibitor therapy.

Summary: For this study enrolment is still going on, first patient first visit dated 30 Apr 2021 and planned final report date is Mar 2023. Total no of subjects enrolled were 17. There was a SAE reported to the sponsor, but it was deemed related to patient's disease course Graft-versus-host disease and not related Investigational product (IP) (mRNA-1273). Report did not send to the FDA. No significant safety findings have been identified in the above study during the reporting period of this PBRER.

Short Tittle: T-Cell immunity

Title: T-Cell immunity

Description for T-Cell immunity: Recently, two mRNA vaccines to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have become available, but there is also an emergence of SARS-CoV-2 variants with increased transmissibility and virulence. A major concern is whether the available vaccines will be equally effective against these variants. The vaccines are designed to induce an immune response against the SARS-CoV-2 spike protein which is required for viral entry to host cells. Immunity to SARS-CoV-2 is often evaluated by antibody production, while less is known about the T-cell response. Here we developed, characterized, and implemented two standardized, functional assays to measure T-cell immunity to SARS-CoV-2 in uninfected, convalescent, and vaccinated individuals. We found that vaccinated individuals had robust T-cell responses to the wild type of spike and nucleocapsid proteins, even more so than convalescent patients. We also found detectable but diminished T-cell responses to spike variants (B.1.1.7, B.1.351, and B.1.1.248) among vaccinated but otherwise healthy donors. Since decreases in antibody neutralization have also been observed with some variants, investigation into the T-cell response to these variants as an alternative means of viral control is imperative. Standardized

measurements of T-cell responses to SARS-CoV-2 are feasible and can be easily adjusted to determine changes in response to variants. Estimated completion date is 25 Feb 2024.

Summary: For this study enrolment has been completed, first patient first visit dated in 2022 and actual/planned final report date is Sep 2023. No AEs have been reported and no significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: SCQM

Title: N/A

Summary: For this study enrolment has been completed, first patient first visit dated in 03 Apr 2021 and actual/planned final report date is Feb 2023. Total number of subjects enrolled were 912. No AEs were reported. No significant safety findings have been identified for the above study during the reporting period of this PBRER.

Short Tittle: COVERALL

Title: Risk factors for infection with SARS-CoV-2 and for life-threatening evolution of COVID-19 in patients with autoimmune diseases in Switzerland.

Summary: For this study enrolment has been completed, first patient first visit dated 26 Oct 2022 and actual/planned final report date is 31 Dec 2023. Total number of subjects enrolled were 80. No AEs were reported. No significant safety findings have been identified for the above study during the reporting period of this PBRER.

Short Tittle: AP-HA

Title: N/A

Summary: For this study enrolment has been completed, first patient first visit dated in 22 Aug 2022 and actual/planned final report date is Aug 2023. Total number of subjects enrolled were 414. No AEs were reported. No significant safety findings have been identified for the above study during the reporting period of this PBRER.

9.1.2 Licensing partners studies

9.1.2.1 Completed trials

<u>Sponsored by the Moffitt Cancer Center</u>:

Study or Protocol Number: MCC 21536

Immunogenicity of a Third Dose of mRNA-1273 Vaccine (Moderna) Among Cancer Patients.

Country: US

Dosing details: mRNA-1273 100 µg.

Summary: Planned enrolment is about 400 subjects and number of subjects enrolled and exposed to mRNA-1273 were 336. Start date for this study was 10 Sep 2021 and study was completed by 29 Jul 2022. No safety concerns were reported. No new efficacy or effectiveness information has been obtained. No regulatory actions were taken for safety reasons.

Sponsored by Sanofi:

Protocol or Study Number: QHD00028

A Phase 2, open-label study to assess the safety and immunogenicity of Fluzone® high dose quadrivalent (Influenza vaccine), 2021-2022 formulation and a third dose of Moderna COVID-19 vaccine (mRNA-1273 vaccine) administered either concomitantly or singly in adults 65 years of age and older previously vaccinated with a 2-dose schedule of Moderna COVID-19 vaccine.

Country: US

Dosing details: Eligible participants were randomly assigned to 1 of 3 treatment groups in a 1:1:1 ratio corresponding to:

- concomitant administration of Fluzone High Dose Quadrivalent and COVID-19 mRNA Vaccine,
- administration of Fluzone High Dose Quadrivalent alone, and
- administration of COVID-19 mRNA Vaccine alone.

Fluzone High Dose Quadrivalent vaccine, 2021-2022 formulation.

Moderna COVID-19 Vaccine (mRNA-1273 vaccine): Each dose contained 100 µg of mRNA (formulated in SM-102 LNPs).

Summary: Planned enrolment was about 100 participants in each arm and number of subjects enrolled were 100 participants in Group 1 (concomitant), 92 participants in Group 2 (QIV-HD alone), and 104 participants in Group 3 (mRNA-1273 alone) and actual subjects exposed to mRNA-1273 were 100 participants in Group 1 (concomitant), and 104 participants in Group 3 (mRNA-1273 alone). Start date for this study was 16 Jul 2021 and last contact with patient was on 08 Feb 2022. Clinical study report has been finalized on 15 Sep 2022. No detrimental effect of

concomitant administration on the immune response to both Fluzone high dose quadrivalent and mRNA-1273 vaccine. The combined reactogenicity of Fluzone high dose quadrivalent and mRNA-1273 vaccines administered concomitantly was similar to that after administration of mRNA-1273 vaccine alone. Reactogenicity was lower for Fluzone high dose quadrivalent vaccine single administration. No significant safety findings were identified during the reporting period. Overall, concomitant administration of Fluzone High Dose Quadrivalent and mRNA-1273 vaccines was found to be safe with no safety concerns identified during the study conduct.

Sponsored by the Takeda:

Study or Protocol Number: TAK-919-1501

A Phase 1/2, Randomized, Observer-Blind, Placebo-Controlled Trial to Evaluate the Safety and Immunogenicity of TAK-919 by Intramuscular Injection in Healthy Japanese Male and Female Adults Aged 20 Years and Older.

Country: Japan

Dosing details: mRNA-1273 100 µg, 2 doses with 28 days interval.

Summary: Planned enrolment is 200 subjects (active: placebo=150:50) and number of subjects enrolled were 200 of which 150 subjects were exposed to mRNA-1273. TAK-919 is same as mRNA-1273. Start date for this study was 21 Jan 2021. Study was completed on 15 Sep 2022. In the overall study period analysis, TAK-919, administered 28 days apart, demonstrated a well-tolerated and acceptable safety profile in the participant population enrolled in this study in both age groups (≥20 to <65 years old and ≥65 years old). No new safety findings were observed since the primary analysis until Day 57. Data in the overall study period analysis provided evidence of the robust immunogenicity of TAK-919 when administered as 2 doses separated by 28 days.

Sponsored by DMID of National Institute of Allergy and Infectious Diseases (NIAID):

Protocol or Study Number: mRNA-1273-P101/20-0003/NCT04283461

A Phase 1, open-label, dose-ranging study to access the safety and immunogenicity of 2019-nCov Vaccine (mRNA-1273) in Healthy Adults.

Country-US

Dosing details: In this study doses were divided into below mentioned groups and all groups had option of booster dose 100 µg.

1. Cohort 1 ages 18-55 25 µg mRNA-1273

2. Cohort 2	ages 18-55	100 µg mRNA-1273
3. Cohort 3	ages 18-55	250 µg mRNA-1273
4. Cohort 4	ages 56-70	25 µg mRNA-1273
5. Cohort 5	ages 56-70	100 µg mRNA-1273
6. Cohort 6	ages 56-70	250 µg mRNA-1273
7. Cohort 7	ages ≥71	25 µg mRNA-1273
8. Cohort 8	ages ≥71	100 µg mRNA-1273
9. Cohort 9	ages ≥71	250 µg mRNA-1273
10. Cohort 10	ages 18-55	50 µg mRNA-1273
11. Cohort 11	ages 56-70	50 µg mRNA-1273
12. Cohort 12	ages ≥71	50 µg mRNA-1273

Summary: Planned enrolment was about 140 subjects and actual subjects exposed to mRNA-1273 were 120. Start date for this study was 16 Mar 2020 and projected end date is 26 Apr 2023. No safety concerns were reported. Dose of 250 µg was not well tolerated (previously reported). No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. Dose of 250 µg was not well tolerated (previously reported). Immunogenicity data was submitted to FDA and published. ModernaTx, Inc. has all the immunogenicity data and papers generated. Preliminary CSR was published in Feb 2021. Follow-up for booster is still ongoing.

9.1.2.2 Ongoing trials

Sponsored by DMID of NIAID:

Protocol or Study Number: mRNA-1273-P102/21-0002/NCT04785144

A Phase 1, open-label, randomized study to access the safety and immunogenicity of a SARS-CoV-2 variant vaccine (mRNA-1273.351) in naïve and previously vaccinated adults.

Country-US

Dosing details: In this study, dosing was conducted in 2 different arms and further 2nd arm was divided into 8 arms according to the doses as follows:

1. ARM 1A: 50 µg 1273.35,
2. ARM 1B: 25 µg 1273+25 µg 1273.351,
3. ARM 2A: 100 µg 1273/100 µg 1273/50 µg 1273.351,
4. ARM 2B:50 µg 1273/50 µg 1273/50 µg 1273.351,
5. ARM 2C: 100 µg 1273.351/100 µg 1273.351,
6. ARM 2D: 50 µg 1273.351/50 µg 1273.351,
7. ARM 2E: 100 µg 1273/100 µg 1273.351,
8. ARM 2F:50 µg 1273/50 µg 1273.351,
9. ARM 2G:50 µg 1273 + 50 µg 1273.351/50 µg 1273 + 50 µg 1273.351,
10. ARM 2H:25 µg 1273 + 25 µg 1273.351/25 µg 1273 + 25 µg 1273.351.

Summary: Planned enrolment was about 210 subjects and actual subjects exposed to mRNA-1273 were 135. Start date for this study was 29 Mar 2020 and projected end date is Apr 2023. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons.

Protocol or Study Number: 21-0012

A Phase 1/2 study of delayed heterologous SARS-CoV-2 vaccine dosing (Boost) after receipt of EUA vaccines.

Country-US

Dosing details: mRNA-1273 - 100 µg; mRNA-1273-50 µg, 1273-211-100 µg.

Summary: Planned enrolment was about 433 subjects and actual subjects exposed to mRNA-1273 were 423. Start date for this study was 28 May 2021 and projected end date is 14 Dec 2023. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. ModernaTx, Inc. has all the immunogenicity data and papers generated. Immunogenicity reports have been submitted to the FDA. This study has additional manufacturers to ModernaTx, Inc.; for this reason, total enrolment exceeds that noted here.

Protocol or Study Number: mRNA-1273-P511/22-0004

Phase 2 Clinical Trial to Optimize Immune Coverage of SARS-CoV-2 Existing and Emerging Variants - COVID-19 Variant Immunologic Landscape Trial (COVAIL Trial).

Country-US

Dosing details: In this study, dosing was conducted in 6 different arms as follows:

1. Arm 1: 1 Dose Prototype mRNA-1273, = (99);
2. Arm 2: 1 Dose Beta (B.1.351) + Omicron (B.1.1.529) = (100);
3. Arm 3: 2 Dose Beta (B.1.351) + Omicron (B.1.529) = (102);
4. Arm 4: 1 Dose Delta (B.1.1529) = (101);
5. Arm 5: 1 Dose Omicron (B.1.1.529) = (100);
6. Arm 6: 1 Dose Omicron (B.1.1.529) + Prototype 1273 = (100).

Summary: Planned enrolment was about 600 subjects and actual subjects exposed to mRNA-1273 were 602. Start date for this study was 30 Mar 2022 and projected end date is 28 Oct 2023. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. 194 breakthrough infections to date, sequencing of the variants is ongoing, as well as correlates of protection study being conducted. Manuscript reporting on serological data through day 91, for stages 1-3, being prepared.

Sponsored by Glaxo SmithKline (GSK):

Protocol or Study Number: 217670 (ZOSTER-091)

A Phase 3, randomized, open-label, controlled, multicenter study to evaluate the immune response and safety of both herpes zoster subunit vaccine in healthy adults aged 50 years and older and the influenza virus vaccine in healthy adults aged 18 years and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.

Country-US

Dosing details: mRNA-1273 50 µg per dose (embedded in SM-102 LNPs); water for injections q.s. 0.5 mL;

Flu D-QIV: Flu Quadrivalent Influenza vaccine 15 µg per strain/dose;

HZ/su: Varicella-Zoster Vaccine gE (50 µg) and AS01B: QS-21 (50 µg), MPL (50 µg), liposomes; water for injections q.s. 0.5 Ml.

Summary: Planned enrolment was about 1,546 subjects and actual subjects exposed to mRNA-1273 were 1,534. Total enrolment was 1,546 (12 either withdrew/screen-failed). Start date for this study was 07 Oct 2021 and projected end date is estimated in Feb 2023. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons.

Sponsored by National Cancer Institute (NCI):

Study or Protocol Number 000115

A Trial of the Safety and Immunogenicity of the COVID-19 Vaccine (mRNA-1273) in Participants with Hematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumors on PD1/PDL1 Inhibitor Therapy, Including Booster Doses of Vaccine.

Country: US

Dosing details: The vaccine will be administered in 2 doses, 28 days apart. Participants will receive an IM injection (0.5 mL) of mRNA-1273 on Day 1 and Day 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394).

Summary: Up to 120 participants will be enrolled, 1) 60 participants with solid tumor malignancies who have initiated programmed cell death 1(PD1)/programmed cell death ligand 1(PDL1) inhibitor therapy as part of standard of care and are deemed to have a stable regimen without the need for any immunosuppressive therapy or corticosteroids; 2) Sixty participants with leukemia, lymphoma, multiple myeloma and participants post-allogeneic stem cell transplant will be enrolled based on their perceived risk of immunosuppression. Till 17 May 2022, 17 subjects were exposed to mRNA-1273. Start date for this study was 27 Apr 2021 and estimated study completion date is 25 Feb 2024. No significant safety findings in this ongoing CT have been identified during the reporting period.

Sponsored by the University of California, Los Angeles (UCLA):

Study or Protocol Number: COVID-19 Version 2.0

Phase I/II, Open-label Dose-Escalation Trial of High Dose mRNA-1273 Booster for Lung Transplant Recipients.

Country: US

Dosing details: 50 ug (n=20), 100 ug (n=20), and 200 ug (n=20).

Summary: Planned enrolment was about 60 subjects and number of subjects enrolled and exposed to mRNA-1273 were 19. Start date for this study was Mar 2022 and project end date is 27 Feb 2023. No safety concerns were reported. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. Only 4 participants have been enrolled and data analysis has not yet commenced.

Sponsored by South Africa Medical Research Council (SAMRC):

Study or Protocol Number: Sisonke 4 (SHERPA)/mRNA-1273-P508

Sisonke Heterologous mRNA-1273 boost after prime with Ad26.COV2.S (SHERPA study). Open-label, phase 3 study to evaluate the effectiveness of heterologous mRNA-1273 boosting of the single or two dose Ad26.COV2.S COVID-19 vaccine among health-care workers in South Africa.

Country: South Africa

Dosing details: 50 ug.

Summary: Planned enrolment was about 15,000 subjects and number of subjects enrolled and exposed to mRNA-1273 were 12,340 subjects. Actual recruitment end date is 12 Nov 2022 and expected last visit is May 2023. Ninety-six AEs have been reported, of which 17 were Grade 1 Related AEs and 3 were Grade 2 Related AEs. Nine SAEs have been reported, all of which were Not Related to the study product. Eight AESI have been reported, 4 of which were Related to study product. Five hundred and sixty-six cases of Reactogenicity have been reported, none of which were Grade 3 or higher. Thirteen Breakthrough infections have been reported, one of which resulted in Death. The remaining breakthrough infections were Mild or Asymptomatic infections. There are no safety concerns, new efficacy/effectiveness information or regulatory actions taken to report.

Sponsored by Merck, Sharp and Dohme (MSD):

Study or Protocol Number: V110-911-00

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a

Booster Dose of SARS-CoV-2 mRNA Vaccine in Healthy Adults 50 Years of Age or Older.

Country: US, including Puerto Rico

Dosing details: Participants enrolled in the concomitant groups will receive either V110 or V114 (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive placebo.

Summary: Planned enrolment is about 1,300 subjects and total subjects enrolled were 850 subjects and all 850 subjects enrolled were exposed to mRNA-1273. Start date for this study was 12 Jan 2022 and project end date is planned to be 27 Jul 2023. No safety concerns were reported. No new efficacy or effectiveness information has been obtained. No regulatory actions were taken for safety reasons.

Study or Protocol Number: V503-076-00

A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9v Human papillomavirus and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age.

Country: US

Dosing details: 50 µg primary series (2 doses of 50 µg 28 days apart).

Summary: Planned enrolment is about 400 subjects and number of subjects enrolled and exposed to mRNA-1273 were 81. Start date for this study was 28 Mar 2022 and project end date is estimated as 03 Apr 2024. No new safety concerns, and no regulatory actions taken for safety reasons during the reporting period. There is no information that would affect the safety profile of the product with no AESIs identified in trial participants through the reporting period. There is no new efficacy, effectiveness, or immunogenicity information.

Sponsored by the University of Southampton (CoV Boost):

Study or Protocol Number: RHM MED1781

A randomized, phase II UK multicenter study to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2.

Country: UK

Dosing details: mRNA-1273.529 50 µg.

Summary: For mRNA-1273.529 50 µg, planned enrolment is about 205 subjects and number of subjects enrolled and exposed to mRNA-1273 were 209. Start date for this study was 18 Feb 2022 and project end date is 31 Nov 2023. No SAEs are reported to ModernaTx, Inc. Interim analysis is not yet complete for efficacy and effectiveness information. No regulatory actions have been taken for safety reasons.

For mRNA-1273.214 50 µg, planned enrolment is about 100 subjects and number of subjects enrolled and exposed to mRNA-1273 were 96. Start date for this study was 25 Jul 2022 and project end date is 31 Nov 2023. No SAEs are reported to ModernaTx, Inc. Interim analysis is not yet complete for efficacy and effectiveness information. No regulatory actions have been taken for safety reasons.

9.2 Medication Errors

Please, refer to Section 16.3.6.7.1 for a cumulative evaluation on medication/vaccination errors.

10 NON-CLINICAL DATA

No relevant new safety finding was identified in non-clinical in vivo and in vitro studies during the reporting period of this PBRER.

11 LITERATURE

A global literature search and analysis was performed utilizing Embase®, Medline® and PubMed databases for abstracts for the reporting period 19 Jun 2022 to 17 Dec 2022. The literature search was performed for the publications related to elasomeran and for publications related to the class mRNA COVID-19 vaccines. The product search terms included elasomeran, mRNA-1273, Moderna COVID-19 Vaccine, SPIKEVAX, CX-024414, TAK-919, SPIKEVAX pre-filled syringe, SPIKEVAX Bivalent Original/Omicron BA.4-5, SPIKEVAX bivalent Original/Omicron BA.1. Find the complete global literature search strategy used for Medline and Embase search under Appendix 12.1a and search strategy used for PubMed under Appendix 12.1b.

A local literature search was performed for ModernaTx, Inc. vaccine approved countries for the journals which were not indexed in Medline or Embase using product names as key search terms. Please find the journal list under Appendix 12.1c. Literature search strategy for medical topics can be found under Appendix 12.1d.

During the reporting period, there were a total of 24,239 abstracts retrieved and upon removal of duplicates 19,365 abstracts were reviewed (full text reviewed as required) from the global search. There were 6,730 local journal searches performed, and 236 abstracts were reviewed. From all the searches performed, three (3) articles were identified with relevant new safety information and are summarized below: For more detailed information and full text articles please refer to Appendix 12.2.

A Disproportionality Analysis for Association of Systemic Capillary Leak Syndrome with COVID-19 Vaccination Using the World Health Organization Pharmacovigilance Database[6]

Park J et al. performed a disproportionality analysis using VigiBase data to investigate the association between different types of COVID-19 vaccines and systemic CLS (SCLS). Cases with MedDRA PT of SCLS associated with BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 vaccines were extracted. From VigiBase, 48 cases after BNT162b2, 12 cases after mRNA-1273, and 41 cases after ChAdOx1 nCoV-19 were obtained for SCLS. Disproportionality was evaluated by calculating the information component or reporting odds ratio (ROR) using the entire database and also a viral vaccines data subset. The ChAdOx1 nCoV-19 vaccine showed a significantly positive association with SCLS by IC_{025} of 0.71 (95% CI, 0.24–1.12) and ROR_{025} of 1.68 (95% CI, 1.23–2.29) using the entire database as the comparator. Additionally, a disproportionality analysis was performed for the data reported by physicians and other healthcare professionals, to minimize reporting bias. The authors noted a significant potential signal of disproportionality of SCLS in ChAdOx1 nCoV-1 when using the entire database (IC_{025} = 0.42, ROR_{025} = 1.12) and when using all viral vaccines (IC_{025} = 0.36, ROR_{025} = 1.22) as comparators. On the contrary, no significant potential signal of disproportionality for SCLS was noted for the two mRNA-based vaccines when applied comparators were the entire database (IC_{025} = −0.36, ROR_{025} = 0.65) and all viral vaccines (IC_{025} = −0.44, ROR_{025} = 0.71). The author concluded that there was no potential safety signal for developing SCLS noted with mRNA COVID-19 vaccines but, suggested extensive research for establishing diagnostic criteria for SCLS and elucidating the causal relationship between SCLS and the COVID-19 vaccines.

Breast Cancer Screening and Axillary Adenopathy in the Era of COVID-19 Vaccination [7]

The authors present two cases of women recently vaccinated with elasomeran who were subsequently studied with mammography for breast cancer screening. Both women had mammographic evidence of lymphadenopathy, which the authors report may occur in 2.4 to 35%

of women and may persist as long as 43 weeks, with higher incidence following mRNA than vector vaccines. On biopsy, one patient was found to have benign reactive lymphadenopathy; the other patient, in contrast, was found to have metastatic adenocarcinoma. As many as 1% of breast cancers may present as isolated axillary lymphadenopathy. The authors review professional societies' evolving recommendations and summarize that: women with a personal history of breast cancer should receive vaccination on the contralateral side to the breast cancer; screening mammography should not be delayed following COVID-19 vaccination; isolated unilateral axillary lymphadenopathy ipsilateral to the side of recent COVID-19 vaccination without other suspicious imaging findings may be considered Breast Imaging-Reporting and Data System (BI-RADS) category 2 (benign) without follow-up imaging or BI-RADS category 3 (probably benign) with follow-up imaging in greater than 12 weeks if increased clinical concern; and more cautious management, including possible biopsy, should be undertaken for patients with concurrent suspicious imaging findings, with adenopathy contralateral to the site of vaccination, or for patients with high risk or with a personal history of breast cancer.

Retinal Vascular Occlusion after COVID-19 Vaccination: More Coincidence than Causal Relationship? Data from a Retrospective Multicenter Study [8]

Feltgen N et al. conducted a retrospective multicenter study using data from the German Retina Society which invited 50 retina clinics to participate in an investigation of retinal vascular occlusive disease (RVOD) and a potential association with vaccination against SARS-CoV-2. The study period was 01 Jun 2021 to 31 Jul 2021 (2 months,) a time of widespread vaccination in Germany. Data from patients with central and branch retinal vein occlusion (CRVO and BRVO), central and branch retinal artery occlusion (CRAO and BRAO), and anterior ischemic optic neuropathy were retrospectively collected according to a defined protocol. The study participants were randomly selected from residents' registration offices (City of Mainz and District of Mainz-Bingen, Germany,) and at the initial examination the overall participation rate was 55.5 percent. This study took a mixed-methods approach to ensure the highest probability of detecting any association between RVOD and COVID-19 vaccination. In case-by-case analysis, a total of 508 patients were included. Three hundred and twenty-one study participants (76.2%) were vaccinated at least once before the RVOD onset, and 221 patients received BNT162b2 (BioNTech/Pfizer), followed by 57 ChadOx1 (AstraZeneca [AZ]), 21 mRNA-1273 (ModernaTx, Inc.), 11 Ad26.COV2.S (Johnson & Johnson) and 11 received an unknown vaccine. The other 89 patients had not received a COVID-19 vaccine. Seventy patients (21.8% of the vaccinated patients) were vaccinated within 2 weeks of RVOD onset, 85 (26.5%) had received in 2-4 weeks, 44 had received

(13.7%) between 4 and 6 weeks, and 122 participants had received (38.0%) more than 6 weeks before RVOD onset. When examining the time-dependent distribution between vaccinations and RVOD, the author observed no events within the first 4 weeks after SARS-CoV-2 vaccination, regardless of the disease or vaccine administered. No clear relationship between vaccination and RVOD was found from this data. In the case-control analysis, a comparative analysis was performed between the patients with RVOD and healthy controls from the general population recruited by the Gutenberg Health Study (GHS). The author compared the probability of being vaccinated in the previous four weeks between RVOD patients and the population-based GHS sample. In the unadjusted conditional logistic regression analysis, there was noted one significant association: a lower risk for CRAO after vaccination. The case-control study integrating population-based data from the GHS found no evidence of an increased risk after COVID-19 vaccination within the last four weeks. Further adjustment with the most complete data on diabetes, obesity, arterial hypertension, smoking, and the use of anticoagulation did not alter this finding. There was no significant temporal shift forward found when comparing the vaccination time point between the cases and controls. In this retrospective multicenter study on RVOD onset and COVID-19 vaccination status, the author found no increased risk of retinal vascular occlusion.

12 OTHER PERIODIC REPORTS

No other PBRERs have been written during the reporting period for elasomeran, elasomeran/imelosomeran and elasomeran/davesomeran.

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

During the reporting period, no new data emerged that indicated a lack of efficacy from interventional, non-interventional, retrospective studies or from the review of literature articles.

14 LATE-BREAKING INFORMATION

There were no potentially important safety, efficacy and effectiveness findings that arose during the preparation of this report after the DLP.

15 OVERVIEW OF SIGNALS: NEW, ONGOING OR CLOSED

15.1 Validated signals during the reporting period

ModernaTx, Inc. has an established signal management process that includes signal detection, validation, prioritization, and assessment. During signal detection, data sources are screened for new safety information related to elasomeran. Following initial review of available data, a determination is made on the basis of the nature and the quality of the new information whether the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis, at which point those topics are referred for further evaluation and are considered as "validated signals." Potential signals may be identified from any data source, including but not limited to safety data from ModernaTx, Inc.-sponsored CTs, non-interventional studies, spontaneous AE reports, published literature, regulatory safety surveillance databases (e.g., Eudravigilance, vaccine adverse event reporting system [VAERS]), and communications from external sources, including regulatory agencies, and (if applicable) business partners. As part of the ModernaTx, Inc.'s routine pharmacovigilance activities, weekly to monthly signal detection analyzes are performed on the following data sources: ModernaTx, Inc. global pharmacovigilance database (Argus platform) using a defined signal detection methodology (both qualitative and quantitative aggregated analyzes), signals of disproportionate reporting from regulatory databases (e.g., Eudravigilance, VAERs), published literature that involves targeted keyword searches in widely recognized databases (i.e., Medline, Embase), health authority websites screening, review of publicly available competitors' labels, as well as social media.

This routine aggregate review also includes O/E analyzes, which are performed as described in Appendix 11.3.

During the reporting period of this PBRER, 3 signals were closed and refuted, 1 signal was closed and categorized as a Potential Risk (not important), 2 signals were ongoing and lastly 1 signal of "Capillary Leak Syndrome (CLS) (Re-evaluation)" was closed as a refuted signal before the reporting period of this PBRER, but not presented in PBRER#3, is presented here for completeness. The list of ongoing/closed signals is presented in Table 15.1 below and detailed presentation of all signals is included in Appendix 4.1.

Table 15.1 Status of Validated Signals

Signal	Cross reference to the corresponding procedure for which a safety evaluation or regulatory request has been closed during the reporting period	Status (Ongoing /Closed)	Outcome (Refuted/ Substantiated)	Assessed in another regulatory procedure (Safety summary report or a variation)
IgA Nephropathy*	EMEA/H/C/ Periodic Safety Update Single Assessment (PSUSA)/ 00010897/202112	Closed	Refuted	PBRER#3: closed PBRER#4: Important potential risk for PSUR Monthly summary safety report (MSSR)#13 MSSR#14
Heavy menstrual bleeding (re-evaluation)	PRAC Signal procedure (European Pharmacovigilance Issues Tracking Tool [EPITT] No. 19780)	Closed	Refuted	PBRER#3 PBRER#4: closed MSSR#14 MSSR#15
Myocarditis and pericarditis (re-evaluation)	Health Authority Request	Closed	Refuted	PBRER#4: closed MSSR#15 MSSR#16 MSSR#17
Product label confusion leading to underdosing of Bivalent vaccines (.214, .222)	Spontaneous Reports Routine Signal Detection Other (Product Quality Complaints, Requests for clarification from HCPs (Canada, Germany))	Closed	Potential Risk (Not Important)	PBRER#4: closed MSSR#16
Capillary Leak Syndrome (Re-evaluation)**	PRAC Signal procedure (EPITT ref. No. 19743)	Closed	Refuted Signal	PBRER#4: closed
Amenorrhea (re-evaluation)***	PRAC Signal procedure (EPITT No. 19781)	Ongoing	Pending	PBRER#3: closed PBRER#4: MSSR#14 MSSR#15 MSSR#16 MSSR#17
Pemphigus and pemphigoid***	PRAC Signal procedure (EPITT No. 19860)	Ongoing	Pending	PBRER#4

*In addition to the RMP safety concerns, IgA nephropathy was included as an important potential risk in PSUR, as an outcome of the previous PSUSA procedure EMEA/H/C/PSUSA/00010897/202112.
**Signal of CLS was closed before the reporting period of this PBRER but has been presented in PBRER#4 for completeness.
***Both the Signals were closed and refuted by the MAH after the DLP, but the PRAC assessment is pending. Once the assessment is completed by PRAC, detailed evaluation reports will be appended in PBRER#5.

15.2 Requests from Health Authorities or regulatory bodies

During the reporting period, requests for a cumulative review of the following safety topics (not considered as signals) were received. The respective analyzes are presented in the referenced sections of this PBRER.

1. Autoimmune or autoinflammatory conditions (Section 16.3.5.7)
2. Arrythmia (Section 16.3.6.1.1)
3. Mechanical Urticaria/Dermatography (Section 16.3.6.5.1)
4. SAEs and Death/s in the Pediatric population (6 months to 17-years-old) (Section 16.3.6.7.7)

16 SIGNAL AND RISK EVALUATION

16.1 Summaries of Safety Concerns

Table 16.1 provides the Summary of Safety Concerns as per RMP v3.0 approved on 01 Mar 2022 in place at the beginning of the reporting period.

Table 16.1 Summary of Safety Concerns valid at the beginning of the reporting period (as per RMP v3.0 approved on 01 Mar 2022)

Important identified risks	• Anaphylaxis • Myocarditis • Pericarditis
Important potential risks	• Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease
Missing information	• Use in pregnancy and while breast-feeding • Long-term safety • Use in immunocompromised subjects • Interaction with other vaccines • Use in frail subjects with unstable health conditions and comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders.

During the reporting period, the elasomeran RMP v3.0 was updated to v4.0 approved on 23 Jun 2022 to remove 'anaphylaxis' as an important identified risk and reclassify it as an

identified risk (not important). While anaphylaxis, remains as an identified risk for the product, as with any other biologicals, it does not have a considerable impact on the benefit-risk balance of the vaccine. Furter v4.0 was updated to v4.1 to include the data on individuals 6 months of age and older and v4.1 was later updated to v4.2 (approved on 01 Sep 2022) to include elasomeran/imelasomeran as a new medicinal product to the RMP and to add the INN elasomeran/imelasomeran with no additional changes to the list of safety concerns. RMP v4.2 was updated to v4.5 (not approved and information consolidated with v6.3) to include elasomeran booster dose for children 6 to 12 years of age. Using RMP v4.2, a new version was updated to v5.0 (approved on 06 Oct 2022) to reclassify category 2 studies within the Pharmacovigilance Plan (PV) (mRNA-1273-P301, mRNA-1273-P203 and mRNA-1273-P204) to category 3 studies related to the application to move the conditional marketing authorization for elasomeran to a full marketing authorization. Later RMP v4.2 and v5.0 merged with the addition of elasomeran/davesomeran indication and other changes to create v6.0 (not approved - information merged into v6.3) with no additional changes to the list of safety concerns. Further RMP v4.1, v4.5 and v6.0 merged to create v6.1 (not approved information merged into v6.3) with updated indication to include individuals 6 months of age and older for elasomeran original, updated the indication for elasomeran/imelasomeran for use in individuals 6 years of age and older, updated the indication for elasomeran/davesomeran for use in individuals 12 years of age and older. Lastly, RMP v6.1 was updated to create v6.3 (approved on 15 Dec 2022) to update indication and posology for all the 3 products and product details to include the 0.10 mg/mL dispersion for injection supplied as a multidose vial and associated strengths and posology with no additional changes to the list of safety concerns.

Table 16.2 Summary of Safety Concerns valid at the end of the reporting period (as per RMP v6.3 approved 15 Dec 2022)

Important identified risks	• Myocarditis • Pericarditis
Important potential risks	• Vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease
Missing information	• Use in pregnancy and while breast-feeding • Long-term safety • Use in immunocompromised subjects • Interaction with other vaccines • Use in frail subjects with unstable health conditions and comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular

	disorders) • Use in subjects with autoimmune or inflammatory disorders.

16.2 Signal Evaluation

A summary of the results of evaluations of validated signals that were evaluated/re-evaluated and closed (rejected/refuted or considered to be potential or identified risks following evaluation) during the reporting interval is provided below.

Four signals were closed during the reporting period. Based on a scientific evaluation of the available information, three of the closed signals were refuted [IgA nephropathy, Heavy menstrual bleeding (re-evaluation), and Myocarditis and pericarditis (re-evaluation)], and one signal [Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran)] was categorized as a Potential Risk (not important). Two validated signals [Amenorrhea (re-evaluated) and Pemphigus and pemphigoid] were ongoing at the DLP of the reporting period. In addition, one validated signal [CLS (Re-evaluation)], which was closed as a Refuted Signal before the reporting period of this PBRER, but not presented in PBRER#3, is presented here for completeness.

16.2.1 IgA Nephropathy

IgA nephropathy was closed and refuted based on evaluation performed by ModernaTx, Inc. in Jul 2022, however, it is being monitored further and provided in Section 16.3.6.6.1.

16.2.2 Heavy menstrual bleeding (re-evaluation)

Table 16.3 Heavy menstrual bleeding (re-evaluation)

Signal evaluation criteria	Summary
Source	Heavy Menstrual Bleeding (HMB) was evaluated as a signal based on a trigger from PRAC (EPITT No. 19780) and was refuted as a signal on 30 Mar 2022. A new signal for HMB (re-evaluation) was opened and validated (by default) based on the communication received from PRAC on 13 Jun 2022.
Background	As of 09 Mar 2022, more than 50,000 reports of menstrual changes or unexpected vaginal bleeding following COVID-19 vaccination have been reported through the yellow card surveillance. Similar reports received by the US VAERS. Overall, to date there is no definitive evidence to demonstrate an association between menstrual disorder and vaccination. The basic biology of the menstrual cycle is a complex, coordinated sequence of events. Normal variations exist within women over the lifespan. Menstrual cycle features such as volume, pain and PMS symptoms are subjective 1,2 and data are necessarily collected, in healthcare as well as research, by self-report. Menstrual disorders are very common, as perturbed by environmental factors such as stress, extreme

Signal evaluation criteria	Summary
	exercise, eating disorders, obesity, and infection. **Hypothetical Biological Mechanisms**: The relationship between HMB and elasomeran is unclear. Some hypothetical biological mechanisms in the literature include immune response leading to changes in hormones driving the menstrual cycle and endometrial inflammatory response mediated by immune cells in the lining of the uterus and alterations in coagulation system, which is critical component of the endometrial function at menstruation. ACE-2 receptors have been found on the ovarian and endometrial tissue and hence vaccination can hypothetically affect ovarian hormone production and/or the endometrium response at menses.
Methodology	The assessment of HMB in association with the use of elasomeran in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources is described below. • Clinical Trial Data: Two clinical studies (mRNA-1273-P301 and mRNA-1273-P203) sponsored by ModernaTx, Inc. were reviewed using the following MedDRA v 23.0 preferred terms, "Menorrhagia", "Polymenorrhagia", "Menometrorrhagia", "Polymenorrhea", and "Vaginal hemorrhage". • External Databases: VAERS and EudraVigilance Data Analysis System (EVDAS) were reviewed for the PTs: Heavy menstrual bleeding, Menometrorrhagia, and Polymenorrhagia. • Non-clinical: Developmental and reproductive toxicity (DART) studies in pregnant and lactating female Sprague Dawley rats were performed to assess the potential effects of elasomeran on fertility and pre and postnatal. • Review of the Pharmacovigilance Database: Post-marketing data for validated signal of heavy menstrual bleeding events were retrieved from the Company safety database using the following three MedDRA preferred terms: "Heavy menstrual bleeding", "Menometrorrhagia", and "Polymenorrhagia" with a DLP of 18 Jun 2022, using MedDRa version 24.1. • Clinical literature search review: A focused literature search and review was performed using PubMed and Google Scholar databases. Multiple search strategies were used to identify articles related to HMB and COVID-19 vaccines.
Results	Clinical Trial Data: *mRNA-1273-P203 Study with data cut-off of 31 Jan 2022:* In study mRNA-1273-P203, three participants were identified who reported the Treatment Emergent Adverse Events (TEAE) of HMB via unsolicited reporting. All three cases were in the mRNA-1273 arm and two of the three participants had a medical history or use of concomitant medication that provided a plausible alternate explanation for the HMB. The median age of the 3 cases was 13 years (range 13-15). All three cases were considered non-serious, two had recovered and all three cases were assessed as not related to mRNA-1273 by the principal investigator. *mRNA-1273-P301 with data cut-off date of 05 Apr 2022*: In study mRNA-1273-P301, the MAH performed an updated cumulative review using data from Part A, Part B and Part C. Of the 13,252 female participants who received mRNA-1273 primary series in Part A or Part B, 67 female participants were identified using the HMB-specific PTs. They reported the treatment-emergent adverse event of heavy menstrual bleeding via unsolicited reporting. When restricted to female participants of reproductive age (18-55 years), 58 of the 7421 female participants, reported HMB. The

Signal evaluation criteria	Summary
	median age was 44 (range 20-54), 6.9% were postmenopausal, ~76% had other risk factors for HMB, majority of events were non-serious, and recovered or recovering and 8.6% of cases were assessed as related by the principal investigator. External Databases: • VAERS: following are the EB05 observed for these PTs. No Disproportionality was observed: • Heavy menstrual bleeding (EB05: 0.795; N= 2,416) • Menometrorrhagia (EB05: 0.737; N=50) • Polymenorrhagia (EB05: 0.469; N=2) • EVDAS: Disproportionality was observed in the EVDAS database. The ROR for each PT is listed below: • Heavy menstrual bleeding (ROR: 3.76; N=5,242) • Menometrorrhagia (ROR: 2.96; N=219) • Polymenorrhagia (ROR: 1.54; N=6) Non-Clinical Data: No elasomeran-related effects or changes in mating and fertility and ovarian/uterine examinations were observed. Epidemiological studies: Using the spontaneous reported data (DLP of 18 Jun 2022), and the background incidence rate estimated by [9] the observed to expected analyzes was performed. In the observed to expected analysis, there were 5,727 cases of HMB cumulatively (reporting rate of 28.3 per 100,000 person-years). Overall incidence described in Stalhman et al, 2017 was 1009 per 1,00,000 person-year, corresponding to the 204,485 cases expected. The rate ratio was 0.03 (95% CI 0.03, 0.03). Considering demographic subgroups, the rate ratio for all age and gender strata were <= 0.5. Currently, the Observed expected analysis does not support an association between HMB and elasomeran. The sensitivity analysis (assuming 25% and 50% capture of the observed cases) does not change this interpretation). Review of the Pharmacovigilance Database: Cumulatively, as of 18 June 2022, the search criteria yielded a total of 5,791 cases with 6,291 events of which 999 events were serious. Of the 5,791 cases, 1,118 (19.3%) were serious, 647 (11.2%) were medically confirmed and none had a fatal outcome. Cumulatively, majority of the reported events (84.1%; 5,121) were non-serious. Of the 5,791 case reports, 91 cases required hospitalization with no reported intervention. As expected, most cases (84.8%; 4,908) were among women of reproductive age, specifically 18-49 years of age. Only 0.52% (30/5,791) of the total reports received were among adolescents 12-17 years of age. The mean age was 36.7 years, and the median age was 37.0 years (range 0.0 to 81.0). Cumulatively, 96.6% (5,594) of the reports were from regulatory authorities and 3.4% (197) were spontaneously reported to the MAH. Most of the cases were received from the EEA (4,122; 71.2%) and UK (1,088; 18.8%). Cumulatively, when the dose number immediately preceding the event was known, more events were reported after Dose 1 (24.4%) than Dose 2 (20.2%), Dose 3 (8.8%) or Dose 4 (<0.1%). This should be interpreted with caution as the dose number was unknown in almost half (46.6%) of the reported events; and the global vaccine administration/exposure

Signal evaluation criteria	Summary
	data are limited for the various doses. When time to onset and dose number was known, the average Time to Onset (TTO) was 15.3 days (SD: 83.5) and the median TTO was 6.0 days. Cumulative data does not present clustering of cases by dose and TTO; however, it is difficult to interpret the TTO without putting it into context of the menstrual cycle including what phase of menstrual cycle vaccination occurred. **Serious Events of Heavy Menstrual Bleeding:** Cumulatively, there have been 999 serious events of heavy menstrual bleeding-specific PTs reported by 915 serious cases of which 83 cases were medically confirmed, and none had a fatal outcome. Distribution by age, gender, source, and region of origin is similar to the cumulative distribution presented above. Of the 915 serious case reports, 91 (9.9%) cases reported hospitalization with no reported intervention. According to the WHO- Uppsala Monitoring Center (UMC) causality assessment of the 885 serious cases, none was assessed as "Certain or Probable"; although there were case reports with elements of positive rechallenge causality was deemed "Possible" because of the lack of clear biological plausibility, natural background variation in menstrual cycle, lack of evidence of a full resolution of HMB prior to subsequent vaccination in most of the case reports, and incomplete and insufficient information needed to perform a comprehensive case and causality assessment to determine the presence or absence of other plausible alternate explanation(s) for HMB. 8.5% (75) of the 885 cases were assessed as "Possible", 4.4% (39) cases as "Unlikely" and 87.1% (771) were "Unassessable" **Confounders for Heavy Menstrual Bleeding**: Overall, 39.5% (350/885) of the cases had at least one confounder and 47.3% (419/885) had extremely limited information and so the lack or presence of a confounder could not be determined. Given that HMB has many causes, the list of confounders was extensive and included: 1) age >=45 or <18; 2) coagulopathy such as immune thrombocytopenia, von Willebrand's disease, heparin, hemorrhagic diathesis, thrombocytopenia, anticoagulants; 3) infections such as confirmed or suspected COVID-19, endometritis; 4) endocrine causes such as hypothyroidism, Polycystic ovary syndrome, obesity, autoimmune thyroiditis, DM, overweight, autoimmune hypothyroidism, type 1 DM, type 2 DM, Basedow's disease, hyperthyroidism, hyperprolactinemia, pituitary tumor, thyroiditis, breastfeeding, menopausal symptoms indicating perimenopausal status; 5) hormonal therapy such as contraception, hormone replacement therapy, tamoxifen; 6) history of abnormal menses such as HMB; and 7) structural causes such as uterine leiomyoma, adenomyosis, uterine polyp, uterine disorder, endometriosis. **All case reports of rechallenge of heavy menstrual bleeding with subsequent vaccination**: In summary, of the 1,501 (25% [1501/5791]) unique cases reviewed (all cases that reported at least 3 doses of a COVID-19 vaccine, cases coded as positive rechallenge in the database, serious cases), 69 (4.6% [69/1501]) had evidence of recurrence of HMB after subsequent vaccination. However, in the setting of natural variation in the menstrual cycle, high background incidence of HMB, and lack of evidence of a full resolution of HMB prior to subsequent vaccination for most of the cases, it is very difficult to assess whether recurrence of HMB with the subsequent vaccination is truly a positive rechallenge using spontaneous passive reports that have incomplete data regarding gynecological history including baseline menstrual cycle characteristics, medical history, concomitant medications, diagnostic evaluation and results, treatment, and clinical course. Clinical literature search review: A recent systematic literature review by [10] evaluated

Signal evaluation criteria	Summary
	14 studies published from Mar 2020 to May 2022; these studies included a total of 78,138 vaccinated female participants and determined that 52% participants reported some form of menstrual change after vaccination. In this analysis, menorrhagia, metrorrhagia, and polymenorrhea were the most commonly observed menstrual change following vaccination and overall, the incidence rate of menstrual abnormalities varied widely from 0.83% to 90.9% across different studies evaluating all types of COVID-19 vaccine. As the authors pointed out, all of the studies were limited by lack of comparator groups and the heterogeneity in cohorts limits the generalizability of the results. These studies cannot establish a causal relationship and support the need for well-designed prospective and longitudinal studies such as ongoing prospective cohort studies that are designed to study heavy menstrual as an outcome after SARS-CoV-2 vaccination (e.g., National Institutes of Health funded studies conducted by Boston University, Harvard Medical School, John's Hopkins University, Michigan State University, and Oregon Health and Science University) (Available at https://www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation). Overall, the literature search does not support a causal link between HMB and COVID-19 vaccines, including elasomeran.
Discussion	This validated signal of HMB was re-evaluated in the context of PRAC request received on 13 Jun 2022. The Global Safety Database (GSDB) was queried including validated, clinical, and spontaneous worldwide cases received from all sources (HCP, regulators, literature, and consumers) reported from the mRNA-1273 vaccine (Moderna COVID-19 vaccine). Overall, the observed to expected ratios for HMB using post-marketing data and expected rates from Europe and the United States do not provide evidence of an association of HMB with elasomeran. The reporting rate was 28.3 per 100,000 person-years. The observed number of cases was lower than the expected number of cases with a rate ratio of 0.03 (95% CI 0.03, 0.03). Among women of reproductive age, all the events and a vast majority (91.4%) of the events of HMB in the P203 and P301 CTs, respectively were non-serious and majority had medical history or concomitant medications that provided alternate explanations for HMB. However, information regarding participants baseline menstrual cycle characteristics are not collected in any of the ongoing ModernaTx, Inc. sponsored CTs and in the setting of expected normal variation of menstrual cycles, it is difficult to interpret data regarding HMB in CT participants without knowledge of baseline menstrual characteristics especially given the lack of a placebo group. There is a geographic disproportion in the origin of reports of heavy menstrual period with majority of reports originating from EEA (71.2%) and UK (18.8%). Of the 915 serious cases reporting HMB, none were assessed as "Certain" or "Probable"; majority of the cases had limited data and missing critical. Consistent with the Netherlands Pharmacovigilance Center Lareb report, evaluation of recurrence of HMB after subsequent vaccination was challenging, and only a small number of reports had sufficient information to make an assessment. Of the 784 cases reporting at least three doses of COVID-19 vaccine, a small percentage (4.8%) reported recurrence of HMB, however in the setting of natural variation in the menstrual cycle, high background incidence of HMB as well as lack of evidence of a full resolution of HMB prior to subsequent vaccination, the data do not support the suggestion that HMB with the subsequent vaccination is truly a positive rechallenge particularly given the incomplete data from spontaneous passive

Signal evaluation criteria	Summary
	reports. A focused literature search and review did not provide evidence for causal association between COVID-19 vaccines and HMB. The majority of the studies are cross-sectional and collected information on menstrual irregularities, using unvalidated questionnaires. It was difficult to interpret the results from these studies given that HMB is common and may be caused by a multitude of reasons. Although there have been reports of heavy menstrual bleeding after COVID-19 vaccination, it is important to note that normal variations exist within women over the lifespan and menstrual disturbances are common. Additionally, menstrual cycle features (such as bleeding volume) are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification. Patient self-reports, however, can be inaccurate indicators of the quantity of blood loss. Furthermore, there is no clear biological plausibility; theoretical hypotheses proposed include immune response leading to changes in hormones driving the menstrual cycle and endometrial inflammatory response mediated by immune cells in the lining of uterus. However, to date there is no definitive evidence to demonstrate any causal association between menstrual disorders and vaccination. Furthermore, the published data are not able to determine the frequency with which people experience HMB following elasomeran or determine whether there is a link between elasomeran and HMB; studies were limited due to lack of unvaccinated control group, recruitment of participants retrospectively, use of unvalidated questionnaires, selection, and recall bias. Despite the limitations, findings from these studies were reassuring, the reported changes were small compared to natural variation and quickly reverse. There is also no clear biological plausibility linking elasomeran and HMB; all cases reviewed (clinical trial and post-marketing data) were only temporally associated with elasomeran and a vast majority of them had medical conditions or were on concomitant medications that provided other plausible alternate explanations. Last, the number of reports of menstrual disorders and vaginal bleeding is low in relation to both how common menstrual disorders are and the number of people who have received COVID-19 vaccines to date (as of 18 Jun 2022, worldwide 1,252,320,706 elasomeran doses were distributed and 662,871,167 elasomeran were administered). Of these, 184,939,184 [27.9% of all doses] doses were administered in the women of childbearing potential [12-49 years]). Thus, there is insufficient information to establish a causal relationship between the administration of elasomeran and the development of HMB.
Conclusion	Overall, based on the analysis of all available safety data as of 18 Jun 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran and the development of HMB. No new or emerging safety issue of concern was identified. This health authority validated signal is refuted and no change to the RSI, labeling or RMP is required. The benefit-risk profile of elasomeran continues to be positive and the MAH will continue to monitor events for HMB through routine pharmacovigilance activities.

16.2.3 Myocarditis and pericarditis (re-evaluation)

Table 16.4 Myocarditis and pericarditis (re-evaluation)

Signal evaluation criteria	Summary
Source	Following a request from the Australian's health authority Therapeutics Goods Administration (TGA) to include additional information related to myocarditis and pericarditis in their Package Insert for the elasomeran vaccines, a follow-up signal evaluation was opened to re-evaluate the characterization of the risk of myocarditis/ pericarditis regarding the following: • Have the demographic characteristics of cases of myocarditis/ pericarditis changed or not from the established safety profile. • Has the severity of the cases of myocarditis/ pericarditis changed or not from the established safety profile (e.g., regarding fatal outcomes for reported cases). • Has the clinical presentation of myocarditis/ pericarditis changed or not from the established safety profile (atypical symptoms [e.g., fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough].
Background	After receiving the request from TGA, the Safety and Risk Management Team (SRMT) met on 20 Sep 2022, and concluded: • Important information is missing in the case report provided by the agency, including patient's medical history as well as results for any laboratory test conducted including those for the purpose of identifying any possible viral/bacterial/fungi etiology of the myocarditis. Information related to the first emergency department (ED) visit is also missing and can provide important information. Additionally, there are important confounders in this report that could had contribute to the fatal outcome of this patient. A causal relationship cannot be excluded due to missing information. • The proposed TGA labeling changes will be considered a local Australian variation and do not merit change to the elasomeran CCDS. • The SRMT reviewed and provided edits/comments on the labeling changes proposed by the TGA, which were submitted to the agency. • Independently, the SRMT and labeling committee will review the CCDS to consider any appropriate changes (e.g., update regarding risk with booster doses).
Methodology	The re-evaluation of cases of myocarditis and pericarditis in association with the use of elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran in all patients exposed was performed using the Company's GSDB, and literature. • Review of the Pharmacovigilance Database: The MAH's GSDB was queried as of 18 Sep 2022, for valid case reports of myocarditis and pericarditis received from HCP, HA, consumers, and literature, worldwide, for elasomeran, and for both bivalent vaccines [elasomeran/imelasomeran or elasomeran/davesomeran] using the non-infectious myocarditis/pericarditis MedDRA narrow standardized MedDRA query (SMQ) that contains the following PTs: Autoimmune myocarditis, Autoimmune pericarditis, Carditis, Chronic myocarditis, Eosinophilic myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis, Myocarditis, Myopericarditis, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, and Pleuropericarditis. • Clinical literature search review: Combinations of "Myocarditis/ Pericarditis" AND at least one of mRNA-1273 OR Moderna COVID vaccine OR COVID vaccine OR

Signal evaluation criteria	Summary
	COVID-19 vaccine OR COVID OR SARS-CoV-2.
Results	Review of the Pharmacovigilance Database: **Have the demographic characteristics of cases of myocarditis/ pericarditis changed from the established safety profile?** • Cumulatively, through 18 Sep 2022, a total of 6,469 cases (6,856 events) reporting myocarditis and/or pericarditis have been received. • Majority of cases involved males (4,292; 66.3%) compared to females (2,031; 31.4%); 146 reports (2.3%) did not include gender data. • Mean age of the patients was 37.3 years (SD 16.6), with a median age of 33 years (min: 7 /max: 94); 639 cases did not report age. • Cumulatively, there were 3,409 cases (52.6%) reporting myocarditis and pericarditis events in patients in the 18 to 39-years-old population group, with 2,572 (75.4%) of those cases occurring in males. • Events continued to occur most frequently after the 2nd dose (1,974; 28.8%). • Regardless of dose number, the greatest proportion of events had an onset of less than 7 days from the time of vaccination (2,381; 65.5%), inclusive of 421 events following a third/booster dose (includes reported 3rd and 4th doses). • The median TTO from most recent dose was 3 days (min: 0/ max: 384). Conclusion: The demographic characteristics of cases of myocarditis/ pericarditis have not changed from the established safety profile. **Has the Severity of the cases of myocarditis/ pericarditis changed from the established safety profile (e.g., regarding fatal outcomes for reported cases)?** • Cumulative, as of 18 Sep 2002, there have been 76 cases (1.2% of all reported myocarditis/pericarditis cases) with fatal outcomes. • There were 69 cases with fatal events of myocarditis and/or pericarditis *excluding seven level 5 (Unlikely) cases according to the Brighton Collaboration case definition. No temporal changes in frequencies were observed. • 3 cases included both myocarditis and pericarditis, or myopericarditis, events • 7 cases involved only pericarditis • 55 cases involved only myocarditis • 4 cases of carditis • 59 medically confirmed cases. • Gender: 49 Males (71.0%), 19 Females (27.5%), 1 Unknown (1.4%) • Age: 19 to 94 (Median: 57 year/ Mean: 55 years) • Median TTO is 5 days (min:0/max:150) • Majority of reports after Dose 2 (26; 40%) Conclusion: The number of reported cases with fatal reports has been constant with some small increases at times when the MAH has received bolus of retrospective reports from different countries. **Has the clinical presentation of myocarditis/ pericarditis changed from the established safety profile (atypical symptoms [e.g., fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough])?**

Signal evaluation criteria	Summary
	Out of the 4,164 cases of Myocarditis/ Myopericarditis reported as of 18 Aug 2022: • There are 3,602 cases (85.5%) of Myocarditis/ Myopericarditis without any of the additional PTs included in the report • There are 562 (13.4%) cases reporting both Myocarditis/ Myopericarditis and at least one of the additional PTs • There are no cases reporting ONLY additional PTs. Conclusion: None of those additional PT was present alone in any of the fatal cases. They were always associated with chest pain, dyspnoea, headaches, etc., which is in agreement with the literature, that has reported that the most commonly reported symptoms of myocarditis are chest pain, fever, dyspnoea, and headaches, followed by chills, and fatigue. Clinical literature search review: No new articles were identified that will support any changes to the safety profile of mRNA-1273 for reports of myocarditis/ pericarditis.
Discussion	The MAH conducted a signal evaluation of the validated signal of re-evaluation of characterization of the risk of myocarditis/ pericarditis after elasomeran vaccines exposure, following a request from TGA to include additional information related to myocarditis and pericarditis in their Package insert (PI). The signal evaluation included a cumulative review of the MAH safety database with a DLP of 18 Sep 2022. Analysis of the data showed that this was a refuted signal based on: • The demographic characteristics of cases of myocarditis/pericarditis have not changed from the established safety profile. • The severity of the cases of myocarditis/ pericarditis has not changed from the established safety profile (e.g., regarding fatal outcomes for reported cases). • The clinical presentation of myocarditis/ pericarditis has not changed from the established safety profile (atypical symptoms [e.g., fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough]).
Conclusion	Based on the findings of the safety assessment regarding a re-evaluation of characterization of the risk of myocarditis/ pericarditis after elasomeran vaccines exposure, the MAH considered that this signal was refuted. Based upon the signal assessment, the changes included in the Australian Package Insert will constitute a local label variation. Therefore, no update of the CCDS is required. The MAH will continue to monitor events of myocarditis and pericarditis using enhanced and routine pharmacovigilance surveillance.

16.2.4 Product label confusion leading to underdosing of Bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran)

Table 16.5 Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran)

Signal evaluation criteria	Summary
Source	During the month of Sep 2022, ModernaTx, Inc. became aware of reports of medication errors that were indicating the occurrence of product confusion and product underdosing related to the administration of the bivalent vaccines, elasomeran/imelasomeran and elasomeran/davesomeran. The information came from different sources:

Signal evaluation criteria	Summary
	From Pharmacovigilance: • ModernaTx, Inc. was notified by MHRA that it has been receiving reports associated with underdosing on individuals receiving the bivalent vaccine • Request from Germany to provide guidance to practitioners who have been calling regarding underdosing of individuals and whether they need to be re-vaccinated • Information from Canada indicating "The vial doesn't say Booster" • From Quality: • ModernaTx, Inc. Quality has received a number of complaints regarding misdosing which is being attributed to the Bivalent labeling. Specifically, the reporters are stating that the label indicates both .25 mL and .50 mL and that it's not clear what the dose should be.
Background	Two different issues were identified according to the countries where the bivalent vaccines are authorized, but all going back to labeling and product confusion. In the United States, • The volume of a booster dose of Moderna COVID-19 Vaccine or elasomeran (COVID-19 Vaccine, mRNA) depends on the presentation • Multiple-dose vial of elasomeran with a red cap and a label with a light blue border - Booster Dose is 0.25 mL • Multiple-dose vial of Moderna COVID-19 Vaccine with a dark blue cap and a label with a purple border - Booster Dose is 0.5 mL. • Adults available Booster dose vials (Original and Bivalent) are multiple-dose vial with a dark blue cap and a label with a purple border or a gray border - Booster Dose is 0.5 mL - Product Confusion • The Bivalent Booster container labeling includes 2 different dosing indications – 0.5 mL or 0.25 mL based on age - Underdose • The 0.25 mL is included for future authorization of the pediatric population • In Europe, Canada and the Rest of the World • elasomeran/imelasomeran launch packaging was prepared in the Spring of 2022, using the WHO nomenclature in effect at that time: 0 (Zero)/O (Omicron). • There is no indication that this is a Booster dose on the carton or vial itself - Product Confusion • There is no mention of dose on the carton or vial itself- Underdose • There are two different vial size (2.5 mL and 5 mL) with no indication of the dose - Product Confusion
Methodology	The assessment of product confusion/ product underdose in association with the use of elasomeran/imelasomeran or elasomeran/davesomeran in all patients exposed was performed using the Company's GSDB. The methods of evaluation used in the analyzed data is described below. There is no clinical data related to use of the bivalent vaccines at the lower dose reported for the underdose cases (0.25 ug instead of 0.5 ug). Review of the Pharmacovigilance Database: A cumulative search in GSDB, through 04 Oct 2022 using the family names mRNA 1273 BIVALENT and mRNA 1273 BIVALENT .222 was conducted using the following search strategies: • Product confusion errors and issues • Family name: mRNA 1273 BIVALENT and mRNA 1273 BIVALENT .222 • High Level Term (HLT): Product confusion errors and issues

Signal evaluation criteria	Summary
	• Underdose • Family Name: mRNA-1273 BIVALENT, mRNA-1273 BIVALENT .222 • PT: Accidental underdose, Incorrect dose administered, Underdose • SMQ Medication errors • Family Name: mRNA-1273 BIVALENT, mRNA-1273 BIVALENT .222 • SMQ Medication errors: Broad.
Results	Review of the Pharmacovigilance Database: **Product confusion errors and issues** • There were 70 cases (71 Events) identified • 66 Medically Confirmed (94.3%) /4 Not Medically Confirmed (5.7%). MC cases were reported mainly by healthcare professionals (Pharmacist, nurses and physicians). • 71.4% of the cases (50) are invalid cases and 28.6% of the cases (20) are valid. The cases are invalid as no patient is involved. • 21.4% of the cases (16) were reported for Batch 200002A. All these cases were reported from the same facility in the UK • Most of the cases from UK reported the following PTs "Accidental underdose, No adverse event, Product label confusion". • Example of reports: "Nurse gave 0.25 mL instead of the 0.5 mL of Spikevax bivalent booster" "It is really confusing on the package that it does not say bivalent" • Proportional Fraction Reporting Ratio of bivalent vs monovalent= 402.62. ***Interpretation***: The PT Product label confusion is reported 402 times higher for bivalent than for monovalent. **Underdose** • There were 327 cases (327 Events) identified using this search strategy • 317 Medically Confirmed (96.9%)/10 Not Medically Confirmed (3.1%). MC cases were reported mainly by healthcare professionals (Pharmacist, nurses and physicians). • 11.9% of the cases (39) are invalid cases and 88.1% of the cases (288) are valid. The cases are invalid as no patient is involved. • 29.4% of the cases (96) were reported for Batch 2000011A. All these cases were reported from the same facility in the UK • Example of reports: "Nurse reported that they had administered autumn Spikevax bivalent dose 0.25 ml instead of full 0.5 ml to patient over 80 (high risk patient). The patient was vaccinated a day prior to this report and no guidance was provided by their HAs regarding dosage errors. • Proportional Fraction Reporting Ratio* (PT Accidental underdose, underdose and incorrect dose administered bivalent vs monovalent) of bivalent vs monovalent= 45.84 ***Interpretation***: These 3 PTs are reported 45.84 times higher for bivalent than for monovalent. **SMQ Medication errors** • There were 502 cases (628 Events) with 3 serious cases – SAE did not include an underdose PT or a product label confusion issue. • 454 Medically Confirmed (90.4%) / 48 Not Medically Confirmed (9.621.7% of the cases (104) are invalid cases and 77.5% of the cases (389) are valid. The cases are invalid as

Signal evaluation criteria	Summary
	no patient is involved. • Proportional Fraction Reporting Ratio (SMQ Medication errors) of bivalent vs monovalent= 5.25 ***Interpretation***: Medication errors in general are reported 5 times higher for bivalent than for monovalent.
Discussion	The MAH conducted a signal evaluation of the potential signal of medication errors due to product confusion and/or product underdosing. The signal evaluation included a cumulative review of the MAH safety database with a DLP of 04 Oct 2022. Analysis of the data showed that medications error reports have been received at a higher proportion for individuals vaccinated with one of the authorized Spikevax bivalent vaccines (relative to elasomeran Original). As of the DLP, the majority of the reports do not contain an ADR that can be classified as heat, alcohol, running and massage to the patient, but it may be too early to detect reported impact (lack of effect and breakthrough COVID-19 infections) of an underdose -Lack of efficacy/ Vaccine Failure. The majority of the reports are associated with label/ packaging confusion/ lack of adequate information in both the carton and the vial label, and the identified medication errors issues affect both elasomeran/imelosomeran, and (with a higher reporting ratio) elasomeran/davesomeran. Given that there are no clinical data related to the use of the bivalent vaccines at a lower dose than the one indicated, no recommendations regarding revaccination of individuals who received an underdose can be provided to HAs.
Conclusion	Based on the findings of the safety assessment evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a Potential Risk (Not Important) and was classified as Priority 1 (Urgent (emerging) Safety Issues: Issues which have a significant impact on the product's benefit-risk profile, and which require the most rapid communication and implementation) and that risk minimization measures needed to be implemented in agreement with the respective HAs in the countries where the bivalent vaccines have been authorized. The MAH will continue to monitor events for potential medication errors related to product confusion and/or product underdose using routine pharmacovigilance surveillance.

16.2.5 Capillary Leak Syndrome (Re-evaluation)

Table 16.6 Capillary Leak Syndrome (Re-evaluation)

Signal evaluation criteria	Summary
Source	There were multiple triggers for the evaluation of this topic in 2021 as well as in 2022. According to these multiple requests, ModernaTx, Inc. had to perform a cumulative review of CLS following elasomeran and new information if any identified form the cases. The detailed request on the source, can be found under Appendix 4.2e.
Background	Having considered the available evidence from the ongoing monitoring of this safety topic in the MSSRs and the new case reports from a national database in Italy, the PRAC has recommended that the MAH of elasomeran (Moderna Biotech Spain, S.L) should provide an updated analysis of the association between elasomeran and CLS from all available sources. Based on the review, the MAH should consider whether any precautionary measures are

Signal evaluation criteria	Summary
	considered warranted including an update of the product information and/or the RMP. If warranted, relevant changes to the product information and/or the RMP wording should be submitted. Capillary Leak Syndrome also named Systemic Capillary Leak Syndrome (SCLS) and Clarkson disease is very rare and serious (potentially lethal) [11]. The frequency of episodes can vary widely between patients, with intervals ranging from days to years [11]. The majority of patients have a detectable monoclonal protein in the serum, although the importance of the monoclonal protein in the disease pathogenesis is unclear [11]. Systemic Capillary Leak Syndrome is a diagnosis of exclusion and is often confused with sepsis, angioedema, or anaphylactic shock. Capillary Leak Syndrome are mostly due to viral infections, malignant hematological diseases, inflammatory diseases, treatments such as chemotherapies/anti-tumoral therapies and therapeutic growth factors [12], [13], [14]. The pathophysiology is not fully known, especially on the transient aspect, and it involves a multifactorial endothelial disruption for which mechanisms are still unclear. Damage to endothelial cells causes extravasation of plasma and proteins from the capillaries to the interstitial space, resulting in diffuse edema (mainly in the arms and legs), hypotension, hypoalbuminemia and hemoconcentration [14,15]. A new article was published in Feb 2022 from the EurêClark registry 1, which is an international study group, that gather observations of Monoclonal Gammopathy associated Systemic Capillary Leak Syndrome and prospectively monitor attacks, preventive treatments, complications and outcome of patients. The article mentioned by the PRAC discuss recent reports of first episodes and relapses of Clarkson's disease after receiving any of the COVID-19 vaccines, as well as after infection with SARS-CoV-2. One of the most important points of this article is the burden that the COVID-19 pandemic has brought to patient with Clarkson disease. As the authors mentioned in their article, COVID-19 infection seems to induce very frequently a relapse of Clarkson disease. Another important point noted by the authors was the lack of response to treatment with Intravenous Immunoglobulin (IVIg) to patients infected with COVID-19, including those that may had been asymptomatic, when compared to those that may had experienced a flare temporarily related to the administration to one of the COVID-19 vaccines. The evidence provided in this article only shows that rare disorders like SCLS during conditions like the one we are living today, in which just with elasomeran, as of 31 Dec 2021, more than 500 million people have been vaccinated, continuous surveillance activities need to maintain evaluating the information to becomes available in order to assess any possible associations.
Methodology	The re-assessment of CLS in association with the use of elasomeran in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources is described below: • Clinical Trial Data: PTs Capillary Leak Syndrome and Capillary permeability increased in P301 study. • Review of the Pharmacovigilance Database: 2021-Post-marketing data for potential signal of CLS events were retrieved from the Company safety database using the following MedDRA preferred terms: "Capillary Leak Syndrome and Capillary Permeability Increase" with a DLP of 31 Oct 2021. The term Capillary Leak Syndrome and Capillary Permeability Increase was searched using MedDRA version 24.0. Cases from all sources and relevant literature were reviewed.

Signal evaluation criteria	Summary
	2022-The Company GSDB was queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 Dec 2020 to 31 Dec 2021, worldwide, reported for the elasomeran vaccine (Moderna COVID-19 vaccine Moderna) using the following PTs: Capillary leak syndrome, Capillary permeability increased, and Clarkson disease/syndrome. • Clinical literature search review: A cumulative literature search in PubMed as of 11 Nov 2021 was performed using the following search criteria: (("capillary leak syndrome" [Title/Abstract] OR "capillary permeability increased" [Title/Abstract]) AND "Spikevax"[Title/Abstract]) OR "mRNA-1273" [Title/Abstract] OR ("Moderna"[All Fields] AND "covid19 vaccine"[Title/Abstract])
Results	Clinical Trial Data: No cases with PTs Capillary Leak Syndrome and Capillary permeability increased in P301 study were reported. External Databases: Re-evaluation of information in VAERS as of Dec 2021 did not show disproportionate reporting of events using EB05 > 2 Epidemiological studies: Since SCLS was first characterized in 1960, <500 cases have been described in the medical literature [11]. The typical presentation of CLS associates diffuse severe edema, hypovolemia, hemoconcentration, and hypoalbuminemia [16]. However, this condition is likely under-diagnosed, with possible misclassification as hypotension, edema and/or non-sepsis cardioshock. Formal estimates of incidence are unavailable; however, some sources describe a background rate of one per million, which was applied to estimate expected rates. Six events of CLS and three events of capillary permeability increased (9 events in 8 cases) have been observed (reporting rate 0.05 per 100,000 person-years), which was below the ~16 cases that would be expected for an event occurring at an incidence of 1 per million person-years. Based on the small number of reports to date, stratified analysis is currently largely uninterpretable. Age and age by gender stratified results lack precision, however the occurrence of 1 case in men and 3 cases in women aged 40-49 could be attributable to either chance given small numbers or an increased reporting rate. Review of the Pharmacovigilance Database: 2021: Cumulatively search as of 31 Oct 2021, retrieved 8 cases that were reviewed, and a causality assessment was provided utilizing the WHO-UMC standardized case causality assessment [17]. The majority of cases (7/8) were received from regulatory authorities, and most originated from the EEA (75%), especially 4 cases came from Italy, 1 from Germany, 1 from Spain and 2 from the USA. The majority were in women, 6 cases vs. 2 cases in men. The median age was 46 years-old, the mean was 49 (range from 37 to 64 years). When known (unknown for 4 events), all events of CLS were reported after Dose 2, with a TTO in average of 6.0 days (SD 6.5) and a median of 3.0 days (0 min /14 max). Cases were equally distributed among older ages 40-49 and 50-64 years with 1 case under the age of 40 years. The events duration was in average 4.4 days (SD 5.3) with a median of 4.1 days (0-13). 2022- Cumulatively, through 31 Dec 2021, a total of 9 cases (11 events) of CLS related terms have been reported, with 7 (77.8%) cases medically confirmed. There were 8 serious cases with 1 case with a fatal outcome. The majority of the reports were in females 7 (77.8%) and in patients >50 years of age. Out of the 9 cases, two cases were considered to be a duplicate, i.e., in reference to the same individual ([redacted] [reported in a literature article], and [redacted] [reported by a consumer]), a 46-year-old female with previous medical history of CLS. Based on the updated review of the reported cases with CLS related terms, there were 2 reports that fulfill the Clarkson criteria to be considered confirmed cases

Signal evaluation criteria	Summary
	of CLS. Both cases were considered possible according to the WHO causality assessment. Both reports will be discussed under ITEM 3 as both reports had previous history of CLS. There were 6 reports that were unassessable according to the Clarkson criteria due to the completed lack of laboratory information; and there was one report that was not considered a case of CLS based on the information provided in the report. According to the WHO causality assessment, there were 2 reports considered possible based on a temporal association as well as some laboratory documentation provided; there were 2 reports considered conditional due to only having some information available in the reports but important information missing; there were 3 reports unassessable due to the very little information available; and there were two reports that were considered unlikely related to the vaccine due to some other risk factors and confounders that provided a more plausible explanation for the occurrence of the events. There were two reports of patients identified as having a previous medical history of CLS that experienced a flare of CLS temporarily associated with the administration of elasomeran. Clinical literature search review: Summary: A cumulative search as of 11 Nov 2021 retrieved 361 articles. One article in Jun 2021 describing 3 cases following COVID-19 vaccines: Jansen, Pfizer and elasomeran Articles on Vaxzevria. There was a small number of articles describing CLS and mRNA vaccine and none of these shown any direct temporal association with mRNA vaccines against COVID-19 disease. There are not pathognomonic findings to link vaccine to these AEs. Conclusion: Literature search results did not provide evidence of causal association between mRNA vaccines or elasomeran and CLS.
Discussion	CLS is a serious, well characterized disease. Although rare it is gaining more attention. It is acknowledged that there are no formal estimates of incidence for CLS; thus, it cannot be concluded that observed rate varies from the expected. A cumulative search of GSDB as of 31 Oct 2021, was performed for individuals with medical history of CLS. The search retrieved 8 individuals, after reviewing these 8 cases, 6 were considered CLS. In summary, out of the 8 identified cases, there were 5 cases that were considered as CLS cases; an additional case ([redacted]), although not presenting the hallmarks of CLS, is combined with this CLS cases to a conservative approach because of its fatal outcome. Out of the 6 cases mentioned above with the diagnosis of CLS following elasomeran, 2 did not have a history of CLS and 4 had a history of CLS including the case where the first episode occurred after receiving Vaxzevria; for this case, and based on the reported information it seems the denovo CLS episode is mentioned after Vaxzevria and a flare-up after elasomeran, may be indicating this particular patient's susceptibility to develop CLS, although the potential mechanism of action for the two different vaccines is not known. There is no element in these cases explaining denovo CLS vs. flare-up, except that based on the knowledge of this disease, it is more likely to have recurrent episodes after the initial event, even though the frequency is highly variable between individuals. Re-Evaluation Discussion 2022: SCLS is a rare disorder characterized by episodic increases in vascular permeability resulting in acute losses of protein-rich fluid from the intravascular to the interstitial space. A typical presentation begins with a prodrome of fatigue, dizziness, and flulike symptoms followed by the rapid onset of shock, systemic pitting edema, hemoconcentration, and hypoalbuminemia. All of the diseases causing CLS to share the

Signal evaluation criteria	Summary
	same underlying pathophysiologic abnormality—an increase in capillary permeability to proteins. As a result, there is a loss of protein-rich fluid from the intravascular to the interstitial space. In all cases, hypercytokinemia is believed to be the underlying cause of capillary leak. As of to date there is not a biological explanation that would link elasomeran to the development or flare-up of CLS. As of 31 Dec 2021, an estimated 827,274,740 doses of elasomeran had been distributed; 559,872,937 doses are estimated to have been administered. With 8 reported cases of SCLS in the GSDB, that represents a reporting rate of 0.01 cases of CLS per 1 million doses of elasomeran administered. Analysis of the data reported in the MAH GSDB continues to provide support for a lack of a causal association between CLS and elasomeran. Cumulatively, the reporting rate of CLS for elasomeran is substantially lower than one report per million doses.
Conclusion	Overall, the findings reviewed with respect to elasomeran do not show convincing evidence of a link to CLS, based on the analysis of all the data available regarding the topic of CLS as of 31 Oct 2021, the MAH considers that CLS related events are not presently a safety issue of concern that would justify inclusion of any of these terms in the product information and/or the RMP. The MAH will continue to closely evaluate events of "Capillary Leak Syndrome-related events" using routine surveillance. Based on the re-evaluation of the cases reported for CLS in the MAH's GSDB continues to provide support for a lack of a causal association between CLS and elasomeran. Cumulatively, the reporting rate of CLS for elasomeran is substantially lower than one report per million doses. Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers that CLS related events are not presently a safety issue of concern that require any changes to the product information or the RMP, and the MAH will continue to evaluate events of CLS related events using routine surveillance.

16.3 Evaluation of Risks and New Information

16.3.1 New Information on Important Identified Risks

16.3.1.1 Anaphylaxis

16.3.1.1.1 Source of the New Information

ModernaTx, Inc's. GSDB was queried for valid, clinical, and spontaneous case reports in children <18 years of age, who reported anaphylactic reactions, received from HCP, HA, consumers, and literature, cumulatively (18 Dec 2020 to 17 Dec 2022) and for the PBRER#4 reporting period (19 Jun 2022 to 17 Dec 2022) for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. An additional evaluation was conducted in individuals >18 years of age that received any of the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran as per request from a health authority.

16.3.1.1.2 Background Relevant to the Evaluation

Anaphylaxis, a potentially life-threatening hypersensitivity reaction, can occur after any vaccination. Anaphylaxis may be immunologically or non-immunologically mediated. Most persons recover fully with treatment, but serious complications can occur. Reporting from selected healthcare organizations in the US found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses of vaccines other than elasomeran, administered to both children and adults [18]. Available data suggest a particular patient profile for persons who experience anaphylaxis after vaccination: the vast majority have a history of atopy (history of atopic disease, such as asthma, allergic rhinitis, atopic dermatitis, or food or drug allergy); however, anaphylaxis can occur among persons with no known history of hypersensitivity.

During the reporting period, upon PRAC request Anaphylaxis was removed from the EU-RMP as an important identified risk and reclassified as an identified risk (not important) in the RMP v4.0, approved after the end of the PBRER#3 reporting period, on 23 Jun 2022.

16.3.1.1.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTx, Inc. applied the MedDRA SMQ 'anaphylactic reaction' (narrow scope) to retrieve all cases of AEs suggestive of anaphylaxis from the ModernaTx, Inc. GSDB in children <18 years of age who received elasomeran or any of the bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran. Additional, as per a HA request, cases of anaphylaxis after vaccination with any of the Spikevax bivalent vaccines in individuals ≥18 years of age were also retrieved for evaluation.

To characterize the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration case definition for Anaphylaxis, which includes levels 1-3 of diagnostic certainty, followed by Level 4 (insufficient evidence to meet any level of diagnostic criteria) and level 5 (not a case of anaphylaxis) (Brighton Collaboration, Anaphylaxis 2021).

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran and anaphylaxis to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected

appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 640 literature articles were retrieved using these search criteria for the review period. The literature search results were medically/scientifically reviewed. Most of the articles described the already known association between anaphylaxis and COVID-19 vaccination, and there were also articles that described the importance of having the 3rd and 4th booster vaccination. Overall, detailed review of the articles does not observe any new and significant safety information concerning this previously well-described AE.

ModernaTx, Inc. Vaccine Hypersensitivity/Anaphylaxis Follow-up Questionnaire with the use of Moderna's COVID-19 vaccine (elasomeran)

The targeted follow-up questionnaire (TFQ) is intended to collect structured information on severe cases of anaphylactic reaction including anaphylaxis.

- During the reporting period of this PBRER, a total of 41 TFQs for Vaccine Hypersensitivity/Anaphylaxis were sent by the MAH, of which no responses were received. The response rate to the questionnaire was 0%.

Following approval of EU-RMP version 4.0, dated 23 Jun 2022, Anaphylaxis was recategorized as identified risk (not important) and therefore ModernaTx, Inc. considers, that follow-up questionnaire measures are no longer necessary. Given the extensive use of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and the experience from clinical practice, anaphylaxis is well characterized, where both, healthcare professionals and individuals are recognized to adhere to the anaphylaxis guidance provided in the SmPC and Product Label. Anaphylaxis is considered to have no longer a considerable impact on the benefit/risk balance of COVID-19 vaccines.

Review of the data does not suggest any new identifiable pattern or trend in reports of anaphylaxis that may differ from the already well known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.1.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected, Anaphylaxis

See Appendix 11.3 for tables showing observed vs. expected analyzes. In interpretation of these analyses, it is helpful to consider that anaphylaxis is already an identified risk of elasomeran and that reporting rates are higher for women, as has previously been noted [19]. In addition, there has been considerable attention regarding anaphylaxis, and monitoring at the place of vaccination following administration may increase the likelihood of reporting. Moreover, reports identified using the narrow SMQ for 'anaphylactic reaction' may sometimes instead involve other conditions.

Overview of Cases in Children

For more details on anaphylaxis cases please refer to Appendix 11.4.

The childhood population is categorized in two different age groups:

- Children less than 12-years-old
- Adolescents 12 to 17 years old

Children <12 years of age (Cumulative to 17 Dec 2022)

Cumulatively there is one case reported in this age group in a 9-month-old child, this case was reported during the reporting period of the current PBRER#4. Details of this case are as follows:

[redacted]**):** This spontaneous case concerns a 9-month-old female patient with no medical history reported, who the same day after receiving the 1st dose of elasomeran, experienced the event of Anaphylactic reaction. On the same day, patient had dinner which consisted of salmon, shrimp, potatoes and dairy and asparagus, and the patient developed angioedema and hives after dinner; it was also reported that patient had eaten these food items before and did not have any allergies. It was not sure if the anaphylaxis was due to the vaccine or the food that the patient had for dinner. Patient did not have any known allergies. The patient was treated for anaphylaxis with steroids. No further details on clinical course, other lab test results were reported. It is unclear whether the reported age is correct.

MAH Comment: It is unclear whether the reported age is correct. The meal reportedly eaten by the child is inconsistent with that expected for a nine-month-old. In addition, the allergic reaction followed dinner which suggests the food rather than the vaccine was the more likely cause of the angioedema and hives. According to the Brighton Collaboration case definition this case is considered Level 4, and according to the WHO causality assessment is unassessable.

Adolescents 12 to 17 years of age (Cumulative to 17 Dec 2022)

Cumulatively, a total of 21 cases (19 serious, 0 fatal) of anaphylaxis-related events in patients 12 to 17-years-old have been received, which included 21 events, (19 serious events). Eighteen (18) cases were medically confirmed. Of the 21 cases, 9 were male (42.9%) and 12 were female (57.1%) and ranged in age from 12 years of age to 17 years of age (mean: 15.2 [SD:1.6], median: 16.0). One case was reported during the PBRER#4 reporting period, and that person recovered.

All 21 reports were received from regulatory authorities. Reports originated most frequently from Asia (9 cases/42.2%), followed by EEA (6 cases /28.6%), and Latin America (3 cases/ 14.3).

Table 16.7 Case Distribution by Gender and Age in Adolescent Subpopulation elasomeran) – Cumulative to 17 Dec 2022

Age Group	Prior to Review Period		Review Period		# Cases	% Cases
	# Cases	% Cases	# Cases	% Cases		
12-15Y	9	45.0	0	0	9	42.9
16-17Y	11	55.0	1	100.0	12	57.1
Grand total	**20**	**100.0**	**1**	**100.0**	**21**	**100.0**

Event distribution by dose number and latency are described in Table 16.8. Cumulatively, of the 10 events with known dosing and event onset information, 8 events (38.1%), occurred the day of vaccination (6 events occurred the day of Dose 1 administration and 2 event occurred the day of Dose 2 administration). Dosing and/or event onset information was unknown or not provided for 11 events (52.4%).

Table 16.8 Event Distribution by Dose Number and Time to Onset in Adolescent Subpopulation - Elasomeran) – Cumulative to 17 Dec 2022

Dose Number	TTO (Days)	Prior to Review Period		Review Period		# Events	% Events
		# Events	% Events	# Events	% Events		
Dose 1	Subtotal	7	35.0	0	0	7	33.3
	0 days	6	30.0	0	0	6	28.6
	14-29	1	5.0	0	0	1	4.8
Dose 2	Subtotal	2	10.0	1	100.0	3	14.3
	0 days	1	5.0	1	100.0	2	9.5
	01-02	1	5.0	0	0	1	4.8
Unknown	Subtotal	11	55.0	0	0	11	52.4
	0 days	6	30.0	0	0	6	28.6
	Missing	5	25.0	0	0	5	23.8
Grand total		**20**	**100.0**	**1**	**100.0**	**21**	**100.0**

Most of the events reported cumulatively had an outcome of recovered/ recovering (15; 71.4%). There have been no fatal cases reported in the adolescents age group (Table 16.9). It should be noted that there are limitations in capturing follow-up information with spontaneous reports, such that the category of "not recovered/not resolved" may represent an overestimate for this category of outcome.

Table 16.9 Event Distribution by Outcome in Adolescent Subpopulation- elasomeran – Cumulative to 17 Dec 2022

Event Outcome	Prior to Review Period		Review Period		Total # of Events	% of Total Events
	# Events	% Events	# Events	% Events		
Not Recovered/Not Resolved	4	20.0	0	0	4	19.0
Recovered/Resolved	9	45.0	1	100.0	10	47.6
Recovering/Resolving	5	25.0	0	0	5	23.8
Unknown	2	10.0	0	0	2	9.5
Grand total	**20**	**100.0**	**1**	**100.0**	**21**	**100.0**

Appendix 11.4 contains the salient clinical information concerning the 21 adolescent cases and one child case < 12 years of age. Brighton Collaboration Anaphylaxis case criteria for the diagnosis of anaphylaxis (Brighton-Anaphylaxis 2021) was applied to the 22 cases to evaluate the strength of the evidence to determine if a case fulfils the definition of anaphylaxis. Causality was assessed for each case using the WHO-UMC causality assessment. Four (4) cases reported a medical history of atopy.

Overall, according to the Brighton Collaboration case definition, of the 22 cases (21 adolescent cases and 1 child case), two cases were classified as Level 1 (definitive cases), there were two cases classified as Level 2 (probable cases), seventeen were classified as Level 4 (fails to meet any level of diagnostic certainty), and there was one (1) case that was classified as Level 5 (Not a case of anaphylaxis).

According to the WHO causality assessment, there were 4 reports assessed as probable given not only the temporal relationship between vaccination and the beginning of the events, but also the lack of related medical history that would explain the occurrence of anaphylaxis. There were 17 reports that were considered unassessable due to the lack of information in those reports, including TTO, as well as clinical course. There was 1 report (classified as Brighton Collaboration Level 5) that was not assessed given that it was a not case of anaphylaxis.

Anaphylaxis After Receiving Booster Dose with Elasomeran/imelasomeran

Overview of Cases of Anaphylaxis in Adults > 18 Years of Age Administered elasomeran/imelasomeran

Cumulatively, 11 cases, all serious, (11 serious events) have been reported in adults 18 years of age or older after administration of elasomeran/imelasomeran all these 11 cases were reported during this reporting period.

Of these 11 cases, 6 were medically confirmed, and 1 case had a fatal outcome. The event outcomes were resolved/resolving in the majority of cases. These cases were reported mostly in females (7; 63.6%), three (27.3%) in males, and one case (9.1%) had missing gender information. The median age was 50.0 years (ranging from 23.0 to 80.0 years). Most of the cases were reported via regulatory authority (6; 54.6%), with four cases (36.4%) reported spontaneously and one case (9.1%) from literature. Cases were reported in Japan (4), the UK (4), the Netherlands (2), and Canada (1).

Evaluation of the 11 reports received after administration of elasomeran/imelasomeran according to the Brighton Collaboration case definition showed that there was one (1) report classified as Level 3 (Possible case), there were 5 reports classified as Level 4 (fails to meet any level of diagnostic certainty), and there were 5 cases that were classified as Level 5 (Not a case of anaphylaxis) based on prolonged TTO of the reported events (more than 24 hours to 6 days), as well as the reported presentation of the events described for these patients.

According to the WHO causality assessment, there were 2 reports assessed as possible given the temporal relationship between vaccination and the beginning of the events. Both reports are confounded by the individual's medical history, including Asthma; Colitis ulcerative; and Food allergy for one, and Emphysema; DM; and Chronic obstructive pulmonary disease (COPD). There were 4 reports that were unassessable due to the lack of information in those reports, including TTO, as well as clinical course. There were 5 reports (those classified as Brighton Collaboration Level 5) that were not assessed given that they were not cases of anaphylaxis.

There was one report that had a fatal outcome during this reporting period after administration of elasomeran/imelasomeran Information is presented below:

[redacted] **CA-**[redacted]): Fatal report for a female patient of unknown age who was reported to have experienced anaphylactic shock after vaccination with elasomeran/imelasomeran) (unknown dose number). The patient's medical

history is significant for emphysema, COPD, and diabetes. There were no known allergic reactions in the past. Ten minutes after vaccination, the patient had trouble breathing and lost consciousness. Two doses of epinephrine injection were administered with no improvement, and the patient died. The reported cause of death was anaphylactic shock; it is unknown if an autopsy was performed. No further information is available.

MAH comment: The patient rapidly developed relevant symptoms of anaphylactic shock shortly after vaccine administration leading to a fatal outcome. Risk factors included relevant medical history of emphysema and COPD, which may be contributory to the fatal outcome. The causality is assessed as possible as these signs & symptoms may also be of solely cardiac origin without allergic component and the case is classified as Brighton Collaboration criteria Level 3, given the limited information.

Anaphylaxis After Receiving Booster Dose with elasomeran/davesomeran

Cumulatively, 2 cases (both serious and reporting 2 serious events) have been reported in adults 18 years of age or older after administration of elasomeran/davesomeran. Both cases were medically confirmed, reported in female patients, and had resolved at the time of report. There were no cases with a reported fatal outcome.

Evaluation of the 2 reports received after administration of elasomeran/davesomeran according to the Brighton Collaboration case definition showed that there was one (1) report classified as Level 1 (Definitive case), and there was 1 report classified as Level 4 (fails to meet any level of diagnostic certainty).

According to the WHO causality assessment, one report was assessed as probable, and the other reports was unassessable due to the lack of information in the reports, including TTO, as well as clinical course.

16.3.1.1.5 Discussion

Review of the data received cumulatively and during the reporting period of this PBRER 4 does not suggest any new identifiable pattern or trend in reports of anaphylaxis in children <18 years of age, that may differ from the already known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

In most of the cases where the relevant information was available, these cases were not suggestive of a typical anaphylactic reaction, instead an important confounder of medical histories of atopy including different types of allergies (food, animals, medicines, etc.) were noted in most of the

patients reporting anaphylaxis, indicating that the reported events may be an expression of allergic reactions and not true cases of anaphylaxis.

Additionally, analyzes of cases of anaphylaxis in adults 18 years and over, including the events reported after elasomeran/imelasomeran or elasomeran/davesomeranappear to be generally consistent in nature and severity to those reported with elasomeran. For the case that involved a fatal outcome, the alternative aetiology (emphysema, COPD, and diabetes) presented above also provides a plausible explanation for the fatal outcome.

The MAH will continue to monitor the occurrence of anaphylaxis with elasomeran or elasomeran/imelasomeranand elasomeran/davesomeran via routine pharmacovigilance.

16.3.1.1.6 Conclusion

Based on the analysis of all the safety data received during the reporting period and cumulatively, ModernaTx, Inc. considers that cases of anaphylaxis reported in children here in temporal association with the administration of elasomeran did not raise any new safety issues of concern for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cases of anaphylaxis reported in adults >18 years of age after booster vaccines elasomeran/imelasomeran and elasomeran/davesomeran appear to be generally consistent in nature and severity to those reported with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and did not raise any new safety issues of concern.

The available safety data are not suggestive of any new or emerging safety trends. ModernaTx, Inc. will continue to monitor events for anaphylaxis using routine surveillance. The benefit-risk evaluation remains positive.

16.3.1.2 Myocarditis/Pericarditis

16.3.1.2.1 Source of the New Information

New information presented below includes analysis performed on cases received in the GSDB by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022. An additional request from a health authority was received by the MAH on 07 Feb 2023, regarding the review and discussion on the outcome of myocarditis/pericarditis cases following elasomeran exposure. The health authority requested that the review should include not only case reports, but also any data from (observational) studies and published literature. Additional information was included in the

background (Section 16.3.1.2.2) relevant to the evaluation to address the request for inclusion of published literature on this subject.

16.3.1.2.2 Background Relevant to the Evaluation

An association between myocarditis and/or pericarditis and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events associated with the administration of COVID-19 mRNA vaccines.

The evolution of SARS-CoV-2 has led to the emergence of antigenically divergent and highly transmissible variants with the potential to circumvent infection-induced as well as vaccination induced immunity [20]. Following the emergence of the Delta (B.1.617.2) variant in Summer 2021, the Omicron variant (B.1.1.529) and omicron subvariants (BA.2, BA.2.12.1, BA.4, BA.5), the most antigenically divergent variants known to date, in Fall/Winter 2021-22 caused the highest COVID-19 incidence rates, even in countries with high vaccination coverage [21] [22,23].

Specifically, an evaluation of COVID-19 incidence in the US over time indicates marked increases during the Delta and Omicron variant waves. With the emergence of the Omicron variant, seven-day moving averages for COVID-19 cases were higher compared to all previous waves with peaks observed in excess of 807,000 and peaks in seven-day hospitalization were higher than 159,000. Deaths during the Omicron wave exceeded those observed during Delta with seven-day moving averages peaking above 2,500 [24]. In parallel, real-world data and epidemiological studies indicated a decreased booster vaccine effectiveness during the Omicron [25] [26] [27].

Of major public health concern is whether immunity to early pandemic strains, developed via vaccination (or natural infection), confers protection against newly circulating variants. Administration of a booster dose of 50 μg at least 6 months after administration of the second of 2 doses of the elasomeran primary series greatly enhanced immune responses compared to pre-boost levels. The Omicron variant is partially evasive of previous immunity conferred by COVID-19 vaccines or a previous SARS-CoV-2 infection, which supports additional vaccine booster recommendations [28].

As a result of this new public health concern, the MAH developed two new bivalent vaccines, one containing elasomeran/imelasomeran and elasomeran/davesomeran. Both bivalent vaccines have been authorized as a booster dose in the UK, Canada, Australia, EEA, among other; and the USA respectively as of the DLP of this report. A total of 127,413,973 booster doses of elasomeran/imelasomeran have been delivered to 41 countries and an estimated total of 70,077,685

doses have been administered. Europe, the UK, Asia, and Canada account for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran have been delivered to 25 countries and an estimated total of 60,910,179 doses have been administered. The United States, Canada, Europe, and Asia account for >99% of all doses delivered and administered.

There have been several relevant publications on the risk of myocarditis associated with COVID-19 mRNA vaccines.

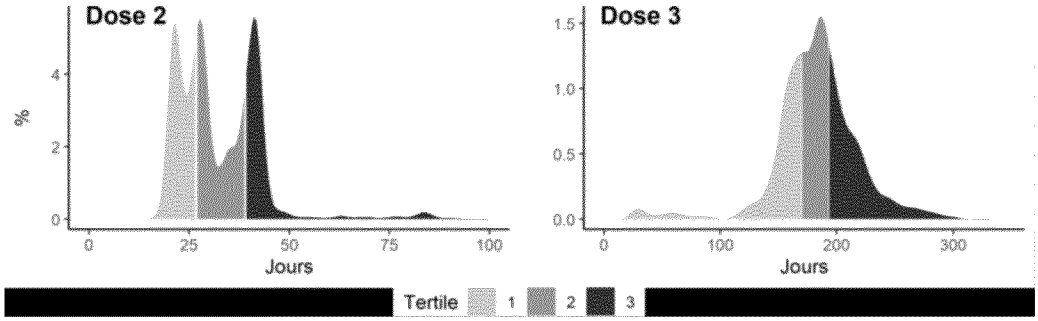
The Epi-Phare group [29] published on 22 Jul 2022, the results of a case-control study using data from the National Health Data System that were linked to national data on COVID-19 vaccination (VAC-SI), as well as screening tests for SARS-CoV-2 (SI-DEP). Cases were defined as all confirmed cases of myocarditis in people aged 12 and over admitted to French hospitals between 27 Dec 2020 and 31 Jan 2022, provided information on the risk for myocarditis associated with a of a third dose of a COVID-19 vaccine, as well as assessing that risk associated with an extended vaccination period (greater than per SmPC) between the 2nd and the 3rd dose (Booster dose) of the vaccine. The authors noted that elasomeran (ModernaTx, Inc.), which had its use suspended on 15 Oct 2021, was made available on 08 Nov 2021, but with use restricted to those aged 30 years and over.

Each case was matched on the date of hospital admission (index date) by age, sex and area of residence to 10 randomly selected controls from the general population (48,900 matched controls). The authors reported 4,890 cases of myocarditis in individuals aged 12 years or older, admitted to French hospitals between 27 Dec 2020 and 31 Jan 2022. The average age of the cases was 39 years old; 72% were male. Individuals aged 50 years and over accounted for 28% of myocarditis cases. The results of the study showed that the risk of myocarditis was increased during the first week following administration of the first, second, and third doses of the BNT162b (Pfizer-BioNTech) and elasomeran (ModernaTx, Inc.) vaccines. For the BNT162b vaccine, the odds ratios were 1.7 (95% confidence interval [CI], 1.3 to 2.2) for the first dose, 5.9 (95% CI, 5.0 to 7.0) for the second dose, and 3.1 (95% CI, 2.3 to 4.3) for the third dose. For the elasomeran vaccine, the odds ratios were 1.9 (95% CI, 1.1 to 3.5) for the first dose, 19 (95% CI, 14 to 25) for the second dose, and 4.1 (95% CI, 2.5 to 6.6) for the third dose.

To estimate risk associated with the second and third doses, the authors assessed risks according to the time since the previous dose classified into tertiles (<27, 27 to 39, and >39 days for the second dose and <170, 170 to 193, and >193 days for the third dose) (Figure 16-1). For both

vaccines, the second and third doses were associated with increased risks of myocarditis regardless of the category of delay since the previous dose. These risks decrease with longer intervals since the previous dose.

Figure 16-1. Distribution of delays between doses of COVID-19 mRNA vaccines



Source: [29].

According to the authors, the excess cases of myocarditis associated with the third dose is globally estimated at 0.25 cases per 100,000 doses of the BNT162b2 vaccine and 0.29 cases per 100,000 doses of the elasomeran vaccine. These rates correspond to one case of myocarditis attributable to vaccination for every 398,000 and 340,000 third doses administered (for BNT162b2 and elasomeran, respectively).

The authors concluded that the risk of myocarditis is increased for the third dose compared with the first dose (first booster dose), although at a lower incidence when compared with the second dose and that myocarditis associated with COVID-19 mRNA vaccines remain infrequent events compared to the number of people exposed. Another conclusion from this study presented by the authors was that the risk of myocarditis decreases with the lengthening of the intervals between each successive dose. "These results help to better characterize the risk of myocarditis associated with mRNA vaccines against COVID-19 and may inform recommendations regarding the administration of booster doses".

During this reporting period, Pasha et al [30] presented information on the evaluation of myocarditis occurring after COVID-19 infection and a subsequent administration of a mRNA COVID-19 vaccine. They concluded that patients with myocarditis secondary to COVID-19 infection may have higher susceptibility to vaccine-related myocarditis, though the mechanism is unclear. The authors hypothesized that the occurrence of myocarditis with COVID-19 infection and recurrence after COVID-19 vaccination could be due to incomplete resolution of primary

inflammation. The SARS-CoV-2 virus has a direct effect on the heart by entry into cardiomyocytes through the angiotensin converting enzyme 2 receptors which are upregulated in patients with underlying conditions, including cardiovascular disease and DM. Several studies have reported that viral replication in infected cardiomyocytes leads to cellular edema and necrosis resulting in contractile dysfunction and myocarditis [31]. In patients with prior COVID-19 infection and myocarditis observed following COVID-19 vaccination, it is difficult to establish if the symptoms are a result of a flare-up after vaccine administration due to incomplete infection resolution. The authors recommended increased vigilance and the utility for evaluation with cardiac magnetic resonance imaging (cMRI) in patients vaccinated with the mRNA COVID-19 vaccine. The cMRI diagnostic criteria for myocarditis are well defined, but the limited availability and increased health-care cost of this diagnostic modality makes this proposal somewhat impractical for general implementation. In most patients, symptoms of myocarditis are mild. Such patients with mild symptoms can be managed with Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and must be instructed to abstain from competitive sports for at least three months, according to the authors.

It is important to note that even though almost all individuals with cases of myocarditis are hospitalized and clinically monitored, most cases follow an uncomplicated clinical course and complete resolution of symptoms is rapidly achieved after receiving only pain management within few days (2 to 4 days). Initial evaluation usually included measurement of troponin level, electrocardiography, echocardiography, and cardiac MRI, which is being recommended as the main modality for confirming the diagnosis of myocarditis since late gadolinium enhancement (LGE) with or without edema in T2-weighted imaging is observed in the majority of patients. In a recent study [32].

conducted at a large pediatric medical center in the US, 16 cases of myopericarditis following COVID-19 mRNA vaccination in patients under 18 years of age, who initially presented from 01 Apr 2021 to 07 Jan 2022, were reviewed with a focus on assessing initial versus follow-up cardiac MRI findings. All cases in the study were associated with receipt of the second dose of the Pfizer COVID-19 mRNA vaccination. All patients included in the study were evaluated by a pediatric cardiologist, underwent ECG, echocardiogram, serial troponin measurements, were admitted for observation with telemetry, underwent cardiac MRI within 1 week of initial presentation and had repeat cardiac MRI at 3-8 months' follow-up The patients' median age was 15 years (range, 12-17 years), were mostly male (n = 15, 94%), White, and non-Hispanic (n = 14, 88%). All patients had chest pain and the most common other presenting symptoms were fever (n = 6, 37.5%) and shortness of breath (n = 6, 37.5%). All patients had elevated serum troponin levels

(median 9.15 ng/mL, range 0.65-18.5, normal <0.05 ng/mL), 12 patients had elevated C-reactive protein levels with median value 3.45 mg/dL (range 0-6.5 mg/dL, normal <0.08 mg/dL), 10 (62.5%) patients had an abnormal ECG, with the most common finding being diffuse ST-segment elevation, 2 patients demonstrated mildly reduced Left ventricular (LV) systolic function on echocardiogram (left ventricular ejection fraction [LVEF] of 45% and 53%, normal >55%) with no dilation. No patients had pericardial effusion.

The initial cardiac MRIs were abnormal in all patients; all showed evidence of edema by T2 imaging, and 15 of 16 had LGE in a patchy subepicardial to transmural pattern with predilection for the inferior LV free wall. LV regional wall motion abnormalities were noted in 2 patients. Cardiac MRI LVEF was mildly decreased in 7 patients (median 54%, range 46%-63%). Cardiac MRI global longitudinal strain measurements were abnormal in 12 (75%) patients (median −16.1%, normal <−18%).

On follow-up, abnormal findings persisted on cardiac MRI at follow-up in most patients, albeit with significant improvements (Figure 16-2). Cardiac edema resolved in all but one patient. Eleven patients (68.8%) had persistent LGE, although there was a significant decrease in the quantifiable LGE from the initial study. Cardiac MRI LVEF was significantly improved from initial, with normal LVEF by echocardiogram for all patients, and none of the patients had regional wall motion abnormalities. Global longitudinal strain remained abnormal in most patients (75%) at follow-up. Despite these persistent abnormalities, all patients had rapid clinical improvement and normalization of echocardiographic measures of systolic function. Four patients complained of intermittent chest pain at follow-up with no identifiable abnormality on evaluation; no therapy or intervention was required. No patient received heart failure medication.

Figure 16-2. COVID-19 Vaccine-Associated Myopericarditis Findings in 16 Patients

Diagnostic assessment	Initial, mean ± SD	Follow-up, mean ± SD	*P* value
Echocardiographic LVEF %	59.4 ± 6.0	62.6 ± 2.8	**<.05**
Electrocardiogram			
Abnormal	10 (62.5%)		
Normal	6 (37.5%)		
Peak serum troponin, ng/mL	9.0 ± 5.2		
Cardiac MRI LVEF %	54.5 ± 5.5	57.7 ± 2.7	**<.05**
Cardiac MRI LGE % (n = 15*)	13.5 ± 8.3	7.7 ± 5.7	**<.001**
Cardiac MRI global longitudinal strain % (n = 15*)	−16.0 ± 1.7	−16.4 ± 2.1	.5

Additional study observations noted that, of the 3 patients that received IVIg, 1 patient who received IVIg alone and 1 patient who received IVIg plus corticosteroid had resolution of LGE; the other had persistence of LGE. Eight patients (5 of whom had persistent LGE) underwent additional 24-hour cardiac rhythm monitoring and 6 patients with persistent LGE underwent exercise tests, all of which were normal.

In conclusion, the authors suggested that the persistence of LGE and abnormal global longitudinal strain warranted further follow-up assessment and larger multicenter studies to determine the ultimate clinical significance of these abnormalities in patients with post–COVID-19 vaccine myopericarditis. One of the big limitations of this study is the total number of patients reported (16) which is very small and limit the ability to draw conclusions about the effect of treatment modalities or to generalize regarding outcomes of vaccine-associated myopericarditis.

In a systemic review study conducted by Woo et al [33], the authors aimed to study previously published case reports and case series associated with COVID-19 mRNA vaccine-related myocarditis and investigate the risk factors related to clinical outcomes. The authors conducted the search on PubMed/Medline, EPub, Scopus, Embase, and Web of Science databases, that include all articles available on patients with COVID19 mRNA vaccine-associated myocarditis published up to 25 Aug 2021. There were 24 studies identified with myocarditis related to immunization with mRNA (BNT162b2 or mRNA-1273) COVID-19 vaccines. Data was collected based on demographic and clinical characteristics, including information on treatments, outcomes, age, sex, onset of symptoms, pre-existing conditions, laboratory results, immunologic assays,

results of electrocardiography and echocardiogram, as well as radiological findings of cMRI, and finally, the length of hospitalization, length of ICU stay, and mortality.

There were 74 patients with myocarditis within the age of 14-40 years old, 49.5% of them were younger than 20 years. Almost all patients (70) were male, and seven patients (9.5%) had underlying medical conditions such as hypertension, diabetes, hyperlipidemia, or endocrinologic disorder. All patients recovered without significant complications, with a third (35.1%) of the patients' symptoms resolving with conservative management. Among the remaining patients, more than half (54.0%) received anti-inflammatory medications such as NSAIDs, colchicine, steroids, or intravenous immunoglobulin. In addition, 16.2% of them were treated with heart failure medications, including beta-blockers, ACE inhibitors/angiotensin-receptor-blocker, diuretics, or inotropic. About 5% of patients (n = 4) experienced complications, including one major (multi-organ failure) and three minor cases (non-sustained ventricular tachycardia).

Twelve patients (16.2%) required ICU care, and about half (43.2%) of the patients were discharged within 4 days. Over two-thirds (78.3%) of patients received the BNT162b2 vaccine, and most (90.5%) patients presented with myocarditis after the second dose of the vaccine. Patients presented to the hospital from 6 h to 16 days after vaccination, with a median time from vaccination of 3 days.

Most patients presented with chest pain (95.9%), accompanied with fever (33.8%), dyspnea (21.6%), headache (14.9%), fatigue (10.8%), and chills (5.4%). Over two-thirds (87.8%) of patients had abnormal ECG findings: ST-segment (77.0%), T-wave (16.2%), and PR interval (14.9%). Echocardiography revealed that about a third (31.1%) of patients had LF dysfunction (ejection fraction <55%) and 21 patients had regional wall motion abnormality. In regard to laboratory tests, all 74 patients showed elevated levels of cardiac enzymes, 64 (86.4%) patients had high levels of C-reactive protein, and 12 (16.2%) patients had a high level of brain natriuretic peptides (BNP), pro-BNP, or NT-pro-BNP. Most patients (79.7%) underwent cMRI studies in hospitals, and 40 of 59 patients (67.8%) had CMR findings suggesting myocarditis, which met the original or modified Lake Louise criteria.

Overall, the study showed that the clinical course of the patients was favorable without mortality, and one-third of patients resolved with conservative care alone, and according to the authors the risk of fatality in myocarditis subjected to mRNA vaccination seems to be low [33].

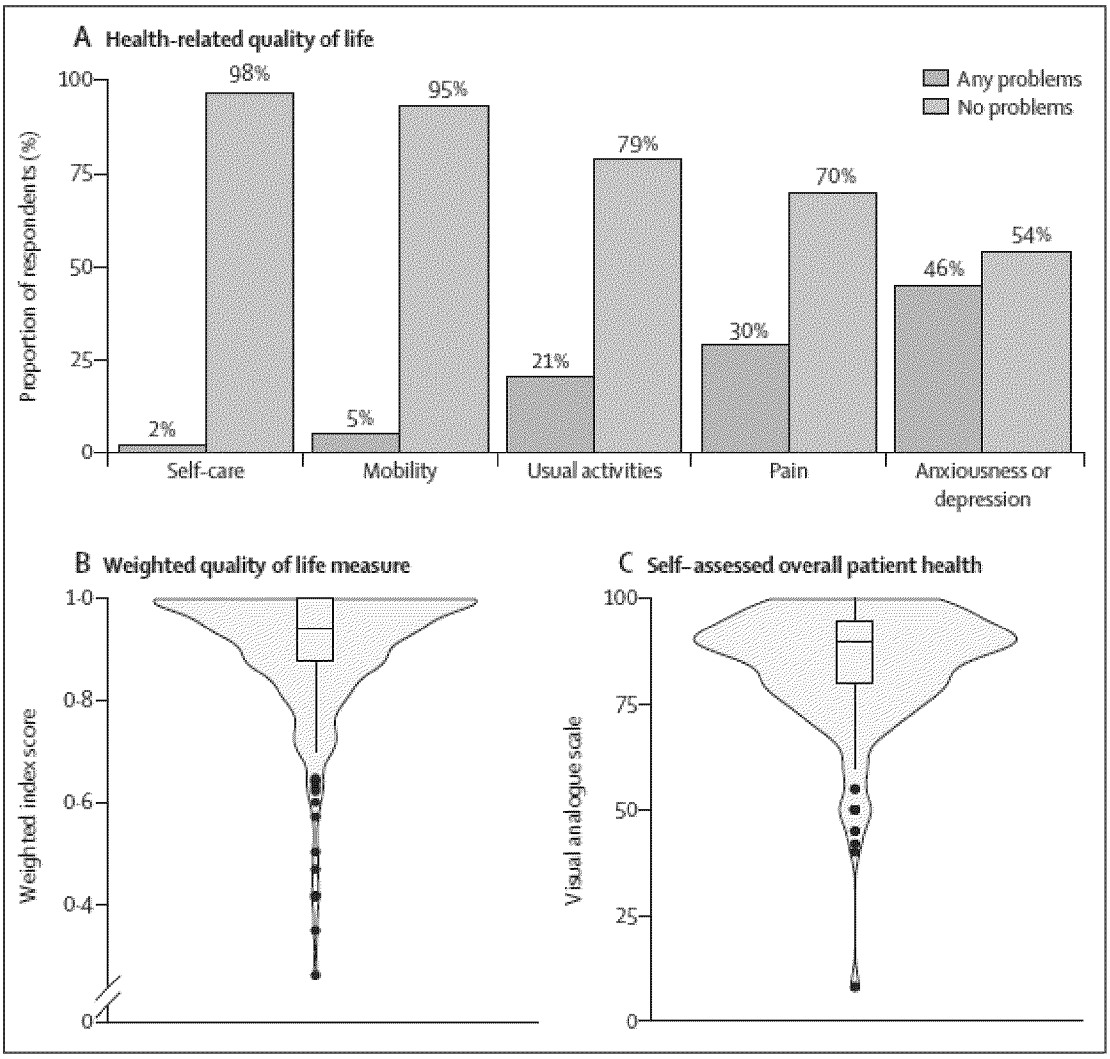
An ongoing follow-up surveillance study [34], conducted by the Centers for Disease Control and Prevention (CDC) included surveys in US individuals aged 12–29 years with myocarditis after

mRNA COVID-19 vaccination, for whom a report had been filed to the VAERS between 12 Jan 2021 and 05 Nov 2021. A two-component survey was administered, one component to patients (or parents or guardians) and one component to health-care providers, to assess patient outcomes at least 90 days since myocarditis onset. Data collected were recovery status, cardiac testing, and functional status, and EuroQol health-related quality-of-life measures (dichotomised as no problems or any problems), and a weighted quality-of-life measure, ranging from 0 to 1 (full health). The EuroQol results were compared with published results in US populations (aged 18–24 years) from before and early on in the COVID-19 pandemic. Between 24 Aug 2021, and 12 Jan 2022, the authors collected information for 519 (62%) of 836 eligible patients who were at least 90 days post-myocarditis onset: 126 patients via patient survey only, 162 patients via health-care provider survey only, and 231 patients via both surveys. Median patient age was 17 years (Interquartile range [IQR] 15–22); 457 (88%) patients were male and 61 (12%) were female. 320 (81%) of 393 patients with a health-care provider assessment were considered recovered from myocarditis by their health-care provider, although at the last health-care provider follow-up, 104 (26%) of 393 patients were prescribed daily medication related to myocarditis.

Of 249 individuals who completed the quality-of-life portion of the patient survey, four (2%) reported problems with self-care, 13 (5%) with mobility, 49 (20%) with performing usual activities, 74 (30%) with pain, and 114 (46%) with depression. Mean weighted quality-of-life measure (0.91 [SD 0.13]) was similar to a pre-pandemic US population value (0.92 [0.13]) and significantly higher than an early pandemic US population value (0.75 [0.28]; $p<0.0001$) (Figure 16-3).

Most patients had improvements in cardiac diagnostic marker and testing data at follow-up, including normal or back-to-baseline troponin concentrations (181 [91%] of 200 patients with available data), echocardiograms (262 [94%] of 279 patients), electrocardiograms (240 [77%] of 311 patients), exercise stress testing (94 [90%] of 104 patients), and ambulatory rhythm monitoring (86 [90%] of 96 patients). An abnormality was noted among 81 (54%) of 151 patients with follow-up cardiac MRI; however, evidence of myocarditis suggested by the presence of both LGE and oedema on cardiac MRI was uncommon (20 [13%] of 151 patients). At follow-up, most patients were cleared for all physical activity (268 [68%] of 393 patients).

Figure 16-3. Self-Assessment of Health-Related Quality-of-Life Among Patients with Myocarditis After mRNA COVID-19 Vaccination



Source: [34].
(A) Bar plot of health-related quality-of-life among patients. Patients were administered the EuroQol 5-dimension 5-severity level questionnaire; for analysis, the five health-related dimensions were dichotomised into the frequency of problems (severity levels 2–5) and no problems (level 1). (B) Violin plot of weighted quality-of-life measure converted from each patient health profile from (A) to an index score between 1 (perfect health) and 0 (equivalent to death). (C) Violin plot of patient self-assessed overall health on a scale from 0 to 100 (with 100 representing best possible health and 0 representing the worst possible health). The denominator for the EuroQol questionnaire was 249 respondents. In the violin plots (B, C), the limits of the boxes denote IQR, and the horizontal line denotes median values. Whisker endpoints are equal to the maximum and minimum values below or above the median plus or minus 1·5 times the IQR. The width of the outer shape around the box plots indicates the probability density of values or responses with a given result.

Despite clinical improvements and normalization of most diagnostic test results, as noted by health-care providers, half of patients (178/357) surveyed continued to report at least one symptom potentially associated with myocarditis after COVID-19 vaccination. One possible explanation for the persistence of symptoms is that approximately 50% of patients reported depression or anxiety, conditions that can manifest as symptoms associated with myocarditis, such as chest pain or palpitations [35]. According to the authors, the significance of the cMRI findings among the subset of patients who received cardiac imaging is unclear. Evidence of ongoing myocarditis on follow-up cMRIs based on modified Lake Louise criteria was uncommon. However, consistent with the few published case series of myocarditis after mRNA COVID-19 vaccination, the authors observed that nearly half of patients (71/151) with follow-up cardiac MRIs had residual late gadolinium enhancement, suggestive of myocardial scarring. In this study the authors did not note the degree of LGE identified during follow-up, but a recent study that assessed serial cardiac MRIs in patients younger than 19 years with myo-carditis after COVID-19 vaccination and persistent LGE showed improvement over time [36].

In a small subset of patients, initial cardiac imaging at diagnosis was normal but follow-up imaging was abnormal. It is possible that clinical findings in these patients continued to evolve after diagnosis. According to the authors, another possibility is that the initial and follow-up imaging results were evaluated by different health-care providers, who had varying interpretations. In previous studies during the pre-COVID era, cardiac scarring related to myocarditis on follow-up MRI was not uncommon, yet its clinical significance has remained controversial.

This study has several limitations including the fact that for the follow-up evaluation could be conducted by different providers and given the absence of clear clinical practice guidelines for the outpatient follow-up of myocarditis, comparing clinical course among patients could be challenging, especially as the authors mentioned no common standard level of care. The authors recognized substantial heterogeneity in the initial evaluation and follow-up of patients, particularly in the cardiac diagnostic imaging received. Current guidelines recommend restricting patients with myocarditis (eg, athletes) from competitive sports for 3–6 months, although it was noted some variability among health-care providers in clearing patients for a return to all physical activity.

A very important limitation in this study is the passive (or spontaneous) nature of VAERS reporting [37]. Some US cases of myocarditis associated with mRNA COVID-19 vaccination will not have been reported; however, it is unclear how cases reported or not reported initially to VAERS could differ. Selection bias is a possible limitation in any survey activity.

Additionally, the authors relied on health-care provider reports for all diagnostic data results. Unlike prospective studies, they did not have access to central interpretation of tests (eg, electro-cardiograms, echocardiograms, and cardiac MRIs). Although this limitation probably introduces some variability into the findings, it also reflects real-world practice and data appeared not to be missing at random. A fifth limitation is the absence of a control group for the analysis of patient symptoms. Control groups are important for contextualizing symptoms.

Although no pre-myocarditis measures were available for the group of patients with myocarditis, the authors found that quality-of-life measures among those with COVID-19 vaccine-associated myocarditis at follow-up were similar to or better than those of contemporary populations studied before or early in the pandemic.

The authors concluded that after at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination, 81% of patients were considered recovered by their health-care provider. At the time of follow-up, these patients reported quality-of-life measures similar to pre-pandemic reports among individuals of similar ages in the USA. 50% of patients reported at least one symptom at follow-up. Among a subset of 151 patients who had follow-up cardiac MRI results, 54% had an abnormal finding. The CDC is conducting additional follow-up on patients who were not considered recovered at least 12 months since symptom onset, to better understand their longer-term outcomes.

A population-based surveillance study [38] was conducted that included persons aged 18–39 years who were members of integrated health-care organizations within the Vaccine Safety Datalink (VSD) and vaccinated with mRNA vaccines manufactured by either of the MAHs. The study population was limited to 18–39-year-olds because these ages have previously been associated with an increased risk for myocarditis and pericarditis following vaccination and both BNT162b2 and elasomeran vaccines are authorized or approved in this age group. The purpose of the study was to estimate the incidence of myocarditis/pericarditis during days 0 to 7 after mRNA vaccination by age (5-39 years old), sex, dose number, and product. All identified potential cases underwent medical record review which verified the diagnosis, assessed timing of symptom onset (which resulted in some onsets shifting to day 0, post-vaccination), and collected clinical details about the event. Cases not meeting CDC case definitions for myocarditis or pericarditis were excluded. Results from the study showed the following findings:

- From 14 Dec 2020 through 31 May 2022 (persons 18–39 years) and 20 Aug 2022 (persons 5–17 years), there were 320 potential and 224 verified cases of myocarditis/pericarditis

identified 1 to 98 days after 6,992,340 vaccine doses as part of primary series COVID-19 vaccination.

- Of these 224 verified cases, 137 (61%) occurred 0 to 7 days after vaccination; 18 were after the first dose (of 3,562,311 doses administered) and 119 were after the second dose (of 3,430,029 doses administered).
- In these age groups, incidence per million doses 0 to 7 days after vaccination was numerically higher in male than in female persons and after Dose 2, although CIs were wide and overlapped across sex for some age groups. Incidence was highest for male adolescents ages 12 to 15 years and 16 to 17 years following Dose 2.
- From 24 Sep 2021 through 20 Aug 2022, 101 potential cases of myocarditis/pericarditis were identified 1 to 98 days after 1,848,723 first booster doses, with 77 (76%) verified with a median onset of 4.5 days after vaccination; 39 cases (51%) were verified in the first week versus 38 cases during the subsequent 13 weeks.
- In all age groups, incidence 0 to 7 days after first booster was higher for male compared to female persons, with adolescent males having the highest incidence in 16 to 17-year-olds and in 12 to 15-year-olds. In adults for whom both vaccine products were available, post-booster incidence was higher in male than female adults and higher in males aged 18 to 29 years compared to males aged 30 to 39 years.

Important strengths of the study included that information was obtained through active surveillance of a large diverse population and by verification of cases through medical record review and physician adjudication. Important limitations include the lack of a control group and precluding causal inference. Cases were also identified only in emergency or inpatient settings using myocarditis/pericarditis–specific International Classification of Disease-10 codes. Thus, cases were not identified if they were seen only in outpatient settings or if they received less-specific diagnosis codes such as chest pain (R07.9). Further limitations included the possibility of reporting and ascertainment bias, potential differences between individuals who received ModernaTx, Inc. versus Pfizer vaccines and underreporting of SARS-CoV-2 infection.

Even though myocarditis and pericarditis have been reported more frequently than expected, mainly in male adolescents and young adults, following receipt of the mRNA vaccines [BNT162b2 (Pfizer COVID-19 vaccine) and elasomeran (ModernaTx, Inc. COVID-19 vaccine)], it is important to note that cases have also been reported in NVX-CoV2373 (Novavax COVID-19

vaccine, a protein subunit vaccine) recipients during the phase 3 trials as well as in their post-authorization safety data. These observations strongly suggest that the risk for myocarditis and pericarditis is not specific to the mRNA platform but is related to the spike protein antigens.

A prominent hypothesis for myocarditis after infection and in rare cases after vaccination is that it is mediated by circulating Spike or Spike-S1 protein, and the interaction of that protein with tissues and antigen-experienced immunity. A prospective pilot study of 13 healthcare workers [39] for 18 years and older, with no known history of SARS-CoV-2 infection was conducted from Dec 2020 to Mar 2021, with the objective of providing evidence that circulating SARS-CoV-2 proteins are present in the plasma of participants vaccinated with the elasomeran vaccine. Plasma was collected from 13 participants at 10-13 timepoints between 1 and 29 days after the first injection and 1-28 days after the second injection. Temporal profiling of SARS-CoV-2 antigens and antibodies were acquired using Ultrasensitive single-molecule array (Simoa) assays providing data on 15 markers to monitor antigen production and immune responses on each participant. Results of the study showed that after the first 100 μg dose, the elasomeran vaccine produced detectable levels of S1 antigen in plasma in 11 participants and spike antigen was detected in three of 13 participants. Nucleocapsid antigen was undetectable or at background levels in all participants after both injections. S1 antigen was detected as early as day one post-vaccination and peak levels were detected on average five days after the first injection. S1 antigen in all participants declined and became undetectable by day 14. After the second vaccine dose, no S1 antigen or spike was detectable, and both antigens remained undetectable through day 56. Out of the 13 healthcare workers, 11 participants had S1 antigen isolated from plasma after the first injection, while nucleocapsid concentrations were insignificant in all participants, confirming that the detected S1 antigen originates from vaccination and not natural infection. The authors concluded that the presence of S1 antigen was likely due to the nature of the encoded mRNA-1273 spike protein, which contains a cleavable S1-S2 site and enables release of S1 protein from the spike trimer. They hypothesize that release of S1 protein could result from cleavage via mammalian cell proteases or circulating proteases. The authors observed an increase in S1 antigen over an initial period of one to five days, suggesting that mRNA translation begins immediately after vaccine inoculation. Interestingly, spike protein appears in three of thirteen participants on average eight days after S1 antigen is produced.

16.3.1.2.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran , elasomeran/imelasomeran, and elasomeran/davesomeranand myocarditis and pericarditis to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 11.5.

A total of 197 literature articles were retrieved using these search criteria. These literature search results were medically/scientifically reviewed and are discussed above, under section Background Relevant to the Evaluation. There was no additional published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

GSDB

During this PBRER reporting period the ModernaTx, Inc. was queried for valid case reports of myocarditis and pericarditis received from HCP, HA, consumers, and literature for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The MAH used the non-infectious myocarditis/pericarditis MedDRA narrow SMQ that contains the following PTs: Autoimmune myocarditis, Autoimmune pericarditis, Carditis, Chronic myocarditis, Eosinophilic myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis, Myocarditis, Myopericarditis, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, Pleuropericarditis.

To characterize the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration Myocarditis/Pericarditis case definition [40] [41] [42].

- Level 1 (Definitive case)
- Level 2 (Probable case)
- Level 3 (Possible case)
- Level 4 is a reported event of myocarditis/pericarditis with insufficient evidence to meet level 1, 2 or 3 of the case definitions
- Level 5 (Not a case of Myocarditis/Pericarditis)

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case (of myocarditis or pericarditis). It is not used to ascertain causality.

The CDC working case definition [43] was used to characterize acute myocarditis and acute pericarditis cases, and was used for medical review of reports identified during this reporting period (19 Jun 2022 to 17 Dec 2022):

- Acute Myocarditis
- Probable
- Confirmed
- Acute Pericarditis

Myopericarditis (This term was used for patients meeting criteria for both Myocarditis and Pericarditis)

Similar to the Brighton definition, the CDC definition identifies the strength of the evidence to support a diagnosis of myocarditis and/or pericarditis. It is not intended to be used for causality assessment. It was established for the purpose of identifying cases observed following receipt of a COVID-19 vaccine.

In contrast, causality assessment (i.e., characterizing the likelihood that a case of myocarditis/pericarditis was attributable to vaccine exposure) was conducted utilizing the WHO-UMC standardized case causality assessment [17].

Further evaluation was conducted in the segment of the reported cases involving patients that were considered (based on epidemiologic characteristics) to be at potentially higher risk for having events of myocarditis and/or pericarditis. This evaluation was conducted in males and females younger than 40 years of age, after the 2nd dose of elasomeran, regardless of the TTO of the events from the administration of the vaccine. An additional, focused evaluation was conducted on all reports involving patients <18 years of age, as well as those who received a 3rd dose or a booster dose.

ModernaTx, Inc. Supplemental Follow-up Questions for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna COVID-19 vaccines (elasomeran, elasomeran/imelasomern, elasomeran/davesomeran)

- During the reporting period of this PBRER a total of 327 TFQs for Myocarditis/Pericarditis were sent by the MAH, of which 9 TFQ responses were received. The response rate to this questionnaire was 3%.
- This very low response rate may be an indicator of the reporter's difficulties to address all the requested follow-up information. It is also important to note that as myocarditis and pericarditis are considered important identified risks for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, respondents may consider that the additional information that is been requested will not provide any new additional information or value to a risk that is already known.
- A low response rate can be due to sampling bias if the nonresponse is unequal among the participants regarding exposure and/or outcome. It also undermines the ability of the collected data and in turn, dilute the reliability of the results, especially when the main purpose of this questionnaire is to collect follow-up information that would allow a better characterization of reports of myocarditis/ pericarditis.
- Given the low response rate, ModernaTx, Inc. concludes that the questionnaire for Potential cases of Myocarditis/ Pericarditis after vaccination with elasomeran is not adequate to collect follow-up information needed for further characterization of these 2 important identified risks. In order to improve the response rate, the questionnaire may need to be simplified and focused on essential information. ModernaTx, Inc. will evaluate and streamline the information requested within the current questionnaire to try to improve response rate by looking at the type of questions asked, the length of the questionnaire, changing from a written response document to maybe a digital approach, among others.

The MAH would like to note that myocarditis and pericarditis are very complex medical entities, as such, follow-up on cases from spontaneous reporting might not be adequate to characterize these important identified risks. The additional pharmacovigilance activities described in the current approved EU- RMP (v6.3) such as the ongoing clinical studies (mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, and 20-0003) as well as ongoing post-authorization safety studies (mRNA-P903, mRNA-1273-P904), the planned specific study mRNA-1273-P910 (Natural history and clinical outcomes of vaccine-associated

myocarditis) and an ongoing study mRNA-1273-P911 (Long-term outcomes of myocarditis following administration of Spikevax) would probably bring more relevant information.

Based on the analysis of all the safety data available as of 17 Dec 2022, the MAH considers cases included under the AESI of myocarditis and pericarditis to be consistent with the well-known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for elasomeran far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.

16.3.1.2.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected

See Appendix 11.3.

Overview of Cases

Myocarditis and Pericarditis (Cumulative to 17 Dec 2022)

Cumulatively, through 17 Dec 2022, a total of 6,702 cases (7,102 events) of myocarditis and pericarditis have been received for all the elasomeran vaccines, including the bivalents. Out of those, 6,677 cases (7,076 events; 6,843 serious events) of myocarditis and/or pericarditis have been reported for elasomeran only, with 4,704 (70.5%) cases medically confirmed. There were 82 cases (85 events) with fatal outcomes.

Table 16.10 Number and Percentage of Reported Cases of Myocarditis and Pericarditis for Elasomeran, Elasomeran/Imelasomeran and Elasomeran/Davesomeran – Cumulative as of 17 Dec 2022

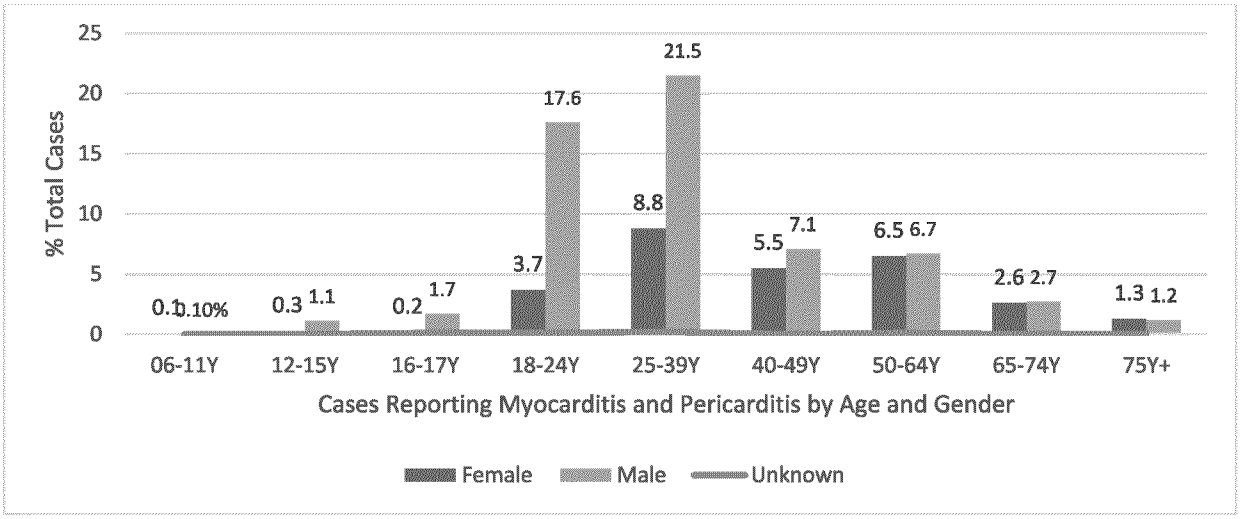
Product Name	PBRER # 3		PBRER # 4		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases		
Elasomeran	5,521	82.4	1159	17.3	6,677	99.6
Elasomeran/imelasomeran	0	0	20	0.3	20	0.3
Elaosmeran/davesomeran	0	0	5	0.1	5	0.1
Grand total	**5,521**	82.4	**1,184**	17.7	**6,702**	100.0

Cumulatively, there were no significant changes observed regarding demographics in the reported cases of myocarditis and pericarditis when compared to this PBRER reporting period, with the majority of cases reporting myocarditis and/or pericarditis continue to involve male. The

proportion of events reported in males (4,420; 66.2%) remains higher when compared to females (2,114; 31.7%) while 143 reports (2.1%) did not report gender information. The mean age of the patients was 37.4 years (SD 16.7), with a median age of 33 years (min 6/max 94); 707 cases were missing age information.

The majority of cases reporting myocarditis and pericarditis events continued to involve males between the ages of 18 to 39-years-old (2,615; 39.2%). Regardless of gender, more than half (52%) of cases were reported in patients in the 18 to 39-year-old age group (Figure 16-4).

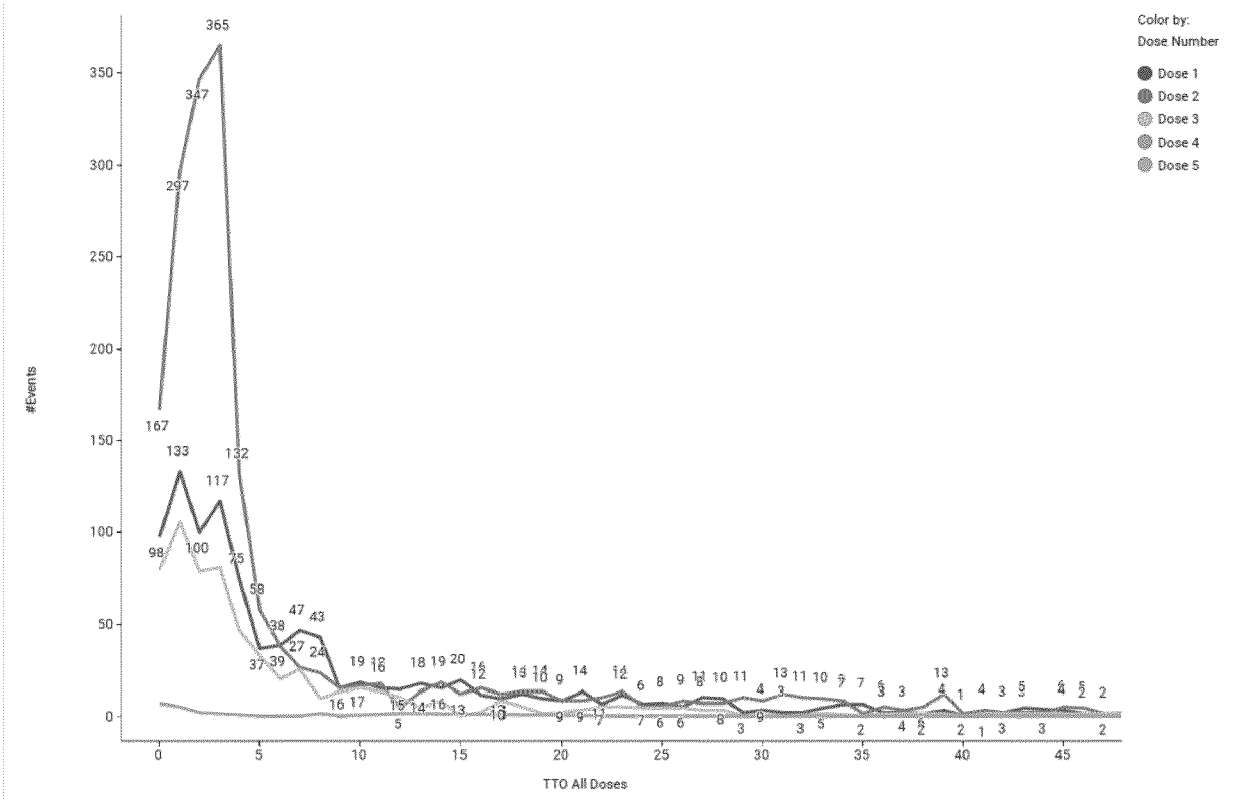
Figure 16-4. Percentage of Cases Reporting Myocarditis and Pericarditis by Age and Gender-Cumulative to 17 Dec 2022- elasomeran



Source: ModernaTx, Inc. GSDB - Monthly Spotfire dashboard

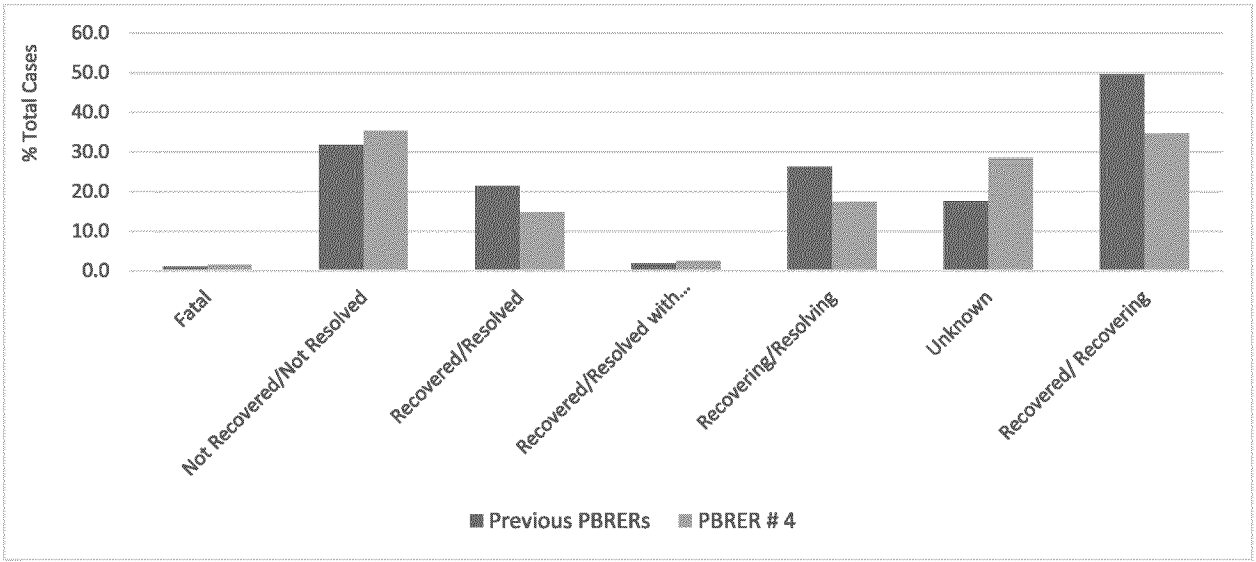
Trending of reported events of myocarditis and pericarditis continued to show that events of myocarditis and pericarditis most frequently occur after the 2nd dose (2,010; 28.4%). In events with known dose number, over half of the events had an onset less than 7 days from vaccination (2,462; 65.5%), inclusive of 457 events following 3rd and 4th doses (Figure 16-5). There were 3,317 events (46.9%) reported unknown dose number.

Figure 16-5 Distribution of Events by Time to Onset Stratified by Dose Number for elasomeran and Spikevax bivalent vaccines – Cumulative to 17 Dec 2022



Cumulative as of 17 Dec 2022, there have been 3,330 events (46.9%) that have reported a recovered/ recovering outcome. In some instances, additional short-term follow-up information has been provided demonstrating a recovery of symptoms within 3 to 6 months after experiencing the event of myocarditis or pericarditis. There is an important number of events (1,384; 19.5%) that did not provide outcome information. There were 2,302 events (32.4%) that had a reported outcome of not resolved. Unfortunately, most of these reports do not have additional follow-up information, and the reported outcome of not resolved may be associated with the outcome at the time of the reporting date of the event, instead of information received after a short-term follow-up (Figure 16-6).

Figure 16-6. Percentage of Cases Reporting Myocarditis and Pericarditis by Reported Outcome-Cumulative to 17 Dec 2022–elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran



* Recovered/Recovering constitute the sum of events reported as recovered/resolved plus Recovered/ Resolved with sequelae and Recovering/Resolving

Cumulative, there are 144 cases that reported an outcome of recovered with sequelae (Appendix 11.5), Out of those 115 (79.9%) did not provided information or description of what the referred sequelae was. The rest of the reports (28; 19.4%) provided limited information like "hoarseness and tightness of chest"; "paralysis of the elbow joint and hand due to right upper arm compartment syndrome, which was caused by the patient removing an arterial sheath"; "brain death", etc. None of these reports provided any detail information that would allow a more detail evaluation of these reports. Additional information is included in Appendix 11.5.

There have been 83 cases (1.6%) (86 events) of myocarditis/ pericarditis reporting a fatal outcome cumulative for individuals vaccinated with elasomeran (82 cases), and elasomeran/imelasomeran (1 case); there has not been any fatal reports after elasomeran/davesomeran vaccination. There were 63 cases (66 events) during the previous reporting periods, and 20 cases (20 events) during the reporting period of this PBRER (Appendix 11.5).

Out of those 83 fatal reports:

- 5 cases included both myocarditis and pericarditis, or myopericarditis, events
- 7 cases involved only pericarditis

- 66 cases involved only myocarditis
- 1 case of Giant cell myocarditis
- 4 cases of carditis
- Gender: 55 Males (66.3%), 26 Females (31.3%), 2 Unknown (2.4%)
- Age: 16 to 94 (Median: 58 year/ Mean: 56 years)
- Median TTO is 5 days (min:0/max:377)
- No important differences on the number of reports after any dose, with 16 (18.8%) after dose 1; 23 (27.1%) after dose 2; 14 (16.5%) after dose 3; and 4 (4.7%) after dose 4. There are 28 (32.9%) cases that dose number was not reported.

Out of those 83 fatal reports:

- There were 7 reports (8.4%) that reported not having an autopsy performed
- There were 37 reports (44.6%) that reported having an autopsy performed
- There were 39 reports (47.0%) that it is unknown if an autopsy was performed

Out of the 37 reports that reported having an autopsy performed:

- There were 28 reports (75.7%) where results were not provided
- There were 9 reports (24.3%) where relevant results were provided. Information on these reports is included in Appendix 11.5.

Additional information on the evaluation of outcomes in individuals with reported events of myocarditis/ pericarditis based on the Interim Report of study mRNA-1273-P903 is included in Appendix 11.5.

Myocarditis and Pericarditis (Reporting Period–19 Jun 2022 to 17 Dec 2022)-elasomeran

During the reporting period of this PBRER, a decreasing trend in the number of reported cases of myocarditis and pericarditis was observed. Noting that relatively more vaccine doses are increasingly being administered as booster doses, this reduction in the number of reported cases may be possibly associated with the observed lower risk for myocarditis/ pericarditis after a 3rd or more doses of elasomeran. As new safety data from the Spikevax bivalent vaccines becomes

available, a lower risk of myocarditis and pericarditis is observed in those exposed to the Spikevax bivalent vaccines, compared to after Dose 2 with elasomeran.

During the reporting period of this PBRER, a total of 1,159 cases (1,236 events) were reported. There were 901 (77.7%) cases medically confirmed. There were 19 cases (20 events) with a fatal outcome.

There were 667 (58.4%) cases of myocarditis and pericarditis reported for males, and 431 (37.2%) reported in females; 51 cases (4.4%) did not include gender information. The mean of the patients' ages was 37.3 years (SD 16.9), with a median age of 34.0 years (min 6/max 91); 217 cases were missing age data.

During the reporting period, myocarditis and pericarditis cases reported continued to involve males aged 18 to 39-years-old at a greater frequency than any other demographic (346, 29.9%) Table 16.11.

Table 16.11 Number and Percentage of Myocarditis and Pericarditis Cases by Age and Gender-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
06-11Y	4	0.3	7	0.6	0	0.0	11	1.0
12-15Y	9	0.8	27	2.3	0	0.0	36	3.1
16-17Y	6	0.5	22	1.9	2	0.2	30	2.6
18-24Y	36	3.1	132	11.4	4	0.3	172	14.8
25-39Y	106	9.1	214	18.5	1	0.1	321	27.7
40-49Y	75	6.5	70	6.0	1	0.1	146	12.6
50-64Y	87	7.5	68	5.9	2	0.2	157	13.6
65-74Y	19	1.6	16	1.4	0	0.0	35	3.0
75Y+	21	1.8	13	1.1	0	0.0	34	2.9
Missing	68	5.9	108	9.3	41	3.5	217	18.7
Grand total	**431**	**37.2**	**677**	**58.4**	**51**	**4.4**	**1,159**	**100**

Of the 1,236 events reported during this reporting period 538 (43.5%) were myocarditis related events, and there were 543 events of (43.9%) pericarditis. Table 16.12.

Table 16.12 Number and Percentage of Myocarditis and Pericarditis Events by PT-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

PT	# Events	% Total Events
Myocarditis	538	43.5
Pericarditis	543	43.9
Myopericarditis	138	11.2
Carditis	8	0.6
Pleuropericarditis	6	0.5
Eosinophilic myocarditis	2	0.2
Pericarditis adhesive	1	0.1
Grand total	**1,236**	**100**

In events with a known dose number, most of the events of myocarditis and pericarditis during this reporting period continued to occur after the 2nd dose (153; 12.4%) and the 3rd dose (126; 10.2%); 858 (69.4%) events did not provide dose information. In the events where TTO was provided, events continue to occur less than 7 days after vaccination regardless of the dose number (244; 64.6%) (Table 16.13). The median TTO was 3 days (min: 0/max: 502).

Table 16.13 Distribution of Reported Events of Myocarditis and Pericarditis by Dose Number and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO All Doses (Days)	# Events	% Total Events
Dose 1	***Subtotal***	***77***	***6.2***
	0 days	20	1.6
	01-02	18	1.5
	03-04	12	1.0
	05-06	1	0.1
	07-13	12	1.0
	14-29	6	0.5
	30+	8	0.6
Dose 2	***Subtotal***	***153***	***12.4***
	0 days	31	2.5
	01-02	46	3.7
	03-04	26	2.1
	05-06	4	0.3
	07-13	6	0.5
	14-29	13	1.1
	30+	27	2.2
Dose 3	***Subtotal***	***126***	***10.2***

Dose Number	TTO All Doses (Days)	# Events	% Total Events
	0 days	10	0.8
	01-02	30	2.4
	03-04	24	1.9
	05-06	10	0.8
	07-13	12	1.0
	14-29	13	1.1
	30+	27	2.2
Dose 4	***Subtotal***	***20***	***1.6***
	0 days	5	0.4
	01-02	5	0.4
	03-04	1	0.1
	05-06	1	0.1
	07-13	6	0.5
	14-29	1	0.1
	30+	1	0.1
Dose 5	***Subtotal***	***2***	***0.2***
	30+	2	0.2
Unknown	***Subtotal***	***858***	***69.4***
	0 days	34	2.8
	01-02	70	5.7
	03-04	37	3.0
	05-06	14	1.1
	07-13	22	1.8
	14-29	28	2.3
	30+	35	2.8
	Event onset prior to first dose reported	0	0
	Missing	618	50
Grand total		**1,236**	**100**

Myocarditis (Reporting Period – 19 Jun 2022 to 17 Dec 2022)-(elasomeran)

During this review period, there were 539 cases (540 events) of myocarditis related events, with or without pericarditis, received; of which all 539 cases were serious. There were 412 cases that were medically confirmed. There were 18 cases with fatal outcomes.

There were 336 (62.3%) cases of myocarditis reported in males and 169 (31.4%) in females, with 34 cases (6.3%) missing gender information. The mean age of the patients was 36.4 years (SD: 18.2) with a median age of 33 years (min: 7/max: 91); age data was missing in 108 cases. During

the review period, events of myocarditis continued to be reported in males between the ages of 18 to 39 years of age at a greater frequency than any other demographic (163; 30.2%) (Table 16.14).

Table 16.14 Number and Percentage of Myocarditis Cases by Age and Gender - Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
06-11Y	3	0.6	7	1.3	0	0.0	10	1.9
12-15Y	3	0.6	22	4.1	0	0.0	25	4.6
16-17Y	1	0.2	13	2.4	2	0.4	16	3.0
18-24Y	13	2.4	73	13.5	3	0.6	89	16.5
25-39Y	33	6.1	90	16.7	1	0.2	124	23.0
40-49Y	31	5.8	33	6.1	0	0.0	64	11.9
50-64Y	37	6.9	28	5.2	2	0.4	67	12.4
65-74Y	10	1.9	7	1.3	0	0.0	17	3.2
75Y+	13	2.4	6	1.1	0	0.0	19	3.5
Missing	25	4.6	57	10.6	26	4.8	108	20.0
Grand total	**169**	**31.4**	**336**	**62.3**	**34**	**6.3**	**539**	**100**

During the reporting period, when dose number and TTO were reported, events of myocarditis most frequently occurred after the 2nd (85; 15.7%) and the 3rd (67; 12.4%) doses of elasomeran. The majority (133; 70.4%) of events most often occurred within 7 days from vaccination (Table 16.15).

Table 16.15 Distribution of Reported Events of Myocarditis by Associated Dose Number and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	***Subtotal***	***21***	***3.9***
	0 days	5	0.9
	01-02	4	0.7
	03-04	5	0.9
	07-13	3	0.6
	14-29	2	0.4
	30+	2	0.4
Dose 2	***Subtotal***	***85***	***15.7%***
	0 days	14	2.6%

Dose Number	TTO (Days)	# Events	% Total Events
	01-02	33	6.1%
	03-04	18	3.3%
	05-06	2	0.4
	07-13	2	0.4
	14-29	5	0.9
	30+	11	2.0
Dose 3	***Subtotal***	***67***	***12.4***
	0 days	5	0.9
	01-02	18	3.3
	03-04	15	2.8
	05-06	5	0.9
	07-13	5	0.9
	14-29	8	1.5
	30+	11	2.0
Dose 4	***Subtotal***	***15***	***2.8***
	0 days	5	0.9
	01-02	4	0.7
	07-13	5	0.9
	14-29	1	0.2
Dose 5	***Subtotal***	***1***	***0.2***
	30+	1	0.2
Unknown	***Subtotal***	***351***	***65.0***
	0 days	11	2.0
	01-02	16	3.0
	03-04	14	2.6
	05-06	3	0.6
	07-13	7	1.3
	14-29	11	2.0
	30+	13	2.4
	Missing	276	51.1
Grand total		**540**	**100**

Pericarditis (Reporting Period 19 Jun 2022 to 17 Dec 2022)- elasomeran

During this reporting period, there were 541 cases (550 events) received that reported pericarditis related events, of which, 426 cases were medically confirmed. There were no cases with fatal outcomes

There were 308 cases (56.9%) reported in males and 228 cases (42.1%) reported in females; 5 cases (0.9%) did not report gender. The mean age of the patients was 39 years (SD: 15.7), with a median age of 36 years (min: 6/max: 82). Age information was missing in 85 cases. Cases with pericarditis events were reported most frequently in patients between 25-39 years of age (182; 33.6%) (Table 16.16).

Table 16.16 Number and Percentage of Pericarditis Cases by Age and Gender - Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
06-11Y	1	0.2	0	0.0	0	0.0	1	0.2
12-15Y	4	0.7	4	0.7	0	0.0	8	1.5
16-17Y	4	0.7	9	1.7	0	0.0	13	2.4
18-24Y	16	3.0	44	8.1	0	0.0	60	11.1
25-39Y	64	11.8	118	21.8	0	0.0	182	33.6
40-49Y	41	7.6	34	6.3	1	0.2	76	14.0
50-64Y	44	8.1	42	7.8	0	0.0	86	15.9
65-74Y	9	1.7	7	1.3	0	0.0	16	3.0
75Y+	7	1.3	7	1.3	0	00.	14	2.6
Missing	38	7.0	43	7.9	4	0.7	85	15.7
Grand total	**228**	**42.1**	**308**	**56.9**	**5**	**0.9**	**541**	**100**

Pericarditis related events reported during the reporting period occurred at a similar rate. There were 56 events (10.2%) after the 2nd dose, 53 events (9.6%) after the 1st dose, and 50 events (9.1%) after the 3rd dose. The majority of the events occurred within 7 days in events with known dose number (98; 60.1%) (Table 16.17).

Table 16.17 Number and Percentage of Pericarditis Events by Dose and TTO - Reporting Period 19 Jun 2022 to 17 Dec 2022- Elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	***Subtotal***	***53***	***9.6***
	0 days	15	2.7
	01-02	13	2.4
	03-04	6	1.1
	05-06	1	0.2
	07-13	9	1.6
	14-29	4	0.7
	30+	5	0.9
Dose 2	***Subtotal***	***56***	***10.2***
	0 days	17	3.1
	01-02	13	2.4
	03-04	5	0.9
	05-06	2	0.4
	07-13	4	0.7
	14-29	7	1.3
	30+	8	1.5
Dose 3	***Subtotal***	***50***	***9.1***
	0 days	3	0.5
	01-02	12	2.2
	03-04	5	0.9
	05-06	4	0.7
	07-13	6	1.1
	14-29	5	0.9
	30+	15	2.7
Dose 4	***Subtotal***	***4***	***0.7***
	01-02	1	0.2
	03-04	1	0.2
	05-06	1	0.2
	30+	1	0.2
Unknown	***Subtotal***	***387***	***70.4***
	0 days	21	3.8
	01-02	52	9.5
	03-04	16	2.9
	05-06	11	2.0
	07-13	15	2.7

Dose Number	TTO (Days)	# Events	% Total Events
	14-29	15	2.7
	30+	18	3.3
	Missing	239	43.5
Grand total		**550**	**100**

Fatal Case Summaries- elasomeran)

During this review period there were 19 cases reporting fatal outcomes for events of myocarditis and pericarditis. Please note: Two additional fatal cases were found upon medical review. Overall, during this reporting period, 21 cases reported a fatal outcome.

Brighton Collaboration Case Classification, CDC Working Case Definition, and WHO-UMC Causality Assessment – Report Period 19 Jun 2022 to 17 Dec 2022-elasomeran

Further evaluation was conducted in the segment of the reported cases involving patients that were considered (based on epidemiologic characteristics) to be at potentially higher risk for having events of myocarditis and/or pericarditis. This evaluation was conducted in males and females younger 40 years of age or younger, after the 2nd dose of elasomeran, regardless of the TTO of the events from the administration of the vaccine. An additional, focused evaluation was conducted on all reports involving patients <18 years of age, as well as those who received a 3rd dose or a booster dose

Following that strategy, the MAH conducted an evaluation of all the cases identified as cases of Myocarditis and Pericarditis utilizing the Brighton Collaboration Case Definition for Myocarditis/Pericarditis [40] which allows classification of the cases on whether they are true cases of myocarditis or pericarditis.

Cases were also evaluated using the CDC working case definition [43] for Acute myocarditis and Acute pericarditis which allows for classification of the cases on whether or not they are probable or confirmed cases of myocarditis and/or pericarditis based on: 1) characteristic symptoms associated with these events; 2) diagnostic test results (e.g. an elevated troponin level or abnormal findings on ECG, echocardiogram, or CMR imaging) that are associated with these syndromes; and 3) absence of other identifiable cause.

Those cases that were classified as Level 1 to Level 3, and probable or confirmed cases of acute myocarditis or pericarditis were assessed using the WHO-UMC causality assessment (which allow the clinician(s) to perform a combined assessment of the reported cases taking into account the

clinical-pharmacological aspects of the case history and the quality of the documentation of the observation [17].

Using the CDC working case definition for myocarditis and/or pericarditis, reported cases of possible acute myocarditis or pericarditis with insufficient evidence or information to meet the case definition were classified as "Unassessable." Reported cases of possible acute myocarditis or pericarditis with evidence of NOT meeting any of the parameters for the case definition were classified as "Not a case."

Following the search strategy mentioned above, there were a total of 200 cases reported in patients 40 years of age and younger, identified as occurring in males (145; 72.5%) and females (51; 25.5%), and 4 (2.0%) that did not provide gender information. There were 117 (58.5%) reports after the 2nd dose, 81 (40.5%) reports after a 3rd dose, and 2 reports (1%) after a 4th dose or booster dose.

According to the Brighton Collaboration case definition for myocarditis and pericarditis from those 200 cases, 39 cases met Level 1 definition, 42 cases met Level 2 definition, and 19 cases met Level 3 definition. The rest of the reports were considered Level 4 (92 cases) based on the lack of information required to make a diagnostic case classification or Level 5 (8 cases) based on other diagnosis that may explain the occurrence of the events.

According to the CDC working definition (used to define myocarditis and pericarditis) [43] there were 75 "Probable" cases of myocarditis, 20 'Confirmed" cases, 96 "Unassessable" cases, and 1 "Acute Pericarditis" case.

According to the WHO causality assessment (used to characterize strength of association between event and vaccine exposure) there were 2 "Probable" cases, and 82 "Possible" cases, with most of the reports considered "possible" based on information provided, including elevated troponin levels, abnormal ECG, Echocardiogram, and CMR Imaging (MRI) results compatible with myocarditis or pericarditis. The rest of the reports were considered conditional, unlikely or unassessable due to the lack of required information (including symptoms, TTO, dose information or both, myocardial biomarkers, and imaging studies information).

Subpopulation Analyzes

Myocarditis and Pericarditis in Adolescents (12 to 17 years old)–Cumulative to 17 Dec 2022-elasomeran

Cumulatively, there were 224 cases (238 events) of myocarditis and pericarditis in adolescents 12 to 17 years of age, with 195 cases medically confirmed. There were 187 (83.5%) cases reported in males, 35 cases (15.6%) in females; and 2 cases (0.9%) did not include gender information. The mean age of the adolescents was 15.4 years (SD: 1.6) and the median age was 16 years (min: 12/max: 17). The majority of the cases reported in adolescents were in males aged 16 to 17 years (111; 49.6%) (Table 16.18).

Table 16.18 Number and Percentage of Myocarditis and Pericarditis Cases in Adolescents (12 to 17 years old) by Age and Gender-Cumulative to 17 Dec 2022

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	19	8.5	76	33.9	0	0	95	42.4%
16-17Y	16	7.1	111	49.6	2	0.9	129	57.6
Grand total	**35**	**15.6**	**187**	**83.5**	**2**	**0.9**	**224**	**100**

Cumulatively, there were 139 events of myocarditis (with or without pericarditis) reported in adolescents who received elasomeran. When dose number and TTO were reported, the greatest proportion of events (59; 42.4%) occurred after dose 2 with the majority (64; 81.0%) of events occurring at a TTO of less than 7 days.

Cumulatively, there were 52 events of pericarditis reported in adolescents who received elasomeran. When dose number and TTO were reported the greatest proportion of events (14; 26.9%) occurred after Dose 2 with the majority (6; 80%) of events occurring at a *TTO of less than 7 days.*

Myocarditis and Pericarditis in Adolescents (12 to 17 years old)–Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

During the reporting period, there were 66 cases (71 events) of myocarditis and pericarditis reported in adolescents 12 to 17 years of age, with 63 cases medically confirmed. There were 49 cases reported in males (74.2%), 15 in females (22.7%); and 2 cases (3%) with missing gender information. The mean age of the adolescents was 14.8 years (SD: 1.7 years) and the median age was 15 years (min: 12/max: 17). Myocarditis and pericarditis cases in adolescents were most often reported in males aged 12-15 years (27; 40.9%) (Table 16.19).

Table 16.19 Number and Percentage of Myocarditis and Pericarditis Cases by Age and Gender in Adolescents (12 to 17 years old) – Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	9	13.6	27	40.9	0	0.0	36	54.5
16-17Y	6	9.1	22	33.3	2	3.0	30	45.5
Grand total	**15**	**22.7**	**49**	**74.2**	**2**	**3.0**	**66**	**100**

Myocarditis (with or without Pericarditis) in Adolescents (12 to 17 years old) – Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

During the reporting period, there were 41 events of myocarditis reported in adolescents 12 to 17 years old who received elasomeran. When dose and time to onset were reported, events were most frequently reported after Dose 2 (21; 51.2%) with the majority (18; 81.8%) of events occurring at a TTO of less than 7 days.

Table 16.20 Number and Percentage of Events Reporting Myocarditis in Adolescents (12 to 17 years old) by Dose and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO All Doses (Days)	# Events	% Total Events
Dose 1	***Subtotal***	***0***	***0***
Dose 2	***Subtotal***	***21***	***51.2***
	0 days	3	7.3
	01-02	10	24.4
	03-04	4	9.8
	05-06	1	2.4
	14-29	2	4.9
	30+	1	2.4
Dose 3	***Subtotal***	***1***	***2.4***
	01-02	1	2.4
Unknown	***Subtotal***	***19***	***46.3***
	0 days	3	7.3
	01-02	4	9.8
	03-04	2	4.9
	Missing	10	24.4

Dose Number	TTO All Doses (Days)	# Events	% Total Events
Grand total		**41**	**100**

Pericarditis in Adolescents (12 to 17 years old) – Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

During the reporting period, 22 events of pericarditis were reported in adolescents 12 to 17 years of age who received elasomeran. When dose number and TTO were reported, events most frequently were reported after Dose 2 (4; 18.2%) with all events occurring at a TTO of less than 7 days.

Table 16.21 Number and Percentage of Events Reporting Pericarditis in Adolescents (12 to 17 years old) by Dose and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022- elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	***Subtotal***	***3***	***13.6***
	0 days	2	9.1
	07-13	1	4.5
Dose 2	***Subtotal***	***4***	***18.2***
	0 days	2	9.1
	01-02	1	4.5
	05-06	1	4.5
Unknown	***Subtotal***	***15***	***68.2***
	0 days	1	4.5
	01-02	3	13.6
	03-04	1	4.5
	05-06	1	4.5
	14-29	0	0
	Missing	9	40.9
Grand total		**22**	**100**

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – Adolescents (12 to 17 years old)- elasomeran

According to the Brighton Collaboration case definition for myocarditis and pericarditis from those 66 cases, 3 cases met Level 1 definition, 13 cases met Level 2 definition, and 13 cases met Level 3 definition. The rest of the reports were considered Level 4 (37 cases) based on the lack of information required to make a diagnostic case classification.

According to the CDC working definition (used to define myocarditis and pericarditis) [43] there were 19 "Probable" cases of myocarditis, 2 "Confirmed" cases, 1 "Acute pericarditis" case and 44 "Unassessable" cases based on the lack of information required to make a diagnostic case classification.

According to the WHO causality assessment (used to characterize strength of association between event and vaccine exposure) there was 1 "Probable" case, 9 "Possible" cases with most of the reports considered possible based on information provided, including elevated troponin levels, abnormal electrocardiogram (ECG), Echocardiogram, and cardiac MRI results compatible with myocarditis or pericarditis. The rest of the reports were considered "Conditional" cases (18), "Unlikely" cases (3) and "Unassessable" cases (35) due to the lack of required information (including symptoms, TTO, dose information or both, myocardial biomarkers, and imaging studies information).

Myocarditis and Pericarditis in Children (<12 years old)- elasomeran

Cumulatively, through 17 Dec 2022, a total of 11 cases (11 events) reporting myocarditis and pericarditis have been received. All cases were medically confirmed. All cases were received during this reporting period. Ten cases (90.9%) were received from Taiwan and one case (9.1%) was received from Australia. Given this reported cluster of cases of myocarditis from only one country (Taiwan), additional information on all these reported cases is being requested from the reporting health authority.

Cumulatively, there were no fatal outcomes. There were 7 cases (63.6%) in males and 4 cases (36.4%) in females. The mean age of the patients was 9.3 years (SD: 1.5) with a median age of 10 years (min 6 /max 11). When dose number and TTO were reported, all doses occurred after Dose 2 and all events occurred at a TTO of less than 4 days. (Table 16.22).

Table 16.22 Number and Percentage of Events Reporting Myocarditis in Children (<12 years old) by Dose and TTO-Reporting Period 19 Jun 2022 to 17 Dec 2022-elasomeran

Dose Number	TTO (Days)	# Events	% Total Events
Dose 2	***Subtotal***	***10***	***90.9***
	01-02	8	72.7
	03-04	2	18.2
Unknown	***Subtotal***	***1***	***9.1***
	07-13	1	9.1

Dose Number	TTO (Days)	# Events	% Total Events
Grand total		**11**	**100.0**

Myocarditis in Children <12 years old (Cumulative to 17 Dec 2022) - elasomeran

Cumulatively, through 17 Dec 2022, a total of 10 cases (10 events) reporting events of myocarditis have been received in children <12 years old, with all 10 cases medically confirmed. There have been more cases reported in males (7; 70%) than females (3; 30%). The mean age of the patients was 9.6 years (SD 1.1), with a median age of 10 years (min: 7 /max: 11). All 10 cases were received during the reporting period.

All 10 events occurred after Dose 2 with a TTO of less than 7 days from vaccination (Table 16.23).

Table 16.23 Number and Percentage of Events Reporting Myocarditis in Children (6-11 Years Old) by Dose and Time to Onset (TTO) –Cumulative to 17 Dec 2022-elasomeran

Dose Number	TTO (Days)	Total # Events	% Total Events
Dose 2	***Subtotal***	***10***	***100***
	01-02	8	80
	03-04	2	20
Grand total		**10**	**100**

Pericarditis in Children <12 years old (Cumulative to 17 Dec 2022) - elasomeran

Cumulatively, through 17 Dec 2022, one medically confirmed case with 1 event of Pericarditis has been received in a child under the age of 12 years of age who received elasomeran. The case was reported during the reporting period and concerned a 6-year-old female who experienced the event of "Pericarditis" approximately 9 days after receiving an unspecified dose number of elasomeran. At the time of this report the event outcome was reported as "Recovered".

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – Children (<12 years old)- elasomeran

Assessment of the children case reports per the Brighton Collaboration Case Definition Myocarditis – Levels of Diagnostic Certainty [40] determined there were 2 cases met Level 1 definition, 6 cases met Level 2 definition, and 3 cases met Level 4 definition.

According to the CDC working definition [43] there was 1 "Acute Pericarditis" case, 7 "Probable" cases, and 3 "Unassessable" cases given that important information was missing including symptoms, myocardial biomarkers, or imaging studies information.

According to the WHO causality assessment there were 8 "Possible" cases based on information provided including elevated troponin levels, abnormal ECG, and Echocardiogram result compatible with myocarditis. Three reports were considered "Unassessable" due to important missing information including laboratory values, dose information, TTO, medical history, clinical course of current conditions.

Myocarditis and Pericarditis in Patients Receiving a 3rd or Booster dose of Elasomeran

Cumulatively, through 17 Dec 2022, a total of 660 cases (689 events) reporting events of myocarditis and pericarditis have been received following a 3rd or booster dose of elasomeran, of which 612 cases were considered serious and 394 were medically confirmed. There were 17 cases with fatal outcomes. The cases involved more males (426; 64.5%) than females (231; 35.0%), with a mean age of 42.3 (SD: 17.4) and a median age of 40 years (min: 13.0/ max: 86.0). When dose number and TTO was reported, the majority (126; 85.1%) of events were reported after Dose 3, with 663 events (96.2%). The greatest proportion (457; 66.3%) of events occurred with a TTO of less than 7 days.

During this reporting period, there were 141 cases (148 events) of myocarditis and pericarditis following a 3rd or booster dose of elasomeran, of which 141 were considered serious and 90 were medically confirmed. There were 11 cases with fatal outcomes. The cases involved 80 males (56.7%) and 59 females (41.8%), with a mean age of 43.5 years (SD: 19.1) and a median age of 40 years (min: 16/max: 86). When dose number and TTO was reported, the majority (126; 85.1%) of events were reported after Dose 3, with 20 events (13.5%) reported after Dose 4, and just 2 events (1.4%) reported after Dose 5. The greatest proportion (86; 51.8%) of events occurred with a TTO of less than 7 days. Please note: 40 additional booster cases were found upon medical review. Overall, during this reporting period, 180 cases of myocarditis and pericarditis were reported following a 3rd or booster dose of elasomeran.

Information for those reports that fulfil the Brighton Collaboration case definition Level 1 to 3, as well as the CDC working case definition probable and confirmed and were classified as possible or probable as per the WHO causality assessment.

Myocarditis and Pericarditis in Pregnancy- elasomeran

During the reporting period, 3 reports of myocarditis among pregnancy cases were received. However, two of the case reports ([redacted] and [redacted]) appear to be

misclassified as a pregnancy case given the lack of information in the reports regarding pregnancy, as well as their advanced age.

Myocarditis and Pericarditis After Receiving Booster Dose with elasomeran/imelasomeran

Cumulatively, and during this review period, there were 20 cases (20 events) received with events of myocarditis and pericarditis reported after receiving a 3rd or booster dose of elasomeran/imelasomeran. More cases were reported in males (13; 65%) than females (5; 25%); 2 cases (10%) did not report gender information. The mean age was 45 years and a median age of 41 years (min: 22/max: 90). When dose number and TTO were reported, the greatest proportion of events occurred after Dose 4 (5; 25%) and the majority (7; 87.5%) of events occurred at a TTO of less than 4 days.

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – 3rd dose or Booster Dose with elasomeran/imelasomeran

Assessment of the individuals receiving a 3rd dose or booster doses with elasomeran/imelasomeran case report per the Brighton Collaboration Case Definition Myocarditis – Levels of Diagnostic Certainty [40] determined one case met Level 1 definition, five cases met Level 2 definition, two cases met Level 3 definition, and 12 cases met Level 4 definition as important information was missing including clinical course, investigations supporting the diagnosis and treatment received, as well as age and TTO in many reports.

According to the CDC working definition [43] there was one "Confirmed" case, one "Acute Pericarditis" case, five "Probable" cases, and 13 "Unassessable" cases given that important information was missing including symptoms, myocardial biomarkers, or imaging studies information.

According to the WHO causality assessment there were five "Possible" cases, one "Probable" case, one "Conditional" case, one "Unlikely" case, and 12 "Unassessable" cases due to important missing information including laboratory values, dose information, TTO, medical history, clinical course of current conditions, etc.

Myocarditis and Pericarditis After Receiving Booster Dose with elasomeran/davesomeran

Cumulatively and during this review period, there were 5 cases (6 events) received of myocarditis and pericarditis after receiving a 3rd or booster dose of elasomeran/davesomeran. There were 4 cases (80%) reported in males, no cases reported in females, and 1 case (20%) was missing gender information. The mean age was 40.3 years (SD: 16.6) with a median age of 41.5 years

(min: 19/max: 59). Of the 6 events reported, 4 events (66.7%) did not report a dose number or time to onset.

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – 3rd dose or Booster Dose with elasomeran/davesomeran

Assessment of the individuals receiving a 3rd dose or booster doses with elasomeran/davesomeran case report per the Brighton Collaboration Case Definition Myocarditis–Levels of Diagnostic Certainty [40] determined one case met Level 1 definition, one cases met Level 2 definition, one case met Level 3 definition, and two cases met Level 4 definition as important information was missing including clinical course, investigations supporting the diagnosis and treatment received, as well as age and TTO in many reports.

According to the CDC working definition [43] there was one "Confirmed" case, two "Probable" cases and two "Unassessable" cases given that important information was missing including symptoms, myocardial biomarkers, or imaging studies information.

According to the WHO causality assessment there was two "Possible" cases, one "Unlikely" case, and two "Unassessable" cases due to important missing information including laboratory values, dose information, TTO, medical history, clinical course of current conditions, etc.

16.3.1.2.5 Discussion

A review of the data received during the reporting period of this PBRER, showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. The same pattern was observed for cases reported after receiving a 3rd or more doses of elasomeran. There were twenty-five reports of myocarditis or pericarditis following exposure to any of the Spikevax bivalent elasomeran/imelasomeran or elasomeran/davesomeran in this reporting period. To date, the safety profile of those reports of myocarditis after any of the Spikevax bivalent vaccines (elasomeran/imelasomeran or elasomeran/davesomeran) does not differ from the elasomeran safety profile, with cases presenting as mild cases, and recovering within a short time following standard treatment and rest. For elasomeran/imelasomeran there were 13 cases reported for males, 5 cases reported for females, and 2 reports that did not identify gender. Elasomeran/davesomeran reported 4 cases for males and 1 report did not identify gender.

Cumulatively, 10 of the 11 cases reporting events of myocarditis in children <12 years of age have been reported from Taiwan even though elasomeran vaccines (Original and both

Bivalents) are authorized for children <12 years old throughout the world in more than 70 countries. Given this reported cluster of cases of myocarditis from only one country (Taiwan), additional information on all these reported cases is being requested from the reporting health authority.

Overall, evaluation of data received during this reporting period of those patients receiving a 3rd dose or a booster dose shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series, as it had been described in the literatures [29,44].

The observed clinical profile of patients experiencing myocarditis/ pericarditis following exposure to a COVID-19 mRNA vaccine continue to present as events that result with a relatively short period of hospitalization, most cases follow an uncomplicated clinical course and complete resolution of symptoms is rapidly achieved and can be effectively treated with a standard medication treatment with ibuprofen and colchicine, without any CMR-detectable consequence [45].

Analysis of safety data housed in the MAH's GSDB, as well as review of the literature, showed that most of the individuals who experienced an event of myocarditis/ pericarditis after vaccination with elasomeran were considered recovered by health-care providers after at least 90 days following the onset of myocarditis/pericarditis. In addition, their quality-of-life measures were comparable to those in pre-pandemic and early pandemic populations of a similar age [34].

Cumulative and periodic data analyzed in this PBRER, support an update of the product information, particularly the sentence related to the severity of myocarditis after vaccination with elasomeran compared to myocarditis in general. An updated version of the SmPC will be proposed by the MAH along with this PBRER procedure.

Based on the analysis of all the safety data available as of 17 Dec 2022, the MAH considers cases included under the AESI of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for elasomeran far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.

16.3.1.2.6 Conclusion

A review of the data received cumulatively and during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the

second dose of the vaccine elasomeran with a TTO of less than 7 days. myocarditis and pericarditis are generally mild and uncomplicated with rapid resolution.

Review of the data also show no difference in the observed safety profile of elasomeran for children (6 months to 12 years of age), the adolescent population (12 years to 17 years of age), or in those individuals receiving a 3rd dose of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when compared to >18 years old. Reporting rates are lower for children than for adolescents and young adults.

During the reporting period of this PBRER, a decreasing trend in the number of reported cases of myocarditis and pericarditis was observed, which can be possibly associated with the observed lower risk for myocarditis/ pericarditis after a 3rd or more doses of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. As new safety data from the elasomeran/imelasomeran and elasomeran/davesomeran becomes available, a lower risk of myocarditis and pericarditis is observed in those exposed to the bivalent vaccines, compared to elasomeran after dose 2.

Based on the information provided by both literature and surveillance sources consistently describing an increase in the incidence of myocarditis, predominantly within the first 7 days following receipt of a second dose of vaccine, that appears largely isolated to younger men (<40 years of age).

Based on the analysis of all the safety data received during the reporting period of this PBRER, ModernaTx, Inc. considers that cases of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulative and periodic data analyzed in this PBRER, support an update of the product information, particularly the sentence related to the severity of myocarditis after vaccination with elasomeran compared to myocarditis in general. An updated version of the SmPC will be proposed by the MAH along with this PBRER procedure. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including 2 ongoing and 2 planned post-authorization safety studies to further characterize them. The benefit-risk evaluation remains positive.

16.3.2 New Information on Important Potential Risks

16.3.2.1 Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

16.3.2.1.1 Source of the New Information

The ModernaTx, Inc.'s GSDB was queried for valid, clinical and spontaneous case reports received from HCPs, HAs, consumers and literature, cumulative from 18 Dec 2020 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.2.1.2 Background Relevant to the Evaluation

Vaccine-associated enhanced diseases are modified presentations of clinical infections affecting individuals exposed to a wild type pathogen after previously having received a vaccination for the same pathogen. Vaccine-associated enhanced respiratory disease refers to disease with predominant involvement of the lower respiratory tract [46]. Given that these enhanced responses are triggered by failed attempts to control the infecting virus, VAED typically presents with symptoms related to the target organ of the infecting pathogen.

Research points to disease enhancement being triggered by one of two major mechanisms although other mechanisms may also contribute. The first and least well characterized is when priming by the initial infection results in a Th2 biased immune response mediated more by myeloid lineage cells, including neutrophils and eosinophils with immune complex formation and complement activation. While this inflammatory phenotype may be preferred for parasitic infections it is not ideal for viruses, for which an adaptive T-cell and antibody mediated Th1 type response is preferable.

This "Th2 biased" phenotype is most associated with enhanced disease as resulting from the formalin-inactivated measles and respiratory syncytial virus (RSV) vaccines. In these cases, post-vaccination exposure of previously naïve vaccines resulted in an immune response characterized by high interleukin (IL) 4, 5 & 13 levels and localized tissue inflammation associated with neutrophil and eosinophil infiltration, immune complex deposition and pulmonary inflammation and obstruction [47].

The second and far better characterized mechanism related to vaccines is antibody dependent enhancement (ADE). This results from the generation of binding but poorly neutralizing antibodies induced by heterologous antigens generated either by heterologous viral strains (e.g., dengue), by

chemically disrupted antigens (e.g., formalin-inactivated RSV and measles) or by epitope altering mutations such as feline infectious peritonitis. These antibodies bind to but do not neutralize the virus and facilitate Fc receptor mediated entry of viable virus into macrophages. This can result in an accelerated and more marked viremia and more severe disease. This scenario is the one associated with dengue vaccine virus, its virus and vaccine-associated ADE. Antibody dependent enhancement for dengue can also result from sub-neutralizing concentrations of neutralizing antibodies, such as that seen in infants as maternal antibodies wane [47].

The potential for any SARS-CoV-2 vaccine to potentiate subsequent SARS-CoV-2 viral infection has been hypothesized. This hypothesis is based upon the observation that antibody responses may paradoxically be misdirected to facilitate viral cell entry, thereby resulting in a more severe infection than would have occurred in the absence of vaccine priming. In the case of coronaviruses, it has been observed that in laboratory studies in which cats were exposed to large inocula of wild type feline coronavirus, the experimental animals were at elevated risk for feline when subsequently exposed to wild type virus. A commercial feline coronavirus vaccine has been available for some years, with no reported increase in the incidence of feline peritonitis [48] to the knowledge of the MAH, there have been no cases of VAED in humans who have been repeatedly exposed to any of the 4 common human coronaviruses, or to the viruses causing SARS, Middle East respiratory syndrome (MERS), or SARS-CoV-2.

There is currently no widely accepted case definition for VAED; however, a recent publication by the Brighton Collaboration provides some guidance for assessment of potential VAED in COVID-19 [46]. In this guidance, it is suggested that VAED may be identified first as a vaccine failure (i.e., VAED requires exposure to and infection by SARS-CoV-2 in a person who has been fully immunized). The authors acknowledge that there is presently no pathognomonic set of clinical findings to characterize VAED. Furthermore, case classifications that can be readily applied to individual level data from spontaneous reporting are not defined. The Brighton Collaboration working group states that a definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. Probable cases must show an increase in severity or rates of atypical findings when compared to a non-vaccinated control group, however this criterion must be considered at a population or group level rather than an individual level. Given that there have been numerous epidemiologic studies evaluating effectiveness of mRNA vaccines in millions of vaccinees and given that there have not been findings showing an increased risk of COVID-19 disease in vaccinees (or a subgroup of vaccinees) compared to those not vaccinated, real-world evidence for occurrence of VAED is lacking. Moreover, there is an

absence of medical literature supporting the existence of VAED due to elasomeran or mRNA vaccines against COVID-19.

The authors further suggest that the clinical presentation must then be recognized as atypical or severe. It is further suggested that assessment of the type and frequency of clinical presentations is recommended. Clinical parameters of interest include respiratory, cardiovascular, hematological, inflammatory, renal, gastrointestinal, and central nervous system conditions.

Both vaccine efficacy and safety have been studied in animal models with many vaccines including SARS-CoV-1 candidate vaccines [49]. Whole-inactivated viral vaccines developed in the 1960s against both respiratory syncytial virus (RSV) and measles elicited VAED when vaccinated children were subsequently naturally infected. These adverse outcomes were associated with T-helper (Th) 2-skewed CD4+ T-cells and the induction of poor-quality antibodies with little to no neutralizing activity. Animal models, where this immune profile is elicited after vaccination, recapitulate RSV and measles VAED with hallmarks of increased inflammation and pulmonary eosinophilia after challenge that exceeds that in unvaccinated control animals [50].

Elasomeran was evaluated to determine whether it might elicit potentially adverse immune responses that could be associated with VAERD [51]. This was performed by comparing antibody and T-cell responses generated from subprotective and protective doses of elasomeran (0.1 and 1 mg, respectively) to those elicited by regimens previously associated with disease enhancement following infection. The immunological and safety signature of elasomeran in challenge studies using the mouse-adapted SARS-CoV-2, passage 10, lethal challenge virus (MA10) [52,53]. BALB/c mice were immunized twice with whole-inactivated SARS-CoV-1 or SARS-CoV-2virus, heat-denatured spike protein (S-2P), or elasomeran. Whole-inactivated virus and denatured S-protein were formulated with alum to recapitulate conditions that resulted in VAED in a prior preclinical coronavirus vaccine study [54]. These regimens consistently induced low to moderate concentrations of S-binding and neutralizing antibody and Th2-skewedS-reactive CD4+ T-cells. After viral challenge, these mice were partially protected from weight loss and viral replication yet displayed enhanced pulmonary inflammation and eosinophil infiltration. In contrast, elasomeran elicited potently neutralizing antibodies and a balanced or type-1-skewed response, particularly at the 1 mg dose, and mice were protected from viral replication and lung inflammation after viral challenge. Importantly, a subprotective mRNA dose of 0.1 mg was associated with reduced immunopathology after challenge compared to the control and Th2-skewing groups. These results demonstrate that elasomeran elicits potent antiviral immunity and a favorable immune profile not associated with VAERD, even at sub-protective doses.

As of the DLP of this PBRER, SARS-CoV-2 vaccines have not been associated with VAED in preclinical studies or in any ongoing or completed clinical studies for elasomeran, nor in any post-marketing reports received in the GSDB. Even with the potential for new variants/serotypes of SARS-CoV-2, to provoke sub-neutralizing antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as it was the case for SARS-CoV-2 variant Omicron, which demonstrates a drop in neutralizing antibody titres in patients who have received two doses of a mRNA COVID-19 vaccine [55]. Despite this drop in neutralization, enhancement of disease has not been reported. Infection with other variants of SARS-CoV-2 have also been shown to impact antibody binding to SARS-CoV-2 and its variants post-vaccination through imprinting, but no disease enhancement has been reported in these cases either [56]. Seasonal coronaviruses also appear to provide a level of back-boosting or cross-protection in some individuals [57,58]. Cross-reactivity has been observed between SARS-CoV-1 and SARS-CoV-2, which results in improved vaccine-induced immune responses by provoking the generation of broadly- neutralizing antibodies against a wide variety of coronaviruses [59]. Waning antibody levels, which are a cause of ADE in dengue virus infection, have been observed 6 months following vaccination with a dengue vaccine [60,61]. However, regarding vaccination with COVID-19 vaccines, a level of protection is still being observed to date in vaccinated people and there have been no documented cases of VAED owing to this or any other cause in SARS-CoV-2. Memory T-cells induced in response to vaccination have been shown to have highly heterogenous antigen-specific responses, which are thought to contribute to long-term protection against severe disease [62]. Even with robust antibody escape as seen in Omicron, T-cell responses are likely to be sustained [63].

Gartlan *et al.*, [47] reviewed the literature surrounding the phenomenon of VAED in pathogenic human coronaviruses, including MERS-CoV, SARS-CoV-1 and SARS-CoV-2. According to the author, histopathological data of poor quality and a lack of consistency in defining severe pathology and VAED in preclinical studies of MERS-CoV and SARS-CoV-1 vaccines in particular make it difficult to interrogate potential cases of VAED, but overall, the authors concluded that genetic vaccine platforms (mRNA and viral vectors) are in theory less likely to induce associated enhanced disease than inactivated vaccines or natural infection. This is because genetic platforms ensure that responses are generated against unmodified neutralizing epitopes, encoded by the platform, while inactivated whole-virus vaccines have a wider variety of epitopes for the immune system to generate responses against.

Based on all the information provided the MAH is proposing the removal of VAED including VAERD as an Important Potential Risk from the Spikevax EU-RMP, and to continue monitoring VAED including VAERD through routine surveillance.

Regarding the ModernaTx, Inc. Supplemental Follow-up Questions for Reports of Suspected/Confirmed COVID-19 Events with the use of Moderna COVID-19 vaccine (elasomeran)-COVID-19/Vaccine Failure Questionnaire:

- During the reporting period of this PBRER, a total of 1,706 TFQs for Suspected/Confirmed COVID-19 events were sent by the MAH, of which 45 TFQ responses were received. The response rate to this questionnaire was 3%.

This very low response rate indicates that the current requested follow-up information does not substantiate and contribute to additional risk characterization. ModernaTx, Inc. intends and applies within this PBRER procedure to remove VAED as an important potential risk and upon approval no follow-up measures and questionnaires deemed to be necessary.

16.3.2.1.3 Discussion

Although VAED was raised as a safety concern for COVID-19 vaccines early in the pandemic, current evidence does not suggest that this hypothetical construct presents a confirmed risk. More than 772 million elasomeran doses are estimated to have been administered since the first EUA, and it is likely that VAED would have been observed and reported if it were both confirmed and more than a very rare event. Motivation to monitor COVID-19 vaccine recipients for possible VAED arose from sources such as animal models in which pathogenesis suggested a common potential mechanism producing VAED related to RSV vaccines in MERS and SARS-CoV-1 [49]. To date, no pathognomonic presentation of VAED has been recognized following immunization of >902 million individuals with elasomeran vaccines. Further, analysis of the immune profile of elasomeran in a mouse model shows elicitation of a protective immune profile that is not associated with vaccine-enhanced disease upon SARS-CoV-2 challenge [51]. Given the diverse clinical manifestations and sequelae of wild type COVID-19 disease, however, it is nearly impossible to assert that a given clinical course of disease represents enhancement of what would have been observed in the absence of vaccination. As such, identification of VAED at the individual case level continues to be infeasible at this time [46]. At a population level, VAED can only occur as a result of infection with wild type virus following vaccination, and its incidence (if identifiable) would be challenging to ascertain based both upon challenges in diagnosis and in ascertainment through post-authorization data sources (e.g., limitations in the thoroughness of spontaneous

reports). Use of historical incidence data would be unlikely to provide useful context given inextricable linkage to factors such as local incidence of COVID-19 in the source population [64]. Further, severity associated with prevailing variants may change over time, making it difficult to claim that a change in severity is attributable to VAED.

Interpretation of analyzes considering the possibility of VAED has not changed based on data accrued during this review period. Although surveillance for signs of VAED has been conducted by ModernaTx, Inc. and HAs since the EUA, currently available post-authorization data do not provide evidence to support the hypothesis that this phenomenon exists. In the absence of a pathognomonic presentation, ModernaTx, Inc. will continue to review cases of vaccine failure to determine whether discernable changes in population level characteristics of disease presentation vary for vaccine failure events.

The large scale use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered. Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 408,226,293 individuals received a first dose, 275,197,667 received a second dose, 166,419,347 received a third dose, and 62,984,506 received a fourth dose, with third and fourth doses including both original elasomeran and Spikevax bivalent booster dose formulations.

Additionally, the SPEAC working group, recommend the following guidance for duration of surveillance activities related to VAED:

- The Working Group recommended a minimum period of 1 year surveillance for VAED in vaccine CTs where it is potential AESI.

- For any pathogens with a seasonal distribution, it is recommended to continue follow-up through at least two years in case there is variation in strains from year to year which could impact on natural disease severity.

With this large number of doses of elasomeran that has been administered worldwide, no cases of VAED have been reported to the MAH's GSDB. The MAH has a comprehensive and systematic approach to evaluating all available safety information, including that pertaining to VAED. As of the DLP for this PBRER (17 Dec 2022), there is no evidence to support the hypothesis that this phenomenon exists. The MAH is proposing the removal of VAED as an Important Potential Risk from the Spikevax EU-RMP, and to continue monitoring VAED through routine surveillance.

- The MAH has monitored VAED in each PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and given the amount of safety data accumulated given the unprecedent use of these vaccines, the MAH has found no evidence to support the hypothesis that this phenomenon exists or that there is a causal relationship to the vaccine.
- Despite the large number of doses of elasomeran that has been administered worldwide, no cases of VAED have been reported to the MAH's GSDB.
- As of the DLP of this PBRER, SARS-CoV-2 vaccines have not been associated with VAED in preclinical studies or clinical use. Even with the emergence of multiple new variants/serotypes of SARS-CoV-2, with their potential to provoke sub-neutralizing antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as was the case for SARS-CoV-2 variant Omicron, no enhancement of disease has been reported.
- Despite widespread use of the elasomeran vaccines (>800 million individuals vaccinated with at least one dose) there is no convincing evidence to support the hypothesis that VAED exists or that it has a causal relationship to the vaccine.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to VAED.

Based on all the information provided the MAH is proposing the removal of VAED including VAERD as an Important Potential Risk from the EU-RMP, and to continue monitoring VAED including VAERD through routine surveillance.

16.3.2.1.4 Conclusion

After careful review of all new safety data received cumulative and during the reporting period for the safety topic of VAED, the benefit-risk profile for elasomeran, elasomeran/imelsomeran and elasomeran/davesomeran remains favorable.

The MAH has monitored VAED in each MSSR as well as PSUR since EUA (18 Dec 2020) at the request of the EMA. Over the years of analysis and the large scale use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found no evidence to support the hypothesis that this phenomenon exists. The MAH is proposing the removal of VAED including VAERD as an Important Potential risk from the EU-RMP, and to continue monitoring VAED including VAERD through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.3 New Information on Other Potential Risks Not Categorized as Important

None.

16.3.4 New Information on Other Identified Risks Not Categorized as Important

None.

16.3.5 Update on Missing Information

16.3.5.1 Use in Pregnancy

16.3.5.1.1 Source of the New Information

Information presented below includes analyzes performed on pregnancy cases received by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for the elasomeran and bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran). Cumulative data covers the period from 18 Dec 2020 to 17 Dec 2022.

The Company clinical and GSDB was queried for valid case reports of individuals who received elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran before or during pregnancy and reports concerning fetuses/neonates/infants whose mothers were vaccinated during gestation, received from HCP, HA, consumers and literature sources, cumulatively and for the reporting period, worldwide, for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.5.1.2 Background Relevant to the Evaluation

Use of ModernaTx, Inc. COVID-19 vaccines during pregnancy is an area of missing information in the RMP; no CTs were conducted among pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications in this [65] [66]. However, there is recognition that in absence of CTs, vigilant post-EUA passive report monitoring, real-world evidence, and pregnancy registries was needed to continue monitoring the safety of COVID vaccination in pregnant women.

There have been no specific safety concerns identified for COVID maternal immunization. Epidemiological studies have not indicated any increased risk of adverse perinatal outcomes including spontaneous abortion, preterm birth, small for gestational age birth, stillbirth, or neonatal intensive care admission after COVID-19 vaccination during pregnancy [67,68] [69,70] [71,72] [73] [74]. More specifically, a case-control study case-control study from Norwegian registries of 13,956 women with ongoing pregnancies (958 vaccinated) found adjusted odds ratios of 0.91 (0.75 to 1.10) for COVID-19 vaccination in the previous three weeks following a spontaneous abortion and 0.81 (0.69 to 0.95) for vaccination in the previous five weeks, showing no risk of early pregnancy loss after COVID-19 vaccination [71]. Another study used the VSD to analyze the odds of receiving a COVID-19 vaccine in the 28 days before a spontaneous abortion [69]. It found that pregnancies ending in a spontaneous abortion did not have an increased odds of exposure to a COVID-19 vaccination in the previous 28 days compared with ongoing pregnancies.

A large registry-based study of births in Sweden and Norway (28,506 vaccinated; 129,015 unvaccinated) found no significant increased risk of adverse pregnancy outcomes including preterm birth, stillbirth, small for gestational age, or Neonatal intensive care unit (NICU) admission among people vaccinated against SARS-CoV-2 during pregnancy [71]. The results were similar for vaccinations during the second or third trimester, with one or two doses of vaccine, and with different mRNA vaccine types. A large (>10 000 people vaccinated during pregnancy) US based multisite retrospective cohort using VSD, with a diverse population and comprehensive data on vaccination did not find an increase in preterm birth or small for gestational age birth overall, stratified by trimester of vaccination, or the number of vaccine doses received during pregnancy, compared with unvaccinated pregnant women [70].

Another important perinatal outcome of interest after maternal vaccination is risk of fetal anomalies. Given the importance of timing in pregnancy and risk of fetal anomalies, a large cohort study evaluated the association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies and found no difference in incidence of congenital anomalies among people who received at least one dose of COVID-19 vaccine versus unvaccinated people [73]. Importantly, after control for potential confounders such as hemoglobin A1c level in the first trimester and age at delivery, vaccination within the highest risk period for teratogenicity was not associated with presence of congenital anomalies identified by ultrasonography (adjusted odds ratio 1.05, CI: 0.72 to 1.54). Additional studies have not found an increased risk of congenital anomalies among pregnant people received COVID-19 vaccines including elasomeran during pregnancy [72].

Additionally, emerging evidence provide support that infants receive protective benefits from maternal vaccination against COVID-19 [75,76]. One study evaluated the effectiveness of maternal vaccination during pregnancy against COVID-19 related hospital admission among infants during the first six months of life. Of 176 infants admitted with COVID-19, 16% of their mothers had been vaccinated compared with 32% of 203 infants admitted without COVID-19 [75]. Effectiveness of maternal vaccination during pregnancy against COVID-19 related hospital admission in infants aged <6 months was found to be 61% (31% to 78%). Effectiveness of a two dose covid-19 vaccination series was 32% (–43% to 68%) in the first 20 weeks of pregnancy and 80% (55% to 91%) after 21 weeks through 14 days before delivery. The gestational age breakdown has wide confidence intervals and should be interpreted with caution. Overall, completion of a 2-dose mRNA COVID-19 vaccination series during pregnancy seems to reduce COVID-19 related hospital admissions among infants aged <6 months, but the duration of clinical protection remains uncertain.

Although, there are still limited published data regarding elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy, the available data show no increased risk of adverse pregnancy outcomes among people vaccinated against SARS-CoV-2 during pregnancy, supporting recommendations for vaccination of pregnant people against SARS-CoV-2. Post-marketing safety data with elasomeran are relevant to the Spikevax bivalent vaccines because these vaccines are manufactured using the same process. Clinical trials and PMS including post-authorization safety studies thus far demonstrate that the reactogenicity and safety profile of the bivalents are similar and to date, no new safety concerns for the bivalents elasomeran/imelasomeran and elasomeran/davesomeran have been identified.

The MAH is closely monitoring the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in this population through routine pharmacovigilance [77].

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals during pregnancy and while breastfeeding in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of "Use in pregnancy and while breastfeeding" as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals during pregnancy and while breastfeeding through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.1.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports in ModernaTx, Inc. GSDB:

The MAH queried the GSDB for valid case reports of individuals who received elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran before or during pregnancy and reports concerning fetuses/neonates/infants whose mothers were vaccinated during pregnancy (referred to as "pregnancy cases"), received from healthcare providers, HAs, consumers, and the literature, cumulatively (18 Dec 2020 –17 Dec 2022) and for the reporting period (19 Jun 2022 – 17 Dec 2022).

The search strategy used to identify "pregnancy cases" (Pregnancy [MI-PREG&Pts Preg] was comprised of multiple components:

- Argus field "Patient Pregnant" = Yes OR
- MI-Preg (See Product Signaling Strategy Form [PSSF] 9.0) = Yes and Patient Preg = No AND gender=female and Age Group= (12-54) OR
- MI-Preg =Yes AND Patient Preg = No AND Age group <2 y/o OR "missing" AND PREG-Fetal Outcome <> (Empty) OR
- MI-Preg = Yes and Patient preg =No AND Argus field "Child Case Only" = Yes

The MAH reviewed and performed descriptive analysis of all events reported cumulatively and during the reporting period by type of vaccine (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). These analyses were also performed for pregnancy cases who received

three or more doses of elasomeran, pregnancy cases among 12-17 years old (adolescents) and 6-11 years old, as well as children aged 0-5 years old born to mothers who received elasomeran and bivalents during pregnancy. Pregnancy cases are pulled by case identification numbers and contain "All PTs" The PTs that are captured in the Pregnancy and Neonatal Topics MedDRA SMQ are referred to as pregnancy-specific events, and those that are not, are referred to as non-pregnancy-specific events. The cases and events were classified by the SOC, HLT and PT stratified by event seriousness and review period. For the calculation of TTO and the attribution of Dose Number to individual events an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a dose was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number.

Pregnancy outcomes were examined by timing of vaccination/gestational period stratified by prospective/retrospective classification. The "prospective" classification, (if MAH initially received information about the exposure and associated event before the pregnancy completion) should be interpreted with caution because there is a high likelihood of coding errors; there was no evidence in the report to support a "prospective" classification for many of the pregnancy reports. Outcomes were identified using the variable "Pregnancy Outcome". This variable was derived using the strategy below:

- STILLBIRTH, or MI-FULLTERM = YES then the PT term is entered as outcome OR
- Use the response to the "PREG-Fetal Outcome" variable if populated
- Otherwise, classified as "undetermined"

Gestational period was identified using the variable "Gestational Period Group," and categorized into four groups shown below in accordance with the Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/313666/2005)".

- First Trimester
- After first trimester
- Before conception (0-2 weeks)
- Unknown

All fatal cases were medically reviewed and summarized; the fatal section focuses on maternal deaths defined as the death of an individual during pregnancy or within one year of the end of pregnancy from a pregnancy complication, a chain of events initiated by pregnancy, or the aggravation of an unrelated condition by the physiologic effects of pregnancy [78] and deaths of neonates/infants born to mothers who received elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran prenatally. However, the MAH receives reports in which fetal deaths are coded as fatal cases originating from regulatory reports or due to coding discrepancies. Upon medical review, reports coded as "foetal death" and "stillbirth" are classified as spontaneous abortion if they occur before 20 weeks gestational age (GA) and as stillbirth if they occur at ≥20 weeks gestational age. The threshold of 20 weeks is in accordance with the definitions applied in the United States [79]. Stillbirths are summarized in the *Spontaneous abortions, Stillbirths, and Fetal Deaths* section below.

All pregnancy cases reporting a PT from the SOC: Congenital, familial and genetic disorder underwent medical review; two groups of cases were identified: 1) fetuses and neonates with prenatal exposure to a Moderna COVID-19 vaccine with a reported congenital anomaly and 2) non-pregnancy cases with a represented medical history miscoded as an AE, or a pre-existing congenital anomaly detected (such as an arteriovenous malformation or atrial septal defect identified at the time of an AE such as cerebrovascular accident). All reported pregnancy cases reporting congenital malformations with prenatal exposure to a Moderna COVID-19 vaccine were reviewed, adjudicated and classified by MAH physicians using the Metropolitan Atlanta Congenital Defects Program (MACDP) [80] which is a population-based tracking system for birth defects. All major congenital malformations in accordance with MACDP were included in the cumulative observed number of cases.

Appendices for the pregnancy subpopulation analysis are in Appendix 11.6:

- Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event seriousness for Interval and Cumulative (elasomeran)
- Summary of pregnancy outcomes by trimester of exposure, and retrospective/prospective case classification, Reporting Period (elasomeran)
- Summary of pregnancy outcomes by trimester of exposure, and retrospective/prospective case classification, Cumulative (elasomeran)
- Summary of reported congenital anomalies by HLT and PT that occurred in fetuses and

neonates, Reporting period

- Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event Seriousness for Adolescents, Review Period and Cumulative (elasomeran)
- Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event Seriousness for elasomeran/imelasomeran and Cumulative
- Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event Seriousness for elasomeran/davesomeran, Reporting period and Cumulative

Literature Search Methodology:

A targeted literature search for relevant publications on pregnancy and lactation and elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran was conducted on a weekly basis during the PBRER#4 reporting period (19 Jun 2022 – 17 Dec 2022) using PubMed of the National Library of Medicine; search strategy is documented in Appendix 12.1d. Review of the abstracts and titles was performed to identify articles relevant to the safety and benefit/risk profile of vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during pregnancy and lactation. Articles that were excluded were those regarding COVID-19 during pregnancy or lactation, COVID-19 infection of fetuses/neonates, COVID-19 vaccination coverage during pregnancy or lactation, outcomes including safety after COVID-19 vaccination during pregnancy or lactation that did not include a Moderna COVID-19 vaccine, acceptance of COVID-19 vaccination among pregnant or lactating persons, safety of non-COVID-19 vaccinations during pregnancy or lactation, and case reports or case series regarding the use of a Moderna COVID-19 vaccine during pregnancy or lactation. Only articles with information regarding the safety and benefit/risk profile of vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy and lactation were reviewed and only those with new information or substantiative findings that affect the benefit/risk profile of the use of a Moderna COVID-19 vaccine during pregnancy are discussed in this PBRER.

16.3.5.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Pregnancy Cases Who Received Elasomeran

Cumulatively, ModernaTx, Inc. has received 5,131 pregnancy cases with 16,817 events (pregnancy and non-pregnancy-specific), of which 5,467 events were serious, after receipt of

elasomeran. Of the 5,131 pregnancy cases, 2,463 cases were medically confirmed, 1,817 (35.4%) cases were serious, and 32 had fatal outcomes.

During the reporting period, 388 pregnancy cases were identified with 1,298 events (pregnancy and non-pregnancy-specific), of which 403 events were serious, after receipt of elasomeran. Of the 388 pregnancy cases, 181 were medically confirmed and 188 (48.5%) cases were serious. A higher proportion (48.5%) of the cases during the review period were reported as "serious" compared to cumulative period (35.4%). The difference observed in this reporting period might be due to the small numbers of pregnancy cases reported and/or reflects the changing geographic patterns of reporting given it relates to varying country coding practices. Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" with no reported clinical events and are reported as "serious" cases; See Serious and Fatal Cases and Serious Pregnancy-related Events section. Serious cases should be interpreted with caution as many do not meet the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in a given serious case.

Of the 388 pregnancy cases during the reporting period, three were coded as fatal and are discussed in the "*Serious and fatal cases*" section. Of the three fatal cases, there was one maternal death ([redacted]) reported due to postpartum hemorrhage and causality was deemed unlikely due to a prolonged TTO (293 days) after vaccination; the remaining two cases were fetal deaths of pregnancies with prenatal exposure to elasomeran (one spontaneous abortion with congenital anomaly [[redacted]] and causality was deemed unlikely, and one stillbirth with multiple congenital anomalies ([redacted]) and causality was deemed unassessable given the limited available information provided.

The majority of pregnancy-specific cases occurred in the 18 to 39-year age group (Table 16.24), consistent with typical childbearing age. The age distribution for this review period continues to be similar to what was seen previously. Cases in the age group < 6 years of age represent fetuses or children with prenatal exposure to elasomeran. Cases in the age group < 6 years and 12-17 years old are further discussed in the *Children < 6 years of Age with A Medical History of Maternal Exposure to elasomeran During Pregnancy* and the *Adolescent* subsections, respectively, below.

Table 16.24 Age Distribution of Pregnancy Cases* by Review Period and Cumulative – elasomeran

Age Group All (11)	Prior to Review Period		Review Period		# of Total Cases*	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
0-5 months**	38	0.8	8	2.1	46	0.9
6 months - <2 years**	10	0.2	4	1.0	14	0.3
12-15 years***	4	0.1	0	0	4	0.1
16-17 years***	15	0.3	1	0.3	16	0.3
18-24 years	161	3.4	19	4.9	179	3.5
25-39 years	3,550	74.1	257	66.2	3,772	73.4
40-49 years	349	7.3	31	8.0	377	7.3
50-64 years****	57	1.2	3	0.8	60	1.2
65-74 years****	8	0.2	0	0	8	0.2
75 years+****	5	0.1	0	0	5	0.1
Missing	591	12.3	65	16.8	655	12.8
Grand total	**4,783**	**100.0**	**388**	**100.0**	**5,131**	**100.0**

* The addition of the cases from the prior review period and cases from the review period do not always add up to the number of total cases because a case that was reported prior to review period can also be included in this review period if a new event was reported during the review period.
** The cases under 6 years of age represent fetal cases or newborns/children with prenatal exposure to elasomeran and are discussed in the *Children < 6 years of Age with A Medical History of Maternal Exposure to elasomeran During Pregnancy* section.
*** These cases are discussed in the *Adolescent* section below.
**** Cases 50-years or older also include Regulatory Authority cases (that cannot be queried) that report pregnancy in older females, are non-pregnancy cases, and/or are cases with coding errors that will be corrected.

The most frequently reported PTs during the reporting period were reactogenicity events, consistent with the product safety profile and is similar between the reporting period and the cumulative period.

Cumulatively, there have been 20 pregnancy reports with the PT "Myocarditis" and/or "Pericarditis" after receipt of elasomeran resulting in 19 cases. Based on medical review, it was determined that two reports ([redacted] and [redacted]) pertained to the same individual.

During the reporting period, 3 reports of "Myocarditis" among pregnancy cases were received. However, two of the case reports ([redacted] and ([redacted]) appear to be misclassified as a pregnancy case given the lack of information in the reports regarding pregnancy or lactation as well as their advanced age (52 years and 49 years, respectively). See Section 16.3.1.2 for more information.

Pregnancy-specific events – elasomeran)

Cumulatively, there have been 4,659 pregnancy cases with 6,095 pregnancy-specific events of which 2,287 events were serious. Of the 4,659 pregnancy cases with a pregnancy-specific event, 2,325 were medically confirmed, 1,708 were serious cases, and 30 had a fatal outcome.

During the reporting period, 322 pregnancy cases were identified, with 385 pregnancy-specific events of which 194 events were serious. Of the 322 pregnancy cases with a pregnancy-specific event, 163 were medically confirmed, 162 cases were serious, and three had a fatal outcome. (*Note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ*).

After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome, the most frequently reported PTs for this reporting period is similar to the cumulative period. "Abortion spontaneous" is the most frequently reported adverse pregnancy event/outcome for both the reporting and cumulative period. (*Refer to Spontaneous abortions, Stillbirths, and Fetal Deaths evaluations added below*).

A summary table of all pregnancy outcomes, stratified by timing of exposure as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/313666/2005)" is presented in Appendix 11.6.

Serious Pregnancy-specific Events and Fatal Cases– elasomeran

During the reporting period, of the 188 serious pregnancy cases, 150 cases reported 194 serious pregnancy-specific events; 77 cases were medically confirmed. Three cases had a fatal outcome.

After excluding the pregnancy cases reporting only PTs that do not indicate an adverse pregnancy-specific event/outcome, (e.g., "Biochemical pregnancy", "Delivery", "Exposure during pregnancy", "False negative pregnancy test", "First trimester pregnancy", "Foetal exposure during pregnancy", "High risk pregnancy", "Live birth", "Maternal exposure", "Multigravida", "Multiparous", "Normal foetus", "Normal labour", "Normal newborn", "Paternal exposure before pregnancy", "Planning to become pregnant", "Postpartum state", "Pregnancy", "Pregnancy test positive", "Pregnancy with advanced maternal age", "Second trimester pregnancy", "Term baby", "Term birth", "Third trimester pregnancy", "Twin pregnancy", "Ultrasound antenatal screen normal", "Unintended pregnancy", and "Unwanted pregnancy"), there were 132 serious pregnancy cases reporting 164 serious pregnancy-specific events.

Review of the serious pregnancy-specific events during this reporting period did not identify any new safety concerns. These cases reflect obstetric events observed in temporal association with

elasomeran administration. Many of these cases had limited information about past medical and obstetric history, GA at time of vaccination, or onset of AE, diagnostics, treatment, and outcome. Where data were available, confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy [including advanced maternal age, in vitro fertilization, intrauterine insemination, concomitant medications, comorbidities (such as hypothyroidism, diabetes) and previous relevant obstetric history including fetal loss as well as prior history of a pregnancy with congenital anomalies] were present.

Fatal Pregnancy Cases– elasomeran)

During the review period, three pregnancy cases after elasomeran, were coded as fatal and are summarized in Table 16.25. Of the three fatal cases, there was one maternal death ([redacted]); the remaining two cases were fetal deaths of pregnancies with prenatal exposure to elasomeran (one spontaneous abortion with congenital anomaly ([redacted]), and one stillbirth with multiple congenital anomalies ([redacted]) and are discussed in the *Congenital Anomaly and Stillbirth* sections added below.

Table 16.25 Fatal Cases, Review Period– Elasomeran

Case ID	WW Identifier	Country	All PTs	Maternal Age	TTO Dose #	Pregnancy Outcome per Medical Review
[redacted]	[redacted]	[redacted]	Hypovolaemic shock, Postpartum haemorrhage, Uterine atony	30	293 days after administration of an unspecified dose of elasomeran	Maternal Death, Neonatal outcome unknown
			Foetal chromosome abnormality, Turner's syndrome	Unknown	Unknown	Spontaneous Abortion with Congenital Anomaly (Turner's syndrome)
			Dysmorphism, Foetal growth restriction, heart disease congenital, Hypospadias, Multiple congenital abnormalities	Unknown	Experienced events at 23 weeks GA, 9 weeks after administration of unspecified dose of elasomeran	Stillbirth with multiple congenital anomalies

Cumulatively, there have been five cases of maternal mortality reported and summarized in

previous PBRERs. The cases show no pattern or clusters on medical review.

- [redacted] – PBRER #1
- [redacted] – PBRER #2
- [redacted] – PBRER #2
- [redacted] – PBRER #3
- [redacted] – PBRER #4

During this reporting period, there was one case of maternal death, summarized below, which the MAH determined causality as unlikely given the long latency and lack of biological plausibility between elasomeran and uterine atony and postpartum hemorrhage.

[redacted] **(PH-PH[redacted])** This is a regulatory case reported by a health-care professional concerning a 30-year-old female who experienced the unexpected and fatal outcome of hypovolaemic shock, uterine atony and postpartum haemorrhage. The events occurred 293 days after administration of an unspecified dose of elasomeran. The reported causes of death were "Hypovolemic shock, Postpartum hemorrhage and Uterine atony." It is unknown if an autopsy was performed. Information regarding her medical history, obstetrical history, concomitant medications, medical history, clinical course and treatment were not provided. According to the WHO causality assessment this case is considered unlikely, given the long latency and lack of biological plausibility between elasomeran and uterine atony and postpartum hemorrhage.

Cumulatively, there have been four cases of deaths of neonates/infants with prenatal exposure to elasomeran; no concerning pattern or clustering seen. One case was summarized in MSSR #12 and the remaining three cases were summarized in PBRER #3.

- [redacted] – MSSR #12
- [redacted] – PBRER #3
- [redacted] – PBRER #3
- [redacted] – PBRER #3

During this reporting period, there were no fatal cases reported of neonatal/infant death with prenatal exposure to elasomeran, when compared to the cumulative data, no safety concerns were identified from the review of serious and fatal cases received during the reporting period for the pregnancy subpopulation.

Fetal Deaths– Elasomeran

The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth" and are classified as spontaneous abortion if they occur before 20-weeks GA, and as stillbirth if they occur after 20 weeks gestational age. The threshold of 20 weeks is per the definitions applied in the United States [79,81].

Spontaneous and Missed Abortions – Elasomeran

Cumulatively, 674 pregnancy cases reported spontaneous abortion or missed abortion with 700 events of which 669 events were serious (some cases have more than one of the PTs used to identify this group). Of the 674 cases, 405 were medically confirmed, 648 cases were serious and three were coded as fatal (Appendix 11.6).

During the review period, 50 pregnancy cases reported spontaneous abortion or missed abortion with 52 events of which 51 events were serious. Of the 50 cases, 24 were medically confirmed, 50 cases were serious, and no cases were coded as fatal. The mean age of the cases is 33.2 years (SD: 5.2), median age 33 years (range 21-44), and one (2.0%) case had missing age information. Of the cases with available data on the dose number prior to the event, there were more events reported after Dose 2 (9.6%) than Dose 1 (5.8%), Dose 3 (5.8%), and Dose 4 (1.9%). This must be interpreted with caution as one does not know how many pregnant women have received one versus two versus three or more doses; and, of note, 76.9% of events are missing dose information. Although the data are limited, when TTO and dose number were known, the majority of events (66.7%) occurred 30 or more days after vaccination. The median TTO was 42.0 days (range 6-231); there was no unusual clustering by dose or TTO.

Stillbirth – elasomeran)

Stillbirth has varying global definitions based on GA and fetal weight. For the purposes of this PBRER, and as described above, the MAH applied a definition of a fetal death after 20-weeks gestational are [79] [81]. Congenital anomalies, placental dysfunction associated with fetal growth restriction, and maternal medical diseases and obstetric complications (such as pre-eclampsia, chorioamnionitis, and infections such as group B *Streptococcus* and cytomegalovirus) are common causes of stillbirth. Advanced maternal age (over 40 years) has been associated with an increased risk of stillbirth as well. Evaluation of spontaneous, reports is limited due to a lack of complete information, such as medical and obstetric history as well as diagnostic evaluation and results performed to determine the cause of the stillbirth.

Cumulatively, 105 cases were coded as "foetal death" and/or "stillbirth". Upon medical review, 56 cases occurred ≥20 weeks GA (classified as stillbirth) and 45 cases occurred before 20 weeks (classified as spontaneous abortion). One case of "fetal death" did not have GA information and, thus, could not be classified. Of the 105 cases, two cases were mother-fetal linked cases with duplicate events (one coded as "Foetal death" and one coded as "stillbirth"). One case was a duplicate (both coded as "Stillbirth").

During the reporting period, eight cases were coded as "Foetal death" and/or "Stillbirth" (Table 16.26). Upon medical review, three cases occurred ≥20 weeks GA (classified as stillbirth) and five cases occurred before 20 weeks (classified as spontaneous abortion).

Table 16.26 MAH Fetal Death Case Classification of Reports with PTs "Fetal death" and/or "Stillbirth" – Reporting Period and Cumulative– elasomeran

MAH Medical Review Classification	Reporting Period		Prior to Reporting Period		Cumulative	
	# Cases	% Total Reporting Period Cases	# Cases	% Total Prior Cumulative Cases	#Cases	% Total Cumulative Cases
Stillbirth	3	37.5	53	54.6	56	53.3
Spontaneous abortion	5	62.5	40	41.2	45	42.9
Unknown	0	0	1	1.0	1	1.0
Duplicate (not classified)	0	0	3	3.1	3	2.9
Total	**8**	**100.0**	**97**	**100.0**	**105**	**100.0**

During the reporting period, five pregnancy cases that reported stillbirth were identified; three were identified through the medical review of cases that were coded as "foetal death" and/or "stillbirth" and the other two cases ([redacted] [incorrectly coded as SAB] and [redacted] [no pregnancy outcome was coded]) were identified from medical review of pregnancy cases with serious pregnancy-related events. These pregnancy cases noting a stillbirth are summarized in Table 16.27.

Table 16.27 Stillbirths*, Review Period – elasomeran

Case ID (WW Identifier)	All Preferred Terms	Company Comment	WHO-UMC Causality
[redacted]	Stillbirth	This is a regulatory case was reported by another health-care professional is concerning a 33-year-old female with no reported medical history, who experienced the unexpected, serious, event of stillbirth	Unassessable: This report has limited data and is missing critical information including timing of

Case ID (WW Identifier)	All Preferred Terms	Company Comment	WHO-UMC Causality
		and occurred on an unknown interval (no vaccination date was provided) after receiving an unspecified dose of elasomeran. The delivery occurred on the same day of the onset of event which was reported as stillbirth. The outcome of the fetus was stillbirth NOS. No further information on last menstrual period, estimated due date, obstetrical and medical history, clinical course and management of the event was available in the report. It was reported that the outcome of the event has resolved.	vaccination during pregnancy, TTO, the maternal medical and obstetrical history, concomitant medications, complete diagnostic evaluation, whether a fetal autopsy was performed and results if applicable, that is needed for an informed case and causality assessment.
[redacted]	COVID-19 immunization, Stillbirth	This is a regulatory case reported by consumer concerning a 31-year-old female, who experienced the unexpected, serious, event of stillbirth at 39+4weeks GA, 130 days after the third COVID-19 vaccination with the first dose of elasomeran (received at 21 weeks GA). The delivery occurred on the same day of the onset of event which was reported as stillbirth. The outcome of the fetus was stillbirth NOS. Her medical history includes laboratory confirmed COVID-19 during pregnancy at an unspecified time. She had previously completed her COVID-19 vaccination primary series with Comirnaty, with the last dose 203 days prior to receipt of the elasomeran. No further information on her obstetrical history, diagnostic evaluation and results and the clinical course and management of the event was available in the report. It was reported that the event has resolved.	Unassessable: This report is confounded by diagnosis of COVID-19 during pregnancy, as stillbirths have been reported among pregnancies complicated by COVID-19. Additionally, this case report has limited data and is missing critical information including maternal obstetrical history, history of the current pregnancy, concomitant medications, complete diagnostic evaluation, whether a fetal autopsy was performed and results if applicable, that is needed for an informed case and causality assessment.
[redacted]	Stillbirth	This is a regulatory case reported by physician concerning a 39-year-old female, who experienced the unexpected, serious, event of stillbirth at an unknown GA, 18 days after the third COVID-19 vaccination with the first dose of elasomeran (received at an unknown GA). The outcome of the fetus was reported as stillbirth NOS. Her	Unassessable: Although there is temporal association, this case report has limited data and is missing critical information including GA when stillbirth

Case ID (WW Identifier)	All Preferred Terms	Company Comment	WHO-UMC Causality
		obstetrical history includes two prior pregnancies resulting in live births with last pregnancy complicated by uterine rupture. She had previously completed her COVID-19 vaccination primary series with Comirnaty, with the last dose 238 days prior to receipt of the elasomeran. No further information on her medical history, diagnostic evaluation and results and the clinical course and management of the event was available in the report. It was reported that the event has not resolved at the time of the report.	happened, maternal medical history, history of the current pregnancy, concomitant medications, complete diagnostic evaluation, whether a fetal autopsy was performed and results if applicable, that is needed for an informed case and causality assessment.
[redacted]	Abortion spontaneous, Feeling abnormal	This regulatory case concerns a 29-year-old, gravid, female patient with no relevant medical history, who experienced the unexpected, serious (Medically significant, Hospitalization) event of Abortion spontaneous and unexpected, serious (Hospitalization) event of Feeling abnormal. The event Abortion spontaneous occurred 6 days after administration of third dose of elasomeran, the exact date of onset of the event Feeling abnormal was not specified in respect to the administration of third dose of elasomeran, hence latency could not be assessed, there was no information provided regarding the initial two doses. It has been reported that the patient has miscarriage at 21 weeks of pregnancy and the child was not alive. Details of concomitant medications, medical history, clinical course and treatment were not provided. The outcome of the event Abortion spontaneous was unknown while the event Feeling abnormal has resolved at the time of the report. The benefit-risk relationship of elasomeran is not affected by this report. Events' seriousness retained as per Regulatory Authority's report.	Possible: This meets the MAH criteria as a stillbirth (defined as loss ≥20 weeks GA) Causality is possible solely based on temporal association given that this report is missing critical important information such maternal medical history including concomitant medications, prior obstetric history, diagnostic evaluation and results performed to evaluate the stillbirth, and clinical course needed to make an informed case and causality assessment.
[redacted]	Dysmorphism, Foetal growth restriction, Heart disease congenital, Hypospadias,	A female of unknown age experienced a stillbirth at an unknown GA. She had received an unspecified dose of elasomeran at 14 +4 weeks gestation and around 23 weeks gestation, the fetus was diagnosed with multiple congenital malformations,	Unassessable: Without knowing the full spectrum of congenital anomalies, causality regarding congenital anomalies is

Case ID (WW Identifier)	All Preferred Terms	Company Comment	WHO-UMC Causality
	Multiple congenital abnormalities	hypospadias, dysmorphism, fetal growth restriction and congenital heart disease. At an unknown time or interval after maternal vaccination or diagnosis of fetal anomalies, a stillbirth occurred, and the reported cause of death was the multiple congenital anomalies. It is unknown if an autopsy was performed. Maternal medical history of hypothyroidism on Levothyroxine was reported. Information regarding obstetric history, family history of congenital anomalies, ultrasound reports and genetic screening prior to vaccination, diagnostic workup/results related to congenital anomalies and stillbirth and treatment were not provided	unassessable. Additionally, vaccination was at the tail end of period of fetal development where major defects in body structure can occur and the presence of anomalies affecting multiple organ systems a chromosomal anomaly is a plausible alternate cause that has not been ruled out based on the limited available data. Despite temporal association, causality regarding stillbirth is unassessable as this report is missing critical important information such as current and prior obstetric history, ultrasound reports, genetic screening prior to vaccination, diagnostic evaluation, results performed to evaluate the stillbirth, and clinical course.

***** Stillbirth has varying global definitions based on GA and fetal weight. For the purposes of this safety report, the MAH applied a definition of a fetal death after 20-weeks GA per the definitions applied in the United States [79,81].

Based on medical review of the "stillbirth" and fetal death cases >20 weeks gestation age, there is no clear TTO pattern, some cases had clear alternate etiologies, and thus there was insufficient evidence to support causality or demonstrate an increased risk. Many reports had limited data and lacked crucial information to make a robust case and causality assessment; and in addition, it is well known that, typically, up to 60% of stillbirths cannot be attributed to an identifiable fetal, placental, maternal, or obstetric etiology due to lack of sufficient information or because the cause cannot be determined at the current level of diagnostic ability [81]. It was noted that for many of the pregnancy reports coded as "prospective", there was no evidence in the report to support this

classification, thus this classification must be interpreted with caution as there is a high likelihood of coding errors.) Overall, cases of stillbirth and spontaneous abortion received during the reporting period was similar to the cumulative period and no safety concerns were identified.

A summary table of all pregnancy outcomes classified as retrospective and prospective and stratified by timing of exposure, as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/ 313666/2005)", is presented in Appendix 11.6. It was noted that for many of the pregnancy reports coded as "prospective", there was no evidence in the report to support that classification, thus this classification must be interpreted with caution as there is a high likelihood of coding errors.

Congenital Anomaly– elasomeran

During the reporting period, 24 pregnancy cases that reported a PT from the Congenital, familial and genetic disorder SOC were identified and after medical review, no patterns and no safety concerns were identified. Of the 24 pregnancy cases, 14 occurred among fetuses and neonates from pregnancies exposed to elasomeran and 10 occurred in non-pregnancy cases and either represented medical history miscoded as an AE, or a pre-existing congenital anomaly detected in a non-pregnant person. The reported pregnancy outcome of the 14 cases was spontaneous or missed abortion in 1 (7.1%) case, stillbirth in 1 (7.1%) case, live birth in 9 (64.3%) cases, and unknown outcome in 3 (21.4%) cases. Further review of the congenital anomalies, considering the GA at vaccination and foetal development contributed to the assessment of causality. Many cases lacked GA at the time of vaccination and thus causality was unassessable. Although a meaningful comparison of congenital anomalies reported by pregnancy outcome is not possible, there was no clustering or safety concerns seen by pregnancy outcome. Cumulatively, there have been 140 reports of congenital anomalies. Upon medical review, 64 pregnancy reports (some contain parent-child duplicates) occurred in fetuses and neonates and the other 76 reports of congenital anomalies occurred in non-pregnancy cases for aforementioned reasons. Even when considering the cumulative data, there were no patterns and no safety concerns identified.

Subpopulation Analyzes:

Children <6 years of Age with with a medical history of maternal exposure to elasomeran during pregnancy

Cumulatively, there have been a total of 60 cases among children under the age of 6 years with a medical history of maternal exposure to elasomeran during pregnancy reported with 148 events of

which 83 were serious. Of the 60 cases, 25 were medically confirmed, 41 cases were serious, and 6 cases had a fatal outcome. During the reporting period, 12 cases among children under the age of 6 years with a medical history of maternal exposure to elasomeran during pregnancy were identified with 33 events of which 20 were serious. Of the 12 cases, 4 were medically confirmed, 9 cases were serious, and no cases had a fatal outcome.

Given there was no notable difference in the most frequently reported PTs between the review and cumulative period data as well as the small number of cases reported during this reporting period, only the cumulative data for most frequently reported PTs are presented for children under the age of 6 years with prenatal exposure to elasomeran (Table 16.28). After excluding PTs that do not indicate an AE/outcome, the most frequently reported PTs cumulatively were: "Poor feeding infant", "Infantile vomiting", and "Low birth weight baby" reported by 17 cases and do not seem to represent a safety concern. See Table 16.28 for the most frequently reported PTs, with an event count of 2 or more, by seriousness among pregnancy cases under the age of 6 years.

Table 16.28 Most Frequently Reported PTs[1,2] by Seriousness Among Pregnancy- specific cases under the age of 6 years, Cumulative – elasomeran

PT	Non-Serious		Serious		# of Total Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Poor feeding infant	6	4.1	1	0.7	7	4.7
Infantile vomiting	5	3.4	0	0	5	3.4
Low birth weight baby	2	1.4	3	2.0	5	3.4
Premature baby	1	0.7	3	2.0	4	2.7
Atrial septal defect	0	0	3	2.0	3	2.0
Abdominal pain	1	0.7	1	0.7	2	1.4
Bradycardia neonatal	0	0	2	1.4	2	1.4
COVID-19	1	0.7	1	0.7	2	1.4
Death neonatal	0	0	2	1.4	2	1.4
Decreased appetite	1	0.7	1	0.7	2	1.4
Diarrhoea	2	1.4	0	0	2	1.4
Faeces discoloured	1	0.7	1	0.7	2	1.4
Fatigue	1	0.7	1	0.7	2	1.4
Neonatal aspiration	0	0	2	1.4	2	1.4
Pyrexia	1	0.7	1	0.7	2	1.4

PT	Non-Serious		Serious		# of Total Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Respiratory disorder neonatal	0	0	2	1.4	2	1.4
Transposition of the great vessels	0	0	2	1.4	2	1.4
Vomiting	1	0.7	1	0.7	2	1.4

[1] Only PT terms with a cumulative count of 2 or more are presented.
[2] This table excludes PTs that do not indicate an adverse pregnancy-specific event/outcome: "Exposure via breast milk" and "Foetal exposure during pregnancy".

During the review period, nine serious cases among children under the age of 6 years with a medical history of maternal exposure to elasomeran during pregnancy were identified with 23 events of which 20 were serious. Of the nine cases, three were medically confirmed and none had a fatal outcome. These nine cases are summarized below:

[redacted] A 3-day-old term male neonate experienced bradycardia, 156 days after maternal third COVID-19 vaccination. Mother received 2 doses of Comirnaty and one dose of elasomeran at an unknown GA, and it is also unknown the order of these vaccinations. Bradycardia resolved 5 days later. Neonatal evaluation reported (chest X-ray, ECG, ECHO, head ultrasound) was normal except discrete sinus rhythm that was depressed for age with no indication of a rhythm disorder. Causality is "unassessable" because of the extremely limited data reported but this report is heavily confounded by the prolonged TTO. Critical data for case assessment and causality ascertainment are missing including obstetric history, maternal concomitant medications, medical history, status, and history of the pregnancy exposed to elasomeran.

[redacted]**):** A 2-month-old baby girl with relevant medical history of maternal exposure during pregnancy, and her mother received the first dose of elasomeran vaccine in her first pregnancy trimester, as well as a second dose on an unknown date who experienced events of Cleft palate, Eyelid disorder (Attached left eye lids) and Cerebral haemorrhage. Brain ultrasound of the patient showed a grade 2 haemorrhage. Patient had no history of cleft palate in both families of parents and mother did not take other medications during pregnancy. Mother was reported as healthy and non-smoker. It is reported that this infant was the third born with two healthy siblings. Information on pregnancy course including last menstrual period and due date, maternal and neonatal diagnostic tests/procedures, clinical course, and treatment were not provided. This case is unassessable given the inability to establish the

timing of vaccination during pregnancy and temporal association.

[redacted]): A child of unknown age and gender, with maternal use of alprazolam and metformin for an unknown indication and maternal history of receipt of an unspecified dose of elasomeran during pregnancy. Fetal growth restriction was reported; however, temporal association cannot be assessed due to lack of information on onset date of the event and vaccination date. It is reported that the subject was delivered without any congenital anomalies and achieved all the developmental milestones at the time of the report, at an unknown age. No further clinical information was available for medical review. This case is "unassessable" given that temporal association cannot be established, and this report is missing critical information such as maternal history, obstetrical history, diagnostic evaluation and results which are needed for case and causality assessment.

[redacted]): This regulatory authority case reported by another health-care professional concerning a male infant of unknown age, who 18 months and 17 months after his mother received the first and second dose of elasomeran (Original), respectively experienced transposition of the great vessels. Reportedly, a prenatal screening test and prenatal visits did not show the congenital defect. The male infant had surgery 6 days after the detection of the congenital anomaly. No further information on maternal and infant medical history, infant diagnostic evaluation and results and the clinical course and management of the event was available. Outcome was reported as unknown, and patient was hospitalized at the time of the report. Causality is unlikely, the long latency makes a relationship improbable given that the last dose of elasomeran vaccine were received approximately 7 months prior to conception. This case report is missing critical information including maternal medical and obstetrical history, maternal concomitant medications, infant medical history, complete diagnostic evaluation of the infant, that is needed for an informed case and causality assessment.

[redacted]: A female infant, who experienced the unexpected serious (hospitalization and medically significant) events of bronchiolitis at 5.5 months of age, approximately 6 months after maternal receipt of the third dose of COVID-19 vaccine with the first dose of elasomeran at 37+5 weeks GA. Reportedly, the patient's mother was vaccinated with two doses of COVID-19 VACCINE NRVV AD (CHADOX1 NCOV-19) with first vaccine administered 3 days after last menstrual period and second dose administered at 11+4 weeks GA. The infant was delivered at term weighing 2,834 grams (6lbs 4oz) and the mother spent three days at hospital for the delivery. Causality is unassessable because although there is temporal association, critical information about neonatal medical history,

concomitant medications, diagnostic tests or laboratory results and clinical course regarding the event of bronchiolitis was not provided. However, the long latency, the timing of elasomeran during the pregnancy (two weeks prior to delivery) and lack of biological plausibility makes another explanation more likely.

[redacted]: This is a regulatory authority case concerning a 1-day-old, male neonate whose mother received an unspecified dose of elasomeran at 4+1 weeks gestation. The exact date and GA of the onset of the events after vaccination was not specified, events reported ~6 months after vaccination The diagnosis of respiratory disorder neonatal, kidney duplex, prematurity ("33 to 36 weeks"), atrial septal defect, congenital inguinal hernia, infantile apnoea, and bradycardia neonatal was reported. No further details on the pregnancy course, infant clinical course, diagnostic evaluation, and results as well as treatment received were reported. Maternal medical history reported Hypothyroidism and factor V Leiden mutation and pregnancy-related complications reported were cholestasis of pregnancy and pre-eclampsia. Causality is possible regarding the congenital anomalies given the timing of vaccination during early fetal development. However, given the presence of anomalies affecting multiple organ systems a chromosomal anomaly is a plausible alternate cause that has not been ruled based on the limited available data.

[redacted] This is a regulatory authority case concerning a 1-day-old female neonate, whose mother received an unspecified dose of elasomeran at 2+3 weeks gestation. Atrial septal defect was detected at an unknown exact date or GA, event reported ~9 months later. It is reported that maternal medical history included "prophylaxis of neural tube defect and labour induction. Further information regarding Last menstrual period and estimated due data, pregnancy course including prenatal scans, obstetrical history as well as neonatal evaluation and treatment was not provided. Causality is possible given the timing of vaccination during early fetal development. However, septal defects, especially small ones, are a relative frequent finding and this report is missing critical information such as prior obstetric history, neonatal evaluation, and treatment for atrial septal defect, needed to make an informed case and causality assessment.

[redacted]: An infant of unknown age and gender whose mother received an unspecified dose of elasomeran during pregnancy at an unknown date. The infant is described to have experienced the non-serious event of "Foetal exposure during pregnancy" at an unknown GA and the serious event of "COVID-19" at an unknown timing or age. No further information was available for medical review. The case is

"unassessable" given the extremely limited data available.

[redacted]): A child of unknown age and gender who experienced the unexpected, serious (Hospitalization) events of rhinovirus infection and metapneumovirus infection at an unknown date. Maternal history of receipt of an unspecified dose of elasomeran during pregnancy was reported but timing and GA at administration us unknown. The report mentioned the subject was hospitalized for two days; however, no further clinical details were provided for medical review. The outcome of the events was unknown at the time of the report. Although temporal association cannot be established, causality is "unlikely" as these are common viral infections and elasomeran is a nucleoside modified vaccine that does not contain any virus capable of causing viral infection.

Pregnancy Cases Among Children 6-11 Years of Age – elasomeran)

There are no reported pregnancy cases among children 6-11 years of age.

Pregnancy Cases Among Adolescents (12-17 Years of Age – elasomeran)

Cumulatively, 20 pregnancy cases were reported among adolescents (12-17-years of age) with 47 events of which 10 events were serious. Of the 20 cases, 17 were medically confirmed, 4 were serious cases and none had a fatal outcome.

During the reporting period, there was one pregnancy case ([redacted]) reported among adolescents (12-17 years of age) which noted only the non-serious event of "Caesarean section" in a 16-year-old female with no reported medical history or concomitant medication at an unknown GA, ~ 7months after a second COVID-19 vaccination with elasomeran at an unknown GA. It is reported that caesarean section was scheduled.

Cumulatively, most of the reports had PTs: "Product administered to patient of inappropriate age", "Maternal exposure during pregnancy", or "Exposure during pregnancy". No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period; however, the data are limited.

Pregnancy Cases Who Received Three or More Doses of elasomeran)

Cumulatively, 278 pregnancy cases with 758 events (of which 403 were serious events) after receipt of three or more doses of elasomeran have been reported. Of the 278 cases, 70 cases were medically confirmed, 150 were serious cases and none had a fatal outcome.

During the review period, 55 pregnancy cases with 136 events (of which 52 events were serious) after receipt of three or more doses of elasomeran were identified. Of the 55 pregnancy cases, 25 cases were confirmed, 33 were serious cases and none had a fatal outcome.

During the reporting period, after excluding PTs that do not indicate an adverse pregnancy-specific event/outcome, similar to the events reported by pregnancy cases for all doses, the majority of the most frequently reported PTs represent expected reactogenicity for elasomeran. The most frequently reported PTs indicating an adverse pregnancy-specific event/outcome were "Foetal growth restriction" (4 events) and "Abortion spontaneous" (3 events)". The types and distribution of the most frequently reported events during this reporting period is similar to the cumulative period. Overall, based on current available information, regardless of the type of COVID-19 vaccines used for the primary series, no unusual patterns or pregnancy-specific safety concerns were identified.

Pregnancy After Receiving Booster Dose with elasomeran/imelasomeran

During the reporting period, 17 pregnancy cases (66 events) with 4 serious cases (22 serious events) after exposure to a booster dose of elasomeran/imelasomeran have been reported; there were no pregnancy cases with a fatal outcome, stillbirth, or fetus/infant with congenital anomalies after receipt of elasomeran/imelasomeran There were five case reports medically confirmed, the most frequently reported clinical events/PTs represent expected reactogenicity for elasomeran. Of the 66 events reported, 16 were pregnancy-specific events and the only pregnancy-specific event reported in order of decreasing frequency are "Maternal exposure during pregnancy," "Exposure during pregnancy," and "Morning sickness."

See Appendix 11.6 for all pregnancy cases who received a booster with elasomeran/imelasomeran).

Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified.

Pregnancy After Receiving Booster Dose with elasomeran/davesomeran

During the reporting period, 11 pregnancy cases (42 events) with 1 serious case (5 serious events) events after exposure to a booster dose of elasomeran/davesomeran have been reported; there were no pregnancy cases with a fatal outcome, stillbirth, or fetus/infant with congenital anomalies after receipt of elasomeran/davesomeran. There were six medically confirmed cases. The most

frequently reported events/PTs represent expected reactogenicity for elasomeran. The only pregnancy-specific PT reported by all 11 cases is "Maternal exposure during pregnancy."

See Appendix 11.6 for all of pregnancy cases who received a booster dose with elasomeran/davesomeran.

Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified.

Literature Summary of Safety of elasomeran During Pregnancy

The literature reviewed have not identified any maternal, fetal, or neonatal immunization safety concerns with the administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. From the search, 2,622 articles were captured during the reporting period. After exclusion of articles on COVID-19 during pregnancy or neonatal period or lactation, COVID-19 vaccination coverage during pregnancy or lactation, COVID-19 vaccination acceptability by pregnant or lactating persons, safety of other COVID-19 vaccines apart from elasomeran during pregnancy or lactation, case reports and case series of safety of COVID-19 vaccines including elasomeran during pregnancy or lactation, 680 articles underwent full length review and of the 680 articles identified to include regarding safety of elasomeran during pregnancy and lactation, 40 of them were among pregnant persons and of these, two articles [82,83] will be discussed below because they contain new and substantiative findings that positively impact the benefit/risk profile of the use of elasomeran during pregnancy.

1. **COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry, an observational prospective cohort study [83]**

Abstract and Company Comment: This observational prospective cohort study assesses early AEs and perinatal outcomes in pregnant woman who received at least one dose of mRNA vaccine between 01 Mar and 01 Dec 2021 in Switzerland, using the COVI-PREG registry. Among 1,012 vaccinated women, 894 (88.3%) received both primary series injections during pregnancy. Localized pain was the most frequently reported AE (81.3% and 80.5% after the first and second dose, respectively). Events of fatigue and headache were the most frequently reported systemic reactions, particularly after the second dose of elasomeran. There were four severe early AEs: pulmonary embolism, preterm premature rupture of membranes, isolated fever with hospitalization, and herpes zoster. One early spontaneous abortion (8 weeks GA) was reported among 107 patients vaccinated prior to 14 weeks GA. One late spontaneous abortion (16 weeks

GA) was reported among 228 patients vaccinated before 20 weeks GA. There were 33 preterm delivery reported in 513 patients who were vaccinated prior to 37 weeks GA. Among the 530 patients exposed during pregnancy, there were no reports of stillbirth, and 25 neonates were admitted to the intensive care unit. This study data indicated that the most frequently reported events among pregnant women vaccinated with mRNA COVID-19 vaccines were reactogenicity events which is consistent with the product safety profile of these vaccines. Data also indicated that severe events were rare and pregnant women vaccinated with mRNA COVID-19 vaccines did not experience higher adverse pregnancy or neonatal outcomes when compared to historical data on background risks in the obstetric population. These findings provide continued evidence that supports the favorable benefit/risk profile of maternal mRNA COVID-19 immunization including during the first trimester.

2. **Maternal immune response and placental antibody transfer after COVID-19 vaccination across trimester and platforms [82]**

Abstract and Company comment: This cohort biorepository study conducted from January 2021 to September 2021 examined how different COVID-19 vaccine platforms and timing of vaccination during pregnancy may impact maternal and neonatal immunity. The study characterized the antibody profile in 158 pregnant individuals who were vaccinated with one of three COVID 19 vaccines: Ad26.COV2.S, BNT162b2, or elasomeran. This analysis revealed higher vaccine-induced functions and Fc receptor-binding after mRNA vaccination when compared to Ad26.COV2.S, revealed subtle advantages in titer and function with elasomeran when compared to BN162b2, and showed mRNA vaccines demonstrated higher titers and functions against SARS-CoV-2 variants of concern. The study also evaluated transplacental antibody transfer by profiling maternal and umbilical cord blood in 175 maternal-neonatal dyads. This analysis demonstrated first, and third trimester vaccination resulted in enhanced maternal antibody dependent NK-cell activation, cellular and neutrophil phagocytosis, and complement deposition relative to second trimester; and demonstrated that higher transplacental transfer ratios following first and second trimester vaccination may reflect placental compensation for waning maternal titers. These findings provide evidence that supports both the efficacy of mRNA COVID-19 vaccines in pregnant women and how the timing of maternal vaccination can positively impact the maternal-neonatal dyad antibody mediated immunity generated by mRNA COVID-19 vaccines.

16.3.5.1.5 Discussion

During the reporting period, the pattern of the reports remained generally consistent when compared with the cumulative data, and review of the reporting period serious pregnancy-specific events and non-pregnancy-specific events did not identify any safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Reported cases reflect obstetric events observed after administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of AE, diagnostics, treatment and/or outcome. Where data was available, noted confounding factors for spontaneous abortion/foetal deaths and complications of pregnancy included advanced maternal age, invitro fertilization, intrauterine insemination, concomitant medications, comorbidities (such as hypothyroidism), previous relevant obstetric history, and congenital anomalies which predated the vaccination.

Spontaneous abortion was the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster was identified. Cumulatively there are 53 reports classified as stillbirth. Considering that some cases have clear alternate etiologies, there is an absence of a clear TTO cluster, and published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth after COVID vaccination, there is insufficient evidence to support a causal relationship between elasomeran and stillbirth.

The MAH will continue to review and evaluate cases of spontaneous abortion, foetal death and stillbirth, using routine surveillance as well as post-authorization safety studies.

Review of the 14 cases of congenital anomalies received during the reporting period as well as the cumulative data did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with elasomeran.

Review of 9 serious cases received during the reporting period concerning children under 6-years of age who were exposed during gestation did not identify any unusual patterns or safety concerns. There was one pregnancy-related case among adolescents received during the reporting period, and there continues to be an increasing number of pregnancy-related cases following receipt of three or more doses of elasomeran (278 pregnancy cases reporting receipt of three or more doses

of elasomeran). Overall, based on current available information there are no unusual patterns or pregnancy-related safety concerns identified among these subpopulations.

Cumulatively, 28 pregnancy cases were reported to the MAH with an exposure to a booster dose of Spikevax bivalent vaccines [17 cases reported an event after elasomeran/imelasomeran, and 11 cases reported an event after elasomeran/davesomeran. Most events reflect expected reactogenicity. The most frequently reported pregnancy-specific event was "Maternal exposure during pregnancy"]. There were no reports of PTs that indicate an adverse pregnancy event/outcome, or fatal outcomes. No unusual patterns or pregnancy-specific safety concerns have been identified; MAH will continue to review cases that received the bivalent vaccines using routine surveillance.

In-depth literature reviews performed have not identified any safety concerns for the use of elasomeran during pregnancy; however. Thus far, published literature has not identified any evidence of an increased risk of pregnancy, foetal or neonatal complications related to elasomeran maternal immunization. Furthermore, literature demonstrates that there is transfer of maternal antibodies, reduction in COVID-19 in vaccinated pregnant women and early evidence that that infants benefit from passive protection from SARS-CoV-2 infection and severe disease following maternal COVID-19 vaccination, recognition that COVID-19 may be more serious and cause complications for both the mother and the fetus; and thus, in sum, published literature supports the favorable benefit/risk profile of maternal elasomeran immunization. Data on use of Spikevax bivalent vaccines during pregnancy, continues to provide supporting evidence for HAs recommendations for the use of COVID-19 vaccines including elasomeran during pregnancy.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in Pregnancy and while Breastfeeding, the benefit-risk profile for elasomeran remains favorable.

- The MAH has monitored use in Pregnancy and while breastfeeding in each MSSRs as well as PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found: Review of the congenital anomalies reported in the GSDB indicates that the anomalies are varied in type, etiology, and critical GA at exposure; this data would seem to indicate that the anomalies have occurred as part of the background incidence rather than as a result of vaccine exposure.
- Review of the post-marketing safety data does not support a causal relationship between elasomeran, and the birth defects reported to the GSDB.
- It remains difficult to interpret the significance of malformations when they are rare.
- All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug or vaccine exposure.
- At the request of the EMA the following recommendations are included in the SmPC: "elasomeran can be used during pregnancy" and "elasomeran can be used during breastfeeding".
- Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines.
- The MAH continues to evaluate the pregnancy outcomes in reports of elasomeran and bivalent Boosters use during pregnancy via routine pharmacovigilance activities as well as through post-authorization safety studies.
- Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

- Use of the vaccine in pregnant individuals is already included in the product's labeling, and it is embedded in clinical practice and has been recommended by major public HAs.

- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to 'use in pregnancy and while breast-feeding' as long-term safety is being kept.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals during pregnancy and while breastfeeding in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of "Use in pregnancy and while breastfeeding" as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals during pregnancy and while breastfeeding through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.1.6 Conclusion

After review of all new safety data received during the reporting period and cumulatively, the MAH did not identify any safety concerns for maternal immunization and, thus, there is no change to the benefit-risk profile for pregnant woman or their fetuses and neonates. The benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable for use during pregnancy. The MAH will continue to monitor pregnancy-specific reports through routine surveillance and post-authorization safety studies.

16.3.5.2 Use in Breastfeeding

16.3.5.2.1 Source of the New Information

Information presented below includes analyzes performed on spontaneous reports from lactating women who were vaccinated and their children who were exposed to breastmilk from mothers who had been vaccinated (referred to as lactation cases) received by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for COVID-19 ModernaTx, Inc. vaccines: elasomeran and bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran). Cumulative data, also considered in the analyses, cover the period from 18 Dec 2020 to 17 Dec 2022.

The Company GSDB was queried for valid clinical and spontaneous case reports in lactating women, who were vaccinated, and their children who were exposed to breastmilk from mothers who had been vaccinated with elasomeran and Spikevax bivalent COVID-19 vaccines. These case reports were received from HCP, HA, consumers, and the literature, cumulatively and for the reporting period, worldwide.

16.3.5.2.2 Background Relevant to the Evaluation

The use of ModernaTx, Inc. COVID-19 vaccines among breastfeeding women is an area of missing information in the RMP; no CTs were conducted among lactating women. Developmental and reproductive toxicology showed maternal to rat pup transfer of antibodies; however, no data were available on vaccine excretion in human breast milk. Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during breastfeeding to prevent COVID-19 [66]. However, there was recognition that in absence of CTs, vigilant post-EUA passive report monitoring, and real-world evidence was needed to continue monitoring the safety of COVID vaccination among breastfeeding women.

There have been no specific safety concerns identified for vaccinated breast-feeding women and/or their breastfed children. Epidemiological studies have not indicated any increased risk of side-effects in the mother or the breastfed child after vaccination with elasomeran, or decreased milk production [84] [85] [86] [87] [88]. More specifically, a large series of 17,525 women vaccinated with a COVID-19 vaccine of which 6,815 were lactating women (2,596 received elasomeran), 7,809 pregnant, and 2,901 women of reproductive age planning to get pregnant, found that there was no difference in rate of AEs by vaccine type across all groups and the AEs were transient, mild and consistent with reactogenicity events [84] [85] [86] have shown similar findings that elasomeran is well tolerated by lactating women and their children, and side-effects experienced are similar to side-effects in the general population.

Regarding the side-effects among infants exposed to breastmilk from mothers who had been vaccinated with elasomeran, studies show no increased risk in short-term adverse effects. In the large case series by Kachikis *et al* [84] where only 3% and 4.4% of breastfeeding mothers reported to have concerns about the infant after the first dose and second dose, respectively. Few infant events are reported; and the most common side-effects seen among nursing children are transient, non-serious poor sleep and irritability [85] [86].

Regarding impact of vaccination on breastmilk production, most studies have shown that only a small percentage of lactating vaccine recipients report a transient reduction in breastmilk production post-vaccination [84,85,89] surveyed 4,455 breast-feeding mothers (1,714 received elasomeran) determined that 90.1% of mothers reported no change, 3.9% of mothers reported an increase in milk supply and 6.0% of mothers reported a decrease. In the large case series by Kachikis et al [84], 339 (5.0%) and 434 (7.2%) participants reported a decreased milk supply for less than 24 hours after the first and second dose, respectively.

Another topic of interest after vaccination during lactation is presence or absence of COVID-19 vaccine components in breast milk. A study by Golan *et al* [87] analyzed breastmilk samples from seven breastfeeding mothers (two received elasomeran) to determine if PEGylated protein was detectable in human milk after vaccination and they found no increased PEGylated protein concentrations in a subset of samples post-vaccination. A similar study by Golan et al [88] detected no mRNA in breastmilk of six breastfeeding mothers (one received elasomeran) 4-48 hours post-vaccination. Another study of 11 lactating persons who received an mRNA COVID-19 vaccine (five received elasomeran) within six months after delivery, showed the sporadic presence and trace quantities of COVID-19 within 48-hours after vaccination were detected in seven samples from five different participants; however, it was unknown if the detected mRNA is translationally active. ModernaTx, Inc. COVID-19 vaccines do not contain infectious virus and the minimal amount of vaccine components that might cross into breastmilk is likely to be inactivated by the infant's digestive system.

The literature also demonstrates robust secretion and transfer of maternal SARS-CoV-2 antibodies (mainly Immunoglobulin (Ig) A and IgG) induced by vaccination through breast milk, and some studies have showed these antibodies have neutralizing activity indicating potential passive protection to the infant, although the effectiveness is not yet established [90-94]. Although, there is still limited published data regarding elasomeran/imelasomeran and elasomeran/davesomeran during breastfeeding, the available data shows no increased risk of adverse outcomes among people vaccinated against SARS-CoV-2 during breastfeeding, supporting recommendations for vaccination of breastfeeding people against SARS-CoV-2. Post-marketing safety data with elasomeran are relevant to the Spikevax bivalent vaccines because these vaccines are manufactured using the same process. Clinical trials and post-marketing pharmacovigilance thus far demonstrate that the reactogenicity and safety profile of the bivalents are similar and to date, no new safety concerns for the bivalents elasomeran/imelasomeran and elasomeran/davesomeran have been identified.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals during pregnancy and while breastfeeding in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in pregnancy and while breastfeeding as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals during pregnancy and while breastfeeding through routine surveillance. An

updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.2.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports in ModernaTx, Inc. GSDB:

Reports of vaccinated lactating women, and children exposed to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran through breast milk (referred to as lactation cases) were identified from the ModernaTx, Inc. GSDB and are described in this PBRER#4. Data were reviewed by the following time periods: cumulative (18 Dec 2020–17 Dec 2022) and PBRER #4 reporting period (19 Jun 2022–17 Dec 2022).

Lactation cases were identified as any case containing at least one lactation-specific event or PT term identified in the SMQ: "Lactation-specific topics (including neonatal exposure through breast milk)" described in the PSSF 9.0 (Appendix 11.29). Identified lactation cases were pulled by case identification numbers to obtain all PTs reported; the PTs that are captured in the Lactation-specific topics (including neonatal exposure through breast milk) SMQ are referred to as lactation-specific events, and those that are not, are referred to as non-lactation-specific events.

The MAH reviewed and performed descriptive analyzes of all events reported for the reporting and cumulative period by type of vaccine (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). These analyses were also performed for lactation cases who received third or subsequent doses of elasomeran, lactation cases among 12-17 years old (adolescents) and 6-11 years old, as well as lactation cases among children younger than 6 years of age (breastfed children). For the calculation of TTO and the attribution of Dose Number to individual events an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a dose was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number. All fatal cases were medically reviewed and summarized; deaths among lactating women within one year of pregnancy completion is considered a pregnancy-specific death and will be discussed in Section-Pregnancy. Deaths among lactating women occurring more than one year after pregnancy completion or breastfed infants only with a possible exposure to a ModernTx, Inc a COVID-19 vaccine through breastmilk will be discussed here. However, the MAH receives reports in which fetal deaths among breastfeeding mothers are coded as fatal cases, originating from regulatory

reports or due to coding discrepancies. These fetal deaths will be summarized in the Section 16.3.5.1.

Finally, serious lactation-specific cases among children younger than 6 years were medically reviewed and summarized in Appendix 11.7.

Literature Search Methodology:

A targeted literature search for relevant publications on pregnancy and lactation and mRNA COVID vaccines was conducted on a weekly basis during the PBRER#4 reporting period (19 Jun 2022–17 Dec 2022) using PubMed of the National Library of Medicine; search strategy is documented in Appendix 12.1dAppendix 12.1dAppendix 12.1d. Review of the abstracts and titles was performed to identify articles relevant to the safety and benefit/risk profile of vaccination with, elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during pregnancy and lactation. Articles that were excluded were those regarding COVID-19 during pregnancy or lactation, COVID-19 infection of fetuses/neonates, COVID-19 vaccination coverage during pregnancy or lactation, outcomes including safety after COVID-19 vaccination during pregnancy or lactation that did not include a Moderna COVID-19 vaccine, acceptance of COVID-19 vaccination among pregnant or lactating persons, safety of non-COVID-19 vaccinations during pregnancy or lactation, and case reports or case series regarding the use of a Moderna COVID-19 vaccine during pregnancy or lactation. Only articles with information regarding the safety and benefit/risk profile of vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during pregnancy and lactation were reviewed and only those with new information or substantiative findings that affect the benefit/risk profile of the use of a Moderna COVID-19 vaccine during pregnancy are discussed in this PBRER.

16.3.5.2.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Lactation Cases Who Received Elasomeran

Cumulatively, ModernaTx, Inc. has received 2,036 lactation cases (6,922 events) of which 527 were serious cases (2,026 serious events); no cases reported a fatal outcome. There were 508 cases medically confirmed.

During the reporting period, 145 lactation cases (502 events) were identified with 20 serious cases (49 serious events): no cases reported a fatal outcome. There were 63 medically confirmed. A higher percentage (86.2%) of the cases reported during this reporting period were non-serious

compared to the cumulative period (74.1%).

No changes have been observed in the age distribution of the cases of lactating women and their breastfeeding children, cumulative and during the reporting period and it is consistent with the expected age of lactating women and their breastfeeding children (Table 16.29). Note there are some cases that describe mastitis in non-breastfeeding individuals, particularly older women. Additionally, cases coded as males likely represent children who were exposed to breastmilk from mothers who had been vaccinated with Moderna COVID-19 vaccines or data entry and/or coding error.

Table 16.29 Age Distribution for Lactation Cases (Including Breastfed Children) -elasomeran

Age Group All (11)	Prior to Review Period		Review Period		# of Total Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
0-5 months*	88	4.6	8	5.5	96	4.7
6 months - <2 years*	85	4.5	11	7.6	96	4.7
02-05 years	15	0.8	1	0.7	16	0.8
16-17 years**	1	0.1	0	0	1	0.0
18-24 years	32	1.7	1	0.7	33	1.6
25-39 years	1,085	57.2	69	47.6	1,147	56.3
40-49 years	144	7.6	8	5.5	152	7.5
50-64 years	20	1.1	3	2.1	23	1.1
65-74 years	4	0.2	2	1.4	6	0.3
75 years+	4	0.2	0	0	4	0.2
Missing	420	22.1	42	29.0	462	22.7
Grand total	**1,898**	**100.0**	**145**	**100.0**	**2,036**	**100.0**

* The cases under 5 years of age most likely represent children with exposure to elasomeran through breast milk or are a result of data entry and/or coding error.
** Cases in this age group will be discussed in the *Adolescent* section below.

The most frequently reported PTs during this reporting period were consistent with reactogenicity events and common breastfeeding issues such as suppressed lactation and mastitis. Although the frequency and ranking differed, the most frequently reported PTs are generally similar between the reporting period and the cumulative period.

After excluding the PTs that are not lactation-specific (i.e., not included in the SMQ: "Lactation-specific topics [including neonatal exposure through breast milk]), there were 144 lactation cases that had 166 lactation-specific events (13 serious) with 62 cases medically confirmed. Common

breastfeeding-related issues such as "Suppressed lactation," "Mastitis," and "Lactation disorder" remain the most frequently reported events for the reporting and cumulative period after exclusion of PTs that do not indicate an adverse lactation-specific event or outcome. There has not been a significant change in the pattern of PTs reported during the reporting period compared to cumulative period. Most of the lactation-related events were transient occurring within two days after vaccination.

Medical review of the HLT "Lactation Disorders" as performed for the reporting period and the data are similar with the previous cumulative experience; no concerning patterns or notable trends were identified.

All of the serious lactation cases identified as lactation-specific from this reporting period were medically reviewed; many cases lack information on clinical course, outcome, medical history, alternate etiologies/concurrent clinical events. To date, no concerning patterns or notable trends were identified.

Fatal Cases–elasomeran)

Cumulatively, there have been no reported fatal cases of vaccinated lactating women or of children under 6 years of age exposed to breastmilk from mothers who had been vaccinated with elasomeran. One fetal death case ([redacted]) had previously been coded as a fatal lactation case in BSSR 03 and that coding error has been corrected.

Subpopulation Analyzes

Lactation Cases Under 6 Years of Age–elasomeran)

Cumulatively, among children under 6 years of age with exposure to breastmilk from mothers who had been vaccinated with elasomeran (referred to as lactation cases among children under 6 years of age) a total of 208 lactation cases (503 events), with 31 serious cases (86 serious events) were reported; there were no cases reporting a fatal outcome. There were 46 cases medically confirmed. When restricted to only lactation-specific events, 208 cases were reported with 216 lactation-related events of which 23 were serious.

During the reporting period, among children under 6 years of age with exposure to breastmilk from mothers who had been vaccinated with elasomeran there were 20 cases (64 events) reported, with all the cases and events classified as non-serious. There were no fatal outcomes reported during the reporting period. When restricted to only lactation-specific events, the same 20 non-serious cases were included with 20 non-serious lactation-specific events.

Given there was no notable difference in the age, gender and most frequently reported PTs between the reporting and cumulative period as well as the small number of lactation cases among children under 6 years with exposure to breastmilk from mothers who had been vaccinated with elasomeran reported during this reporting period, only the cumulative data will be presented.

Cumulatively, the mean age of lactation cases among children under 6 years is 0.7 years (SD 0.6) and median age is 0.5 years (range 0.0 to 3.0). There were no differences in the number of reports involving males (67; 32.2%), and females (65; 31.3%); there were 76 cases (36.5%) with missing gender information. After excluding PTs that do not indicate an adverse lactation event/outcome, the most frequently reported clinical events were pyrexia, diarrhoea, and vomiting, which are consistent with reactogenicity events expected for elasomeran.

When TTO was known, most of the lactation-related events occurred within two days after vaccination and were transient Appendix 11.7.

Cumulatively, three cases of seizures occurring in infants exposed to elasomeran via breast milk were reported. Of the 3 cases, only one ([redacted]) reported experiencing pyrexia and seizures 26 days after the mother received Dose 1 of elasomeran. The other 2 cases ([redacted] and [redacted]) experienced seizures on the same day the mother received Dose 1 of elasomeran. There is limited information for all three reports and no additional information on outcomes have been received.

Lactation Cases Among Adolescents (12-17 Years of Age)

Cumulatively, one non-serious lactation-specific case ([redacted]) aged 17 years has been reported (previously reported in the PBRER #2). No clinical AEs were reported, and the case has two events: "Maternal exposure during breast-feeding", and "Product administration to patient of inappropriate age". There were no lactation cases among adolescents reported during this review period.

Lactation Cases with Third or Subsequent Doses of elasomeran

Cumulatively, 244 lactation cases were reported with 663 events of which 351 events were serious, after a third, fourth, or fifth dose of elasomeran. Of these 244 lactation cases, 23 were medically confirmed, 115 were serious cases, no case had a fatal outcome, and 61 cases (25%) had a lactation-specific event.

During the reporting period, 23 lactation cases were reported with 55 events of which 12 events were serious, after a third or fourth dose of elasomeran. The vast majority (92.7%) of events were

reported after the third dose and 4 events after the fourth dose. Of the 23 cases, three were medically confirmed, six were serious cases, no case had a fatal outcome, and 14 (60.9%) had a lactation-specific event. Of the 14 lactation cases with a lactation-specific event, there was only one serious case with one serious lactation-specific event of "Suppressed Lactation" after Dose 3 that was transient and short-lived.

Several of the cumulative cases reported represent the use of a heterologous booster dose or do not mention the vaccine type received as the primary series. The majority of events reported, regardless of the vaccine regimen originally received, are consistent with expected reactogenicity seen with elasomeran. No concerning patterns or notable trends were identified.

Lactation Cases After Receiving Booster Dose with elasomeran/imelasomeran

During the reporting period, five non-serious lactation cases who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran/imelasomeran were reported with 22 non-serious events (Table 16.30) of which six were lactation-specific events. When restricted to only lactation-specific events, the PTs reported in decreasing order were "Maternal exposure during breast-feeding", "Mastitis", and "Exposure via breast milk".

Table 16.30 Lactation Cases Who Received or Were Exposed to Breastmilk from Mothers Who Had Been Vaccinated with a Booster with elasomeran/imelasomeran, 19 Jun 2022 to 17 Dec 2022

Case ID	WW Identifier	Case Seriousness	Age	All Preferred Terms	Medical History	Concomitant Medications
[redacted]	[redacted]	Non-Serious	21 years	Erythema, Maternal exposure during breast-feeding, Pain of skin, Skin swelling	Breast-feeding	Not reported
[redacted]	[redacted]	Non-Serious	17 months	Exposure via breast milk, Pyrexia, Rash	PFIZER-BIONTECH COVID-19 VACCINE	Not reported
[redacted]	[redacted]	Non-Serious	39 years	COVID-19 immunisation, Feeling abnormal, Interchange of vaccine products, Malaise, Maternal exposure during breast-feeding,	Not reported	Not reported

Case ID	WW Identifier	Case Seriousness	Age	All Preferred Terms	Medical History	Concomitant Medications
				Vaccination site rash		
[redacted]	[redacted]	Non-Serious	37 years	Mastitis, Maternal exposure during breast-feeding	Breast-feeding	Not reported
[redacted]		Non-Serious	Reported as "elderly"	Chills, Fatigue, Headache, Malaise, Mastitis, Myalgia, Nausea	PFIZER-BIONTECH COVID-19 VACCINE	Not Reported

There has been no fatal lactation case after receipt of elasomeran/imelasomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/imelasomeran.

Lactation Cases After Receiving Booster Dose with elasomeran/davesomeran

During the reporting period, three non-serious lactation cases who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran/davesomeran were reported with eight non-serious events (Table 16.31) of which three were lactation-specific events. When restricted to only lactation-specific events, the PTs reported were "Exposure via breast milk" and "Maternal exposure during breast-feeding".

Table 16.31 Lactation Cases Who Received or Were Exposed to Breastmilk from Mothers Who Had Been Vaccinated with a Booster with elasomeran/davesomeran, 19 Jun 2022 to 17 Dec 2022

Case ID	WW Identifier	Case Seriousness	Age	All Preferred Terms	Medical History	Concomitant Medications
[redacted]	[redacted]	Non-Serious	Not reported	Maternal exposure during breast-feeding, No adverse event	Not reported	Not reported
[redacted]	[redacted]	Non-Serious	3 years	Erythema, Exposure via breast milk, Pain, Rash	Not reported	Not reported
[redacted]	[redacted]	Non-Serious	Not reported	Exposure via breast milk, Immunisation reaction	Not reported	Not reported

There has been no fatal lactation case after receipt of elasomeran/davesomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/davesomeran.

Literature Findings

Literature Summary of Safety of elasomeran During Lactation

The literature reviewed have not identified any elasomeran immunization safety concerns for lactating persons and/or children exposed via breast milk. Two-thousand, six hundred and twenty-two (2,622) articles were captured during the reporting period. After exclusion of articles on COVID-19 during pregnancy or neonatal period or lactation, COVID-19 vaccination coverage during pregnancy or lactation, COVID-19 vaccination acceptability by pregnant or lactating persons, safety of other COVID-19 vaccines apart from elasomeran during pregnancy or lactation, case reports and case series of safety of COVID-19 vaccines including elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy or lactation, 680 articles underwent full length review. Of the 680 articles identified to include regarding safety of elasomeran during pregnancy and lactation, five of them were among lactating persons. The findings from the 5 articles pertinent to safety of elasomeran for lactating persons and/or children exposed to breast milk during this reporting period did not provide new data to impact the benefit-risk profile of the use of elasomeran during lactation for both women and their children. Articles identified continue to reveal no significant safety concerns among vaccinated breast-feeding women and/or their breastfed children or new information about the transfer of maternal SARS-CoV-2 antibodies induced by vaccination to infants via breastmilk, supporting the favorable benefit-risk profile of the use of elasomeran during lactation for both women and their children.

16.3.5.2.5 Discussion

During the reporting period, ModernaTx, Inc. received 145 lactation cases, of which 20 were among children under 6 years of age with exposure to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran via breastmilk. There were no reported fatalities. while vaccination can induce cytokines, which can be passed via breast milk, vaccination while breast-feeding has not been linked to AEs in infants [95]. In fact, women with fever and illness are encouraged to continue breast-feeding given the positive impact of the transfer of antibodies, which has also been reported for COVID vaccines, as well as to support infant nutritional needs [96].

There was no lactation case reported among the 12-17 age group during this reporting period and there were 23 lactation cases reporting receipt of third or subsequent doses, with 60.9% reporting a lactation-specific event. Among the serious lactation-specific events, there was no clustering by dose or TTO and no concerning patterns or notable trends of events reported were identified. Reported events were mild and transient. The pattern of reports remained generally consistent during the reporting period when compared with the cumulative data. No new safety concerns were identified.

Where duration and outcome are available, many of the events (such as decreased lactation) occur within a day after vaccination, and most events were mild/moderate, transient events where information is available. Both in the GSDB and in the literature, reports of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhea, and pyrexia are consistent with the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran or what is expected in the general population [97] [96,98]. Review of the literature to date has not identified any safety concerns related to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccination during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated breast-feeding women and/or their breastfed children as well as transfer of maternal SARS-CoV-2 antibodies induced by vaccination to infants via breastmilk, supporting the favorable benefit/risk profile of COVID vaccination during lactation which continues to provide supporting evidence for HAs recommendations for the use of COVID-19 vaccines including Moderna COVID-19 vaccines during lactation.

The MAH is closely monitoring the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in this population through routine pharmacovigilance [66,99-101]. The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179

doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in Pregnancy and while Breastfeeding, the benefit-risk profile for elasomeran remains favorable.

- Review of the reports of exposure to elasomeran while breastfeeding reported in the GSDB indicates no increased risk in short-term adverse effects. In several epidemiological studies of breastfeeding mothers, very few reported to have concerns about the infant after the first dose and second dose. Few infant events are reported, with the majority of them non-serious and the most common side-effects seen among nursing children are poor sleep and irritability, which indicates they may have occurred as part of the background incidence rather than as a result of vaccine exposure.
- Review of the post-marketing safety data does not support a causal relationship between elasomeran, and AEs reported in breastfed infants to the GSDB.
- SmPC states "elasomeran can be used during pregnancy" and "elasomeran can be used during breastfeeding".
- Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines.
- The MAH continues to evaluate reported outcomes in infants while breastfeeding in reports of elasomeran and bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies.
- Use of elasomeran in pregnancy and while breast-feeding is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

- Use of the vaccine in breastfeeding individuals is already included in the product's labeling, and it is embedded in clinical practice and included in relevant health guidelines.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to Use in pregnancy and while breast-feeding.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals with Use in pregnancy and while breast-feeding in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in pregnancy and while breast-feeding as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals with Use in pregnancy and while breast-feeding through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.2.6 Conclusion

Based on the review of all new safety data received during the reporting period, compared to the cumulative data, for the cases of AEs in breastfeeding women and their children, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The safety of the use of Moderna COVID-19 vaccines among lactating people and events occurring in their breastfed children will continue to be monitored using the routine pharmacovigilance measures.

16.3.5.3 Long-Term Safety

16.3.5.3.1 Source of the New Information

As of the DLP of this PBRER, 26 CTs were ongoing 11 of which are sponsored by ModernaTx, Inc. Two CTs that assessed long-term safety completed during the reporting period. Cumulatively, 52,530 subjects have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.617.2, mRNA-1273.529), in conjunction with mRNA-1283 (including its variants mRNA-1283.211), or placebo in the mRNA clinical development program sponsored by ModernaTx, Inc. The 52,530 represents unique subjects.

16.3.5.3.2 Background Relevant to the Evaluation

Per protocols, the clinical development program has a safety follow-up period of 12 months in the ongoing studies that will assess long-term safety: mRNA-1273-P101 (DMID 20-0003), mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P903, and mRNA-1273-P904, and the completed study that assessed long-term safety: mRNA-1273-P201. Subjects are followed up for 24 months in the Phase 3 Study mRNA-1273-P301. In Study mRNA-1273-P301 the safety follow-up is based on a median

duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183 days (range: 1 to 218 days), or approximately 6 months. The follow-up time is through Day 209 for the Phase 1 Study mRNA-1273-P101 (DMID 20-0003) and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.

16.3.5.3.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The long-term safety profile remains to be characterized through continued trial follow-up, active surveillance for safety, a European post-authorization safety study, and routine pharmacovigilance.

16.3.5.3.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

No results to date.

16.3.5.3.5 Discussion

The long-term safety profile remains to be characterized. In addition to routine pharmacovigilance activities, results from the following studies will be used to evaluate long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Ongoing Studies:

- Study mRNA-1273-P903 (final CSR: 30 Jun 2023)
- Study mRNA-1273-P904 (final CSR: 31 Dec 2023)
- Study mRNA-1273-P203 (final CSR: 31 Jul 2024)
- Study mRNA-1273-P204 (final CSR; 31 Mar 2024)
- Study mRNA-1273-P205 (final CSR: 31 Dec 2023)
- Study mRNA-1273-P301 (final CSR: 31 Dec 2023)

Completed Studies:

- Study mRNA-1273-P201 (final CSR: 30 Sep 2022)
- Study mRNA-1273-101/ 20-0003 (final CSR Main Study: 01 Nov 2022)

16.3.5.3.6 Conclusion

As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor the 2 completed studies (mRNA-1273-P201 and mRNA-1273-P101) which are being assessed to characterize long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

16.3.5.4 Use in Immunocompromised Subjects

16.3.5.4.1 Source of the New Information

New information presented below includes analysis performed on cases received into the GSDB for immunocompromised individuals by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022.

16.3.5.4.2 Background Relevant to the Evaluation

Immunocompromised and/or Immunosuppressed people were excluded from CTs, thus this subpopulation constitutes missing information in the Spikevax RMP. The MAH has been monitoring the safety profile in this subpopulation through routine pharmacovigilance. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, countries are recommending a booster dose (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in immunocompromised individuals, especially now with the bivalent vaccines. The third dose of elasomeran recommended for immunocompromised patients is 100 ug dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 ug dose [102,103].

In general, public health and professional groups recommend COVID-19 vaccination for patients immunocompromised. These recommendations highlight the likely potential benefits of COVID vaccines in this population with the potential risk of more severe COVID infections, sequelae, and

impact on underlying immune-mediated diseases [104-107]. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals immunocompromised after vaccination with elasomeran, and they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran [108] [109]. Analyzes have found a higher risk of hospitalization or death from COVID-19 in those with a variety of immunocompromising conditions, including rheumatic diseases, hematological malignancies, solid organ transplants, and HIV [110,111]. Factors that increase the risk of severe COVID-19 in the general population, such as older age, chronic kidney disease, cardiovascular disease, and other comorbidities, are significant drivers of risk in immunocompromised individuals. Moreover, some immunodeficiencies seem to increase the risk above and beyond traditional risk factors [112]. Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in immunocompromised individuals in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of use in immunocompromised individuals as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in immunocompromised individuals through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.4.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for valid, clinical, and spontaneous case reports for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in immunocompromised individuals, received from health-care providers, HAs, consumers, and literature, for the review period (19 Jun 2022–17 Dec 2022) and cumulatively (18 Dec 2020–17 Dec 2022).

For the purposes of this PBRER#4, the following operational definitions were applied in the analysis of the immunocompromised/immunosuppressed subpopulation:

The "Immunocompromised Subpopulation": Specifically, cases were identified in the MAH GSDB for immunocompromised and immunosuppressed individuals using a past medical history of hematological malignant tumors SMQ, transplantation, primary/innate and acquired immunodeficiency syndromes (including Human Immunodeficiency Virus [90]) and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs.

The "General Population" (all elasomeran data in the ModernaTx, Inc. GSDB: This refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the ModernaTx, Inc's. GSDB. This data is used to compare the AEs and safety profile in the immunocompromised population vs. the general population.

Literature Search Methodology:

The MAH performed a focused search of PubMed for elasomeran/imelasomeran and elasomeran/davesomeran and immunocompromised subjects to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 11.8.

A total of 75 literature articles were retrieved using these search criteria. There was no published information from these articles that described new and potentially important safety information on the safety profile of elasomeran.

16.3.5.4.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases Reported for elasomeran

Cumulatively, there were 7,559 cases (31,444 events) in immunocompromised individuals, of which 2,936 were serious cases (11,514 serious events); there were 199 cases reporting a fatal outcome; 3,829 cases were medically confirmed.

There was a higher number of cases reported cumulatively in females (4,785; 63.3%) when compared to males (2,567;34.0%), with 207 cases (2.7%) missing gender information. Among the reported cases, the median age was 60.0 years with a range of 0.3 year to 101.0 years. Five hundred and seventy-one (571) cases had missing age information. The distribution of cases by age group is presented in Table 16.33 below.

Cumulatively, most of the events reported a resolved/ resolving outcome (13,482; 42.9%), with 8,482 events (30.2%) reported as not resolved. The majority of the cases continue to be reported by regulatory authorities (5,433;71.9%), with most of the cases coming from the United States (50.2%), UK (21.6%) and the Netherlands (8.0%).

During this review period, there were 812 cases (2,931 events) reported in immunocompromised individuals, of which 378 cases were serious (1,287 serious events); there were 12 cases reporting a fatal outcome. There were 269 cases medically confirmed.

Similar to the prior reporting period, during this reporting period there were more cases involving females (483 59.9%) compared to males (292;36.0%), with 37 cases (4.6%) missing gender information. The median age of reported cases was 59.0 years (range: 12.0 years – 95.0 years). Ninety-eight (98) cases had missing age information. The distribution of cases by gender (Table 16.32) and by age group (Table 16.33) is presented below.

Table 16.32 Distribution of Cases by Gender in the Immunocompromised Subpopulation (Review Period and Cumulative) – elasomeran

Patient Gender	Prior to Review Period		Review Period		Total of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Female	4,335	63.8	483	59.5	4,785	63.3
Male	2,293	33.7	292	36.0	2,567	34.0
Unknown	170	2.5	37	4.6	207	2.7
Grand total	**6,798**	**100.0**	**812**	**100.0**	**7,559**	**100.0**

During this review period, as in the previous reporting period, the distribution of cases by age showed that most events reported in the immunocompromised subpopulation occurred in individuals >50 years of age (606; 74.6%) (Table 16.33).

Table 16.33 Distribution of Cases by Age Group in the Immunocompromised Subpopulation (Review Period and Cumulative)

Age Group	Prior to Review Period		Review Period		Total # of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2	1	0.0	0	0	1	0.0
02-05Y	8	0.1	0	0	8	0.1
06-11Y	13	0.2	0	0	13	0.2
12-15Y	7	0.1	7	0.9	9*	0.1
16-17Y	12	0.2	3	0.4	15	0.2
18-24Y	175	2.6	12	1.5	183	2.4
25-39Y	840	12.4	93	11.5	931	12.3
40-49Y	842	12.4	91	11.2	921	12.2
50-64Y	1,909	28.1	244	30.0	2,139	28.3

Age Group	Prior to Review Period		Review Period		Total # of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
65-74Y	1,564	23.0	158	19.5	1,716	22.7
75Y+	953	14.0	106	13.1	1,052	13.9
Missing	474	7.0	98	12.1	571	7.6
Grand total	**6,798**	**100.0**	**812**	**100.0**	**7,559**	**100.0**

Note: Some data changes between prior reporting period and current may result due to case processing, including receipt of follow-up information
*of the cumulative 9 cases, there are five cases ([redacted], [redacted], [redacted], [redacted] and [redacted]) in 12-15Y age group which were reported during the Prior to Review Period but also captured in review period due to case processing changes. Overall, all there are nine cases cumulatively in this age group

During the review period, similar to the cumulative period, the most frequently reported PT in the immunocompromised subpopulation included fatigue, headache, pyrexia, chills, myalgia and nausea. These PTs were comparable to that reported in the general population and reflected expected reactogenicity (Table 16.34). Events of COVID-19 infection is included on the top 10 PTs reported during this reporting period (66; 2.3%) only for the immunocompromised subpopulation. This may be due to a decreased immunogenicity of vaccination and/or the susceptibility to constantly changing variants. This was observed only in individuals receiving elasomeran.

Table 16.34 Top 10 MedDRA Preferred Terms (PT) in the Immunocompromised Subpopulation vs. General Population elasomeran (Review Period and Cumulative)

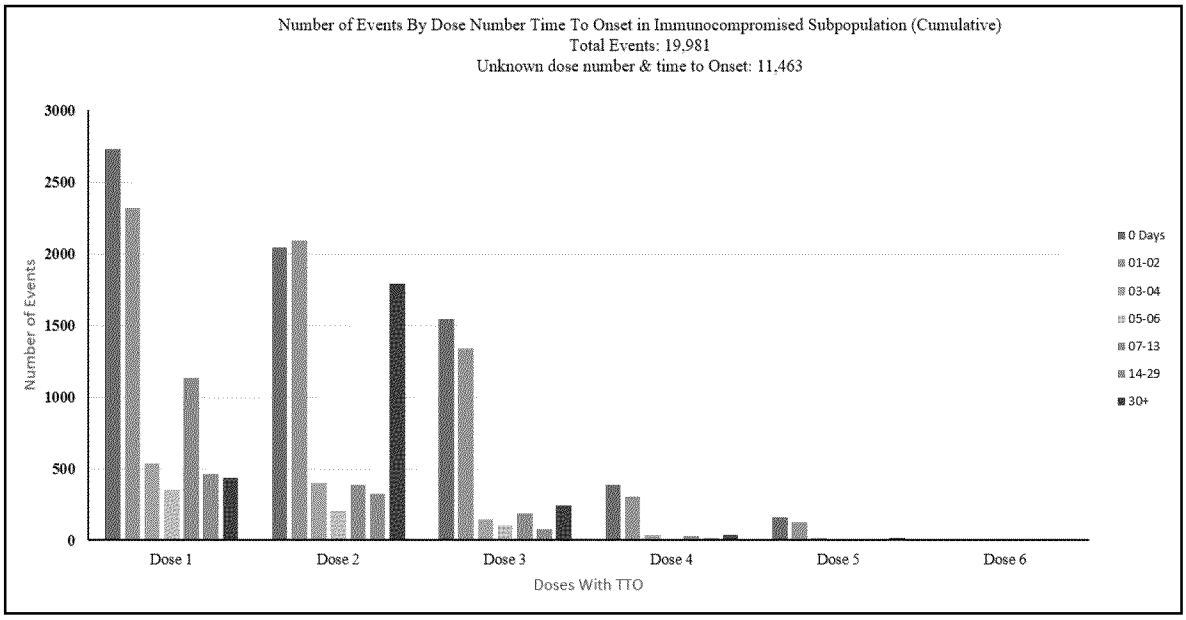
Review Period						Cumulative					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Fatigue	138.00	4.7	Headache	20,326	6.2	Fatigue	1,502	4.8	Headache	146,039	5.8
Headache	121.00	4.1	Fatigue	19,244	5.9	Headache	1,423	4.5	Pyrexia	139,460	5.5
Pyrexia	110.00	3.8	Pyrexia	18,726	5.7	Pyrexia	1,401	4.5	Fatigue	127,184	5.1
Nausea	78.00	2.7	Myalgia	13,373	4.1	Chills	981	3.1	Chills	97,683	3.9
Pain in extremity	74.00	2.5	Chills	11,127	3.4	Myalgia	841	2.7	Myalgia	91,510	3.6
Chills	70.00	2.4	Malaise	10,449	3.2	Nausea	837	2.7	Injection site pain	70,431	2.8

Review Period						Cumulative					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Myalgia	66.00	2.3	Injection site pain	10,156	3.1	Pain in extremity	691	2.2	Nausea	69,913	2.8
COVID-19	66.00	2.3	Arthralgia	8,647	2.6	Arthralgia	670	2.1	Malaise	67,283	2.7
Arthralgia	61.00	2.1	Nausea	8,346	2.5	Malaise	576	1.8	Arthralgia	55,998	2.2
Dizziness	52.00	1.8	Dizziness	8,036	2.5	Pain	548	1.7	Pain in extremity	53,606	2.1

= events, and % = % of events

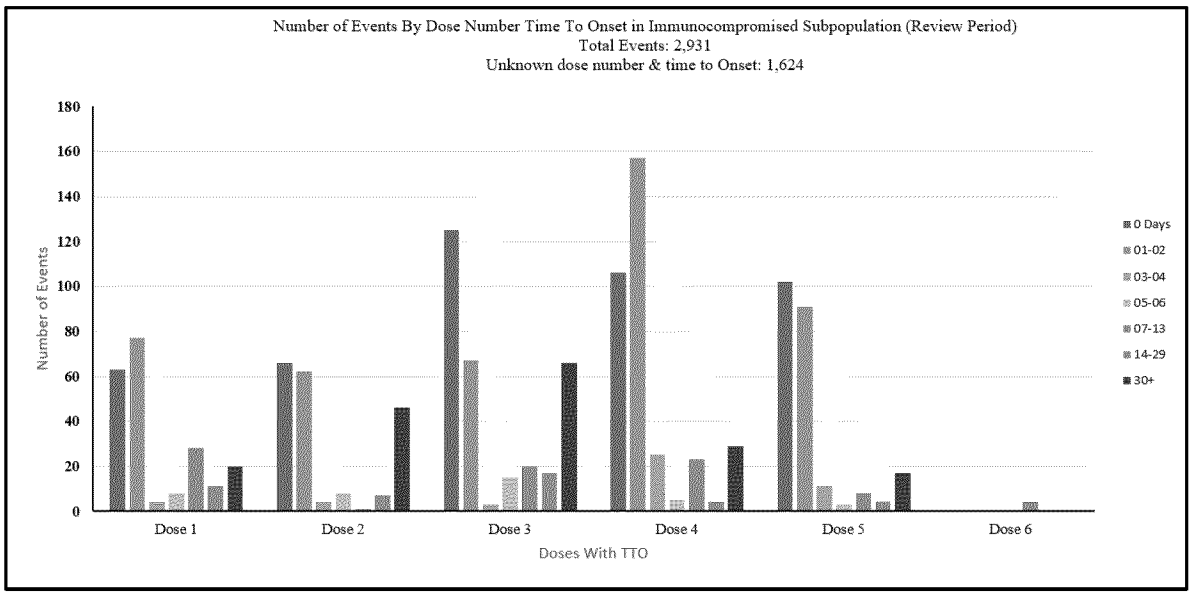
When dose number was known, during the review period, more events were reported after dose 4 (349; 11.9%) and dose 3 (313; 10.7%). This may reflect the general trend of increased uptake of booster doses. Another consideration for this difference was the high percentage of events that were missing dosing information (55.4%) during the reporting period (Figure 16-7 and Figure 16-8). When dose and TTO were known, events most frequently occurred within 2 days of any dose, both cumulatively (41.0%) and during the review period (31.3%), except for events reported after dose 2 that had a bimodal peak within 2 days and 30 days and beyond. Medical review showed that events reported after 30 days were associated with multiple morbidities.

Figure 16-7. Event Distribution by Dose Number and Time to Onset Immunocompromised Subpopulation elasomeran (Cumulative)



Source: ModernaTx, Inc. GSDB – PBRER 4 Spotfire dashboard

Figure 16-8. Event Distribution by Dose Number and Time to Onset Immunocompromised Subpopulation elasomeran (Review Period)



Source: ModernaTx, Inc. GSDB – PBRER 4 Spotfire dashboard

Note that cumulatively, a total of 2,020 cases (including 867 serious and 38 fatal cases) overlap between the subpopulation of those with a medical history of autoimmune/inflammatory diseases (MedHx autoimmune or inflammatory disorders (AI/ID) and immunocompromised/ immunosuppressed subpopulations, as many people with AI/ID are on immunosuppressive therapies. During the reporting period, 274 cases (including 130 serious and 2 fatal cases) overlapped. (Please also refer to the Section 16.3.5.7.

Serious Cases and Events in the Immunocompromised Subpopulation – elasomeran

Cumulatively, there were 2,936 serious cases (11,514 serious events) in immunocompromised individuals with 199 cases reporting a fatal outcome; 1,431 serious cases were medically confirmed. Cumulative there were more serious reports involving females (1,736; 59.1%) than males (1,142; 38.9%), and 2.0% had missing gender information. Among the serious cases, the median age was 59.0 years (range: 13 years-98 years), with 180 cases were missing age information.

Cumulative the majority of the serious cases were reported by regulatory authorities (85.9%), with the three countries to countries being the UK (39.1%), the United States (38.1%) and France (4.2%).

During the review period, there were 378 serious cases (1,287 serious events) reported in immunocompromised individuals, 116 cases were medically confirmed. There were no changes in the gender distribution of reports with more serious cases involving females (224; 59.3%) than males (142; 37.6%); 12 serious reports (3.2%) had missing gender information. The median age of reported cases was 60.0 years (range 13 years-89 years).

Similar to the prior period, the majority of the serious cases were reported by regulatory authorities (79.4%), with the same top three reporting countries: UK (56.6%), the United States (13.2%) and France (3.2%).

The top 3 SOCs during this reporting period were general disorders and administration site conditions (25.5%), nervous system disorders (12.8%), and musculoskeletal and connective tissue disorders (11.4%). The most frequently reported PTs were in line with those seen in the general population (including pyrexia, headache, fatigue, chills and myalgia), and reflect expected vaccine reactogenicity. COVID-19 infection was the most reported PT (1,509; 4.1%) for serious events in the general population during the reporting period, a difference with all events during the reporting

period where COVID-19 infection was identified on the top 10 events for immunocompromised individuals. (Table 16.35).

Serious events must be interpreted with caution, as not all events truly meet the definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases).

Table 16.35 Top 10 Preferred Terms (PT) for Serious Events in Immunocompromised Subpopulation vs. General Population elasomeran (Review Period and Cumulative)

Review Period - Serious Events						Cumulative - Serious Events					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Fatigue	65	5.1	COVID-19	1,509	4.1	Pyrexia	484	4.2	Pyrexia	16,087	3.8
Headache	57	4.4	Vaccination failure	1,151	3.1	Fatigue	452	3.9	Headache	15,358	3.7
Pyrexia	47	3.7	Fatigue	1,118	3.0	Headache	437	3.8	Fatigue	13,569	3.2
Nausea	35	2.7	Headache	1,070	2.9	Nausea	294	2.6	COVID-19	11,402	2.7
Pain in extremity	35	2.7	Pyrexia	967	2.6	Dyspnoea	287	2.5	Nausea	8,974	2.1
Myalgia	29	2.3	Syncope	889	2.4	COVID-19	254	2.2	Dyspnoea	8,772	2.1
Chills	28	2.2	Arrhythmia	797	2.1	Chills	253	2.2	Chills	8,454	2.0
Arthralgia	26	2.0	Myalgia	694	1.9	Dizziness	200	1.7	Myalgia	7,732	1.8
Dizziness	25	1.9	Dizziness	637	1.7	Pain in extremity	182	1.6	Syncope	7,428	1.8
Chest pain	25	1.9	Nausea	577	1.5	Myalgia	181	1.6	Dizziness	6,947	1.7

= serious events, and % = % of Total Serious Events

When dose number was reported, most serious events were reported after dose 4 (240;14.9%), and within 2 days post-vaccination, regardless of vaccine dose and reporting periods.

Fatal Cases in Immunocompromised Subpopulation – elasomeran

Cumulatively, reported cases with a fatal outcome (119 cases; 675 events) in immunocompromised individuals after elasomeran presented with a different demographic distribution when compared

to all reported cases with more cases reported for males (119; 59.8%) than females (79; 39.7%), and one case missing gender information. Median age of reported fatal cases was 72.0 years (Range: 21.0 years -98.0 years), with six cases missing age information. There were more fatal reports among individuals >65years old (141; 70.9%), after dose 2 (323; 47.9%) and after >30 days (292; 43.1%) regardless of dose number.

Cumulative, the top three PT with a specify term in fatal cases were COVID-19 (48; 7.1%), dyspnea (18; 2.7%) and COVID-19 Pneumonia (14; 2.1%. Of the 119 fatal cases, 111 were classified as "frail" (from past medical history and criteria (PT) included in "frail"), indicating that most of fatal cases had multiple risk factors and comorbidities (such as cardiovascular, diabetic, neurological disorders).

Most fatal case reports in immunocompromised individuals after elasomeran were from the United States (69.3%).

During the review period, the 12 fatal cases (21 serious events) reported for immunocompromised individuals, followed the same gender and age distribution as cumulative reports. There were no important differences related to dose number and TTO. There were only 3 specific PTs associated with the fatal reports received during the reporting period, including COVID-19 infection, cardiac arrest and vaccination failure. Four cases were classified as "frail" due to their past medical history and criteria PTs included in "frail", indicating that many of fatal cases had multiple comorbidities (such as cardiovascular, diabetic, or neurological disorders) (Table 16.36).

Table 16.36 Top 10 Fatal Events/Preferred Terms (in Fatal Cases in Immunocompromised Subpopulation (Reporting Period vs. Cumulative) - elasomeran

Report Period			Cumulative		
PT	# of Events	% of Total Events	PT	# of Events	% of Total Events
Death	5	23.8	Death	82	12.1
COVID-19	3	14.3	COVID-19	48	7.1
Cardiac arrest	2	9.5	Dyspnoea	18	2.7
Vaccination failure	2	9.5	COVID-19 pneumonia	14	2.1
			Respiratory failure	14	2.1
			Asthenia	12	1.8
			Cardiac arrest	12	1.8
			Hypoxia	12	1.8
			Pyrexia	12	1.8

Report Period			Cumulative		
PT	# of Events	% of Total Events	PT	# of Events	% of Total Events
			Vaccination failure	11	1.6

Evaluation of the fatal reports in immunocompromised individuals during the reporting period showed that they are heavily confounded by the patient's concurrent comorbidities, including hematologic disorders, cardiovascular disorders, diabetes, COPD, etc., which in almost all the fatal reports where information is provided, are important contributors to the fatal outcome. The medical review of all fatal cases received during the review period is presented in Appendix 11.8. Refer to Section 16.3.6.7.6 and Section 16.3.5.6.

Of the 12 fatal cases reported during the reporting period, 5 cases ([redacted], [redacted], [redacted], [redacted] and [redacted]) included a COVID-19-related diagnoses around the time of death which likely caused or contributed to the fatal outcomes. Table 16.37 summaries the seven fatal cases not associated with COVID-19 that were received during this reporting period in the immunocompromised subpopulation.

Table 16.37 Non-COVID-19 Fatal Cases in the Immunocompromised Subpopulation (Review Period) - elasomeran

Case ID/Age (Years) /Gender	ALL Preferred Terms	Medical History	Case Summary
[redacted] / 57-Years (Male)	Acute kidney injury, Adrenal insufficiency, Anaemia, Cardiac arrest, Cardiac failure, Diarrhoea, Encephalopathy, Haemolysis, Hypofibrinogenaemia, Hypotension, Hypothermia, Kaposi's sarcoma, Liver injury, Malaise, Mycobacterium avium complex infection, Nausea, Respiratory failure, Shock, Thrombocytopenia	[redacted]nfection(C); Left ventricular failure(C); Chronic kidney disease(C); Atrial fibrillation(C)	Comorbidities are strong confounders
[redacted] / 86-Years/ Female	Cardiomyopathy, Chest pain	Chronic lymphocytic leukaemia (CLL)	Case confounded by medical condition
[redacted] / 85-Years (Male)	Death	Atrial fibrillation(C); Cardiac assistance device user(C); Disease risk factor(C); Hypertension(C);	Multiple comorbidities are strong confounders

Case ID/Age (Years) /Gender	ALL Preferred Terms	Medical History	Case Summary
		Hypercholesterolaemia(C); Chronic lymphocytic leukaemia stage 1(C); Cerebrovascular accident(H); Peripheral venous disease(H); Osteoporotic fracture(C); Fractured sacrum(H); Camptocormia(H); Olfacto genital dysplasia(H); Cognitive disorder(C); Bladder neoplasm(H); Transurethral bladder resection; Bradycardia(H); Arrhythmia(H); Atrioventricular block first degree(H); Bundle branch block right(H); Osteoporosis(C); Asthma(C)	
[redacted] / 54-Years (Male)	Chronic lymphocytic leukaemia recurrent, Renal cancer recurrent	Chronic lymphocytic leukaemia (C); Renal cancer(C); Hypercalcaemic nephropathy(C); JANSSEN COVID-19 VACCINE	Case confounded by medical condition
[redacted] / 43-Years (Male)	Death	Drug abuser(H); [redacted] infection(C)	Confounded by immunosuppressive condition.
[redacted] / 63-Years (Female)	Death, Thrombotic thrombocytopenic purpura	Hypertension(C); DM(C); Chronic kidney disease (C); HIV infection(C); Thrombotic thrombocytopenic purpura(C); RITUXIMAB(H)	Multiple immunosuppressive conditions are strong confounders
[redacted] / 58-Years (Male)	Acute kidney injury, Altered state of consciousness, Cardiac arrest, Inappropriate schedule of product administration, Respiratory failure, Thrombotic thrombocytopenic purpura, Ventricular fibrillation	Hypertension(C); Obesity(C); [redacted] infection(C); Antiretroviral therapy	Case confounded by medical conditions

H: Historical Condition; C: Concurrent Condition

Subpopulation Analyzes

Use in Immunocompromised Children (<12 years old) – elasomeran)

Cumulatively, there were 22 cases (59 events) reported in immunocompromised individuals 0-11 years old. All cases were non-serious.

Cumulatively, in the age group 0-5 years, there were 9 cases with 28 events (all non-serious events). One case was reported as exposure via breastmilk in a child less than 2 years of age. Medical review of the cases showed that the height and weight information provided suggested these were adults and thus represented age miscoding errors. There were no reports in this age groups received during this reporting period.

Cumulatively, in the age group 6-11 years, there were 13 non-serious cases with 31 events All 13 cases were medically confirmed. Most of the reported cases involved males (10;76.9%), compared to females (3; 23.1%). The mean age of reported cases was 7.0 years (SD 0.6). All reported events were related to product administration issues. There were no reports in this age groups received during this reporting period.

Review of reports in immunocompromised children (<12 years of age) did not identify any new safety concerns in this subpopulation.

Use in Immunocompromised Adolescents (12-17 years y/o) – elasomeran

Cumulatively, there were reported 24 cases (66 events) of which 6 were serious cases (19 serious events) with no reports of fatal outcome; 19 cases were medically confirmed. Most of the reports involved males (12; 50.0%) compared to females (8; 33.3%) with 4 reports (16.7%) missing gender information. The mean age of reported cases was 15.3 years (SD: 1.5 years) Fifteen (62.5%) of cases were 16-17-year-olds, and 9 cases (37.5%) were 12-15-year-olds.

During this reporting period, there were 10 cases (22 events) reported in immunocompromised adolescents, of which 2 were serious cases (1 serious event); there were cases reporting a fatal outcome; 10 cases were medically confirmed. There were more reports involving males (6; 60%) than females (1; 10.0%) with 3 reports (30.0%) missing gender information. The mean age of reported cases was 14.5 years (SD: 1.5 years). When the outcome of the reports was known, most of them (12; 54.5%) were reported as resolved.

Both cumulatively and during the reporting period, the most frequently reported PT for immunocompromised adolescents was "Product administered to a patient of inappropriate age" most of those reports did not include an AE. Additional PTs included reactogenicity events including pyrexia, myalgia, nausea, headache, dizziness, etc. There were no reports of COVID-19 in the adolescent subpopulation.

Review of reports in immunocompromised adolescents (12–17 years of age) did not identify any new safety concerns in this subpopulation.

Elasomeran Dose 3 and Booster in Immunocompromised Patients

Cumulatively, 1,708 cases (4,797 events) were reported for immunocompromised individuals receiving a 3rd dose or a booster dose; there were 911 serious cases (2,766 serious events), and 19 cases reporting a fatal outcome. There were 491 cases medically confirmed. There were more reports involving females (1,101; 64.5%) than males (556; 32.6%), with 51 reports (3.0%) missing gender information. Most of the reports were in individuals >50 years of age (1,020; 59.7%). The median age of reported cases after dose 3 was 56.5 years, ranging from 7.4 years to 92.0 years.

During the reporting period, there were 332 cases (902 events) reported for immunocompromised individuals after a 3rd dose or a booster dose; there were 170 serious cases (516 serious events), with 2 cases reporting a fatal outcome; there were 86 medically confirmed cases. The reporting pattern of cases regarding age, and gender was similar to that seen in the cumulative period. (See Table 16.38).

Table 16.38 Distribution of Cases by Age in the Immunocompromised Subpopulation, elasomeran Dose 3 or Booster (Report Period and Cumulative)

Age Group	Prior to Review Period		Review Period		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
06-11Y	1	0.1	0	0	1	0.1
12-15Y	0	0	1	0.3	1	0.1
16-17Y	1	0.1	1	0.3	2	0.1
18-24Y	36	2.6	2	0.6	38	2.2
25-39Y	222	16.0	38	11.4	260	15.2
40-49Y	216	15.6	39	11.7	254	14.9
50-64Y	373	27.0	110	33.1	480	28.1
65-74Y	244	17.6	70	21.1	312	18.3
75Y+	176	12.7	54	16.3	228	13.3
Missing	115	8.3	17	5.1	132	7.7
Grand total	**1,384**	**100.0**	**332**	**100.0**	**1,708**	**100.0**

With the exception of COVID-19, the most common PTs reported in immunocompromised individuals after Dose 3 or a booster dose with elasomeran are reflective of expected reactogenicity (Table 16.39).

No differences were noted in serious cases in immunocompromised individuals after a 3rd dose or a booster dose of elasomeran.

Table 16.39 Top 10 Events/Preferred Terms (PTs) in the Immunocompromised Subpopulation vs. General Population, elasomeran Dose 3 and above (Reporting Period and Cumulative)

Review Period – Dose 3 and above						Cumulative - Dose 3 and above					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Headache	51	5.7	Pyrexia	3,581	6.6	Headache	263	5.5	Headache	13,919	6.5
Fatigue	45	5.0	Headache	3,495	6.5	Pyrexia	255	5.3	Pyrexia	13,004	6.1
Pyrexia	40	4.4	Fatigue	3,057	5.7	Fatigue	218	4.5	Fatigue	11,040	5.1
Dizziness	28	3.1	Myalgia	2,489	4.6	Nausea	146	3.0	Chills	9,069	4.2
Nausea	27	3.0	Chills	2,229	4.1	Chills	144	3.0	Myalgia	7,947	3.7
Pain in extremity	26	2.9	Malaise	2,013	3.7	Pain in extremity	127	2.6	Nausea	6,024	2.8
COVID-19	25	2.8	Dizziness	1,411	2.6	Myalgia	126	2.6	Expired product administered	5,503	2.6
Myalgia	23	2.5	Arthralgia	1,396	2.6	Arthralgia	115	2.4	Lymphadenopathy	5,459	2.5
Chills	20	2.2	Nausea	1,344	2.5	Dizziness	106	2.2	Malaise	5,018	2.3
Arthralgia	19	2.1	Lymphadenopathy	1,304	2.4	Expired product administered	105	2.2	Dizziness	4,839	2.3

Fatal Cases and Events - elasomeran 3rd dose or booster

During the reporting period, there were two cases with fatal outcomes reported in males in Switzerland and Taiwan (1 each). Their mean age was 64.0 (SD: 29.7).

During the reporting period, both fatal cases in the immunocompromised subpopulation occurred after dose 4, with TTO of 1-2 days and 14-29 days. This differs from the earlier reported TTO of 1-2 days in the general population, after Dose 3 or booster.

Use in Immunocompromised Subjects After Booster Dose with elasomeran/imelasomeran

Cumulatively there were 88 cases (323 events) reported in immunocompromised individuals after receiving a booster dose with elasomeran/imelasomeran. All these reports were received during the reporting period for this PBRER 4. There were 54 serious cases (173 serious events), with one case (4 events) reporting a fatal outcome; 9 cases were medically confirmed. Most of the events were reported as resolved/ resolving (176; 54.5%). There were more reports involving females (54; 61.4%) than males (31; 35.2%), with 3 reports (3.4%) missing gender information. Most of the cases reported in immunocompromised individuals were in individuals >50 years of age (73; 83.0%%). The distribution of cases by age group is presented in Table 16.40 below.

Table 16.40 Distribution of Cases by Age Group in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/imelasomeran (Report Period and Cumulative)

Age Group	Prior to Review Period		Review Period		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-24Y	0	0	1	1.1	1	1.1
25-39Y	0	0	8	9.1	8	9.1
40-49Y	0	0	6	6.8	6	6.8
50-64Y	1	100.0	16	18.2	16	18.2
65-74Y	0	0	22	25.0	22	25.0
75Y+	0	0	13	14.8	13	14.8
Missing	0	0	22	25.0	22	25.0
Grand total	**1**	**100.0**	**88**	**100.0**	**88**	**100.0**

The most frequently reported PTs in immunocompromised individuals receiving a booster dose with elasomeran/imelasomeran were considered reactogenicity event (fatigue, headache, pyrexia, chills, and Arthralgia) were comparable to the general population receiving a booster dose with elasomeran/imelasomeran. There was no difference in the PTs reported for the serious cases in immunocompromised individuals after elasomeran/imelasomeran (Table 16.41).

Table 16.41 Top 10 Preferred Terms (PT) in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/imelasomeran vs. General Population (Cumulative)

Cumulative Booster Dose with elasomeran/imelasomeran					
Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%
Fatigue	27	8.4	Headache	1,773	8.2
Headache	25	7.7	Malaise	1,612	7.5
Pyrexia	19	5.9	Fatigue	1,507	7.0
Chills	16	5.0	Myalgia	1,491	6.9
Arthralgia	12	3.7	Chills	1,426	6.6
Limb discomfort	12	3.7	Pyrexia	1,209	5.6
Nausea	11	3.4	Arthralgia	1,001	4.6
Malaise	10	3.1	Nausea	999	4.6
Injection site pain	9	2.8	Injection site pain	998	4.6
Myalgia	9	2.8	Injection site inflammation	455	2.1

When dose and TTO were known, events most frequently occurred within 2 days regardless of vaccine dose (57; 17.6%).

Table 16.42 Event Distribution by Dose Number and Time to Onset (TTO) in Patients Receiving Booster Dose with elasomeran/imelasomeran

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 3	***Subtotal***	***15***	***4.6***
	0 days	4	1.2
	01-02	4	1.2
	30+	7	2.2
Dose 4	***Subtotal***	***79***	***24.5***
	0 days	42	13.0
	01-02	26	8.0
	03-04	8	2.5
	07-13	3	0.9
Dose 5	***Subtotal***	***66***	***20.4***
	0 days	26	8.0
	01-02	27	8.4

Dose Number	TTO All Doses (Days)	# Events	% Events
	03-04	1	0.3
	05-06	6	1.9
	07-13	6	1.9
Unknown	***Subtotal***	***163***	***50.5***
	0 days	2	0.6
	01-02	8	2.5
	05-06	2	0.6
	14-29	2	0.6
	Event onset prior to first dose reported	1	0.3
	Missing	148	45.8
Grand total		**323**	**100.0**

Fatal Reports in Immunocompromised Individuals after receiving elasomeran/imelasomeran Vaccination:

Cumulatively, there was only one (1) fatal case reported in an immunocompromised individual after elasomeran/imelasomeran. Details of this case is described below:

Case# [redacted] **(TW-**[redacted] This is a spontaneous case concerning a 50-year-old male patient with medical history of multiple myeloma and bone marrow transplant, who two days after receiving a fifth dose with elasomeran/imelasomeran experienced, dizziness, cold sweat, abdominal bloating and cardiac arrest. He was dead before arriving hospital (reported as out-of-hospital cardiac arrest). The reported cause of death was cardiac arrest. An autopsy was not performed. No further clinical information was provided. The medical history of multiple myeloma and bone marrow transplant are strong confounders. This case is missing relevant information for concomitant medications and clinical course of events, hence assessed as WHO-UMC Unassessable due to the lack of information.

Use in Immunocompromised Subjects After Receiving Booster Dose with elasomeran/davesomeran

Cumulatively, there were 21 cases (69 events) reported in immunocompromised individuals after receiving a booster dose with elasomeran/davesomeran. All these reports were received during the reporting period of this PBRER 4. There were 3 serious cases (3 serious events); there were no cases reporting a fatal outcome. There were 11 cases medically confirmed. There were more

reports involving females (13; 61.9%) than males (7; 33.3%) with 1 case (4.8%) missing gender information. Most events of the cases reported in the immunocompromised individuals occurred in individuals >50 years of age (15; 71.4%). The median age of reported cases was 66.0 years, with range from 23.0 years to 83.0 years

The distribution of cases by age group is presented in Table 16.43 below.

Table 16.43 Distribution of Cases by Age Group in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/davesomeran (Review Period and Cumulative)

Age Group	Review Period		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases		
18-24Y	1	4.8	1	4.8
25-39Y	1	4.8	1	4.8
50-64Y	6	28.6	6	28.6
65-74Y	6	28.6	6	28.6
75Y+	3	14.3	3	14.3
Missing	4	19.0	4	19.0
Grand total	**21**	**100.0**	**21**	**100.0**

The most frequently reported PTs in immunocompromised individuals receiving a booster dose with elasomeran/davesomeran were considered reactogenicity event (fatigue, headache, pyrexia, chills, and Arthralgia). When compared to the general population these events were reported at a higher proportion.

Table 16.44 Top 10 Preferred Terms (PT) in the Immunocompromised Subpopulation Receiving Booster Dose with elasomeran/davesomeran vs. General Population (Cumulative)

Cumulative Booster Dose with elasomeran/davesomeran					
Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%
Pyrexia	6	8.7	Pyrexia	108	1.6
Fatigue	4	5.8	COVID-19	105	1.6
Headache	4	5.8	Pain in extremity	90	1.4
Accidental underdose	3	4.3	Vaccination site pain	88	1.3
Dizziness	3	4.3	Headache	81	1.2
Pain	3	4.3	Fatigue	80	1.2

Cumulative Booster Dose with elasomeran/davesomeran					
Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%
Chills	2	2.9	Chills	72	1.1
Decreased appetite	2	2.9	Underdose	69	1.0
Vaccination site erythema	2	2.9	Myalgia	68	1.0
Vaccination site swelling	2	2.9	Pain	64	1.0

When dose number was reported, there were more reports after dose 4 (20;29.0%), followed by dose 5 (15;21.7%) Table 16.45). When TTO was known, events most frequently occurred within 2 days after any dose.

Table 16.45 Event Distribution by Dose and Time to Onset (TTO) in Patients Receiving Booster Dose with elasomeran/davesomeran

Dose Number	TTO All Doses (Days)	Review Period		Grand total of # Events	Grand total of % of Total Events
		# Events	% of Total Events		
Dose 3	Subtotal	1	1.4	1	1.4
	0 days	1	1.4	1	1.4
Dose 4	Subtotal	20	29.0	20	29.0
	0 days	18	26.1	18	26.1
	01-02	2	2.9	2	2.9
Dose 5	Subtotal	15	21.7	15	21.7
	0 days	9	13.0	9	13.0
	01-02	6	8.7	6	8.7
Unknown	Subtotal	33	47.8	33	47.8
	Missing	33	47.8	33	47.8
Grand total		**69**	**100.0**	**69**	**100.0**

16.3.5.4.5 Discussion

A review of the data received during the reporting period of this PBRER, showed that events reported in immunocompromised individuals continue to primarily occur in individuals >50 years of age, with a higher number of reports involving females, as it is seeing in the general population, with a TTO of less than 7 days.

Review of the safety information included in the MAH's GSDB as well as the literature received during the reporting period of this PBRER did not identify any new safety concerns in immunocompromised individuals. Frequently reported events in the immunocompromised subpopulation were generally comparable to those seen in the general population and were related to reactogenicity events commonly seeing after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. During this reporting period, reports of COVID-19 infection were lower in the immunocompromised subpopulation compared to the general population. This might be due to a higher rate of booster administration in the immunocompromised subpopulation.

Currently, some countries have approved/authorized/recommend a third dose in the primary series as well as a fourth "booster" dose and fifth "second booster" in severely immunocompromised individuals, as well as a third booster dose in mildly immunosuppressed individuals (and the general population) due to waning of immunity and the emergence of new variants. A higher percentage of reports for Dose 3 and Dose 4 during the review period compared to the cumulative likely reflects increased booster vaccination uptake and reporting of booster cases in the immunocompromised subpopulation during this period.

Cumulative review of the safety information has not identified any patterns/trends or specific safety concerns in the immunocompromised population. Serious events and fatal reports are heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported AEs in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population. As of the DLP of this PBRER (17 Dec 2022), the review of the post-marketing safety data has not identified any patterns or specific safety concerns in the immunocompromised population.

The large scale use of elasomeran (and other COVID-19) vaccines through EUA is without historical precedent. As of the end of the reporting period of this PBRER, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of

elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in Immunocompromised individuals, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable.

- Review of the safety data in immunocompromised subjects reported in the GSDB indicates that the general pattern of commonly reported AEs in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population, rather than as a result of vaccine exposure.

- The MAH continues to evaluate "Use in Immunocompromised subjects" in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies.

- Throughout the world all the EUA received for elasomeran includes recommendations for additional doses for immunocompromised subjects

- Use of elasomeran in immunocompromised subjects is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

- Extended use of the elasomeran vaccines in immunocompromised individuals has provided extensive safety information in this subpopulation group to no longer be considered missing information.

- Use of the vaccine in immunocompromised individuals is already included in the product's labeling, and the use of elasomeran in immunocompromised subjects is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to 'use in immunocompromised subjects' as long-term safety is being kept as missing information.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in immunocompromised individuals in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in immunocompromised individuals as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in immunocompromised individuals through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.4.6 Conclusion

Given that this population is at an increased risk for severe COVID-19 infection, based on the analysis of all the safety data available as of 17 Dec 2022, the MAH considers cases included under the immunocompromised subpopulation to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and the benefits for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran far outweigh any possible vaccine-associated risks.

Based on the analysis of all the safety data received during the reporting period and cumulatively in the immunocompromised subpopulation, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The MAH will continue to monitor use in immunocompromised individuals using routine surveillance.

16.3.5.5 Interaction with Other COVID-19 vaccines (Heterologous Vaccine Schedule)

16.3.5.5.1 Source of the New Information

European Medicines Agency/PRAC requested that in this PSUR, the MAH present data, including literature, and discuss the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in relation to heterologous COVID-19 vaccines schedule. The data and discussion should be presented in relevant sections e.g., off-label use, or in addition to the already presented PSUR headline "Interaction with other vaccines (Heterologous Vaccine Schedule)".

16.3.5.5.2 Background Relevant to the Evaluation

Several vaccines have demonstrated efficacy against SARS-CoV-2 mediated disease (herein referred to as "COVID-19"), yet there are limited clinical data on the efficacy/safety or immunogenicity of heterologous vaccine regimens (including those employing different vaccine

platforms, such as vectored vaccines) [113,114]. Currently, various heterologous combinations of COVID-19 vaccines are being used under post- EUA, or post-market authorization, either as heterologous priming (heterologous-prime-boost) or heterologous boost. The heterologous prime-boost vaccination technique is not new as it has a history of deployment in previous outbreaks [115]. However, the difference for the COVID-19 vaccines is that there are different vaccine constructs as well as interchangeability of the mRNA vaccines.

Heterologous priming is also referred to as the "interchangeability" of vaccine products. In a scenario of heterologous priming schedules (commonly referred to as "mix and match" schedules), the second dose uses a different vaccine product than the first dose administered. According to the WHO, reasons for the utility of heterologous priming include "reducing reactogenicity," "increasing immunogenicity," and "enhancing vaccine effectiveness" [116]. However, the WHO also notes that "the most common reason for considering a heterologous COVID-19 vaccine as a second priming dose is lack of availability of the same vaccine in settings with limited vaccine supply or unpredictable supply" [116], the WHO advised that heterologous priming should only be implemented if there is documented "supporting evidence." In the case of heterologous boosting, a vaccine from a different vaccine platform is administered other than the vaccine used to complete the primary vaccine series [116]. In May 2022, WHO has continued with the recommendation of dosing with the heterologous schedule [117].

In 2021, the United States FDA and other developed countries recommended the use of a booster dose for COVID-19 vaccines in eligible populations. In the case of heterologous use in the United States, the FDA had authorized the Moderna COVID-19 Vaccine for use in eligible individuals "as a heterologous booster dose following completion of primary vaccination with a different available COVID-19 vaccine. For example, Pfizer-BioNTech COVID-19 Vaccine and Janssen COVID-19 vaccine recipients 18 years of age and older may receive a single booster dose of the Moderna COVID-19 Vaccine" [117].

COVID-19 vaccines emerging from different platforms differ in efficacy, duration of protection, and side-effects. This 'Mix and Match" landscape will become increasingly complex over time, with increasing number of booster doses. Heterologous prime-boost immunization strategies have the potential to augment COVID-19 vaccine efficacy. Kaku et al examined the immunity induced by either prime and boost with the adenoviral-vectored vaccine ChAdOx1 or prime with ChAdOx1 and boost with a messenger RNA (mRNA) vaccine and reported that heterologous mRNA booster immunization induced higher serum neutralizing antibody and memory B-cell responses against SARS-CoV-2 variants of concern (VOCs) compared with that of homologous ChAdOx1 boosting

[118]. The focus of this review for "Interaction with Other COVID-19 Vaccines/Heterologous Vaccines" data is on 1) Heterologous COVID-19 vaccine administration (i.e., interchange of vaccines ("Mix and Match") and booster; 2) Heterologous vaccine interactions (and other reported interactions, if any; and 3) Safety profile of elasomeran, elasomeran/imelasomeran and elosameran/davesomeran in relation to heterologous COVID-19 vaccines schedule.

Literature Search and Review

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and (Interaction with heterologous vaccines) to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 690 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.5.5.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTx, Inc. queried GSDB for the review period from 19 Jun 2022 to 17 Dec 2022, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following criteria: Heterologous interchange of vaccines.

A cumulative review of potential interaction of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran with other COVID-19 vaccines from other manufacturers was performed using the PT "Interchange of vaccine products" with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran including 4 criteria:

1. PT: 'Interchange of vaccine products'
2. Medical history of manufacturer's vaccine (AstraZeneca, Janssen, Pfizer-BioNTech, Other)
3. Concomitant Medication as in manufacturer's vaccine (AstraZeneca, Janssen, Pfizer-BioNTech, ModernaTx, Inc., Other)

4. Co-suspect as in manufacturer's vaccine (AstraZeneca, Janssen, Pfizer-BioNTech, ModernaTx, Inc., Other).

16.3.5.5.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more information about cases involving interaction with other COVID-19 vaccines (heterologous vaccine schedule) refer to Appendix 11.9.

Overview of Cases - Review Period (19 Jun 2022 to 17 Dec 2022) – Elasomeran

During the review period, there were 13,329 cases (66,025 events, 3,097 serious cases). There were 81 cases (208 events) with fatal outcomes. The majority of reported cases were by regulatory authorities (11,971; 89.8%); originated from the EEA (9,927; 74.5%) followed by the UK (1,625, 12.2%). A high proportion of reported cases were in females (9,170; 68.8%) as compared to males 3,940 (29.6%) and 220 (1.7) has unknown gender information. The most frequent age group for reported cases in the 25-39 years (3,489; 26.2%). The median age of reported cases was 47 years. There were only 65 (0.5%) reported cases in the pediatric age group (less than 12 years) and 43 (0.3%) reports for adolescent subpopulations (12-17 years) (Table 16.46). Of the 66,031 events, 19,718 events (29.9%) Not recovered, 16,021 events (24.3%) had resolved, while 11,612 events (17.6%) had resolving. There were 16,986 (25.7%) events with unknown/missing outcome (Table 16.49).

Table 16.46 Age and Gender Distribution "Interchange of Vaccine Product" Cases (Review Period: 19 Jun 2022 to 17 Dec 2022) – elasomeran

	Review Period							
	Female		Male		Unknown		Total	
Age Group	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases
< 2 years	8	0.1	9	0.1	2	0.0	19	0.1
2-4 years	3	0.0	7	0.1	2	0.0	12	0.1
5-11 years	21	0.2	13	0.1	0	0.0	34	0.3
12-17 years	19	0.1	21	0.2	3	0.0	43	0.3
18-24 years	504	3.8	130	1.0	6	0.1	640	4.8
25-39 years	2,643	19.8	826	6.2	20	0.2	3,489	26.2
40-49 years	1,960	14.7	692	5.2	6	0.1	2,658	20.0
50-64 years	2,132	16.0	1,021	7.7	24	0.2	3,177	23.8

Age Group	Review Period							
	Female		Male		Unknown		Total	
	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases
65-74 years	901	6.8	555	4.2	17	0.1	1,473	11.1
75+ years	485	3.6	371	2.8	18	0.1	874	6.7
missing	494	3.7	295	2.2	122	1.0	911	6.8
Grand Total	**9,170**	**68.8**	**3,940**	**29.6**	**220**	**1.7**	**13,330**	**100.0**

Note- There is overlapping of one case in two age groups

In the review period, The European Economic Area (EEA) reported the highest proportion of cases (9,927; 74.5%). This is due to Europe spearheading the massive global campaign to boost its population with COVID-19 vaccines. Case distribution by region is presented below in Table 16.47.

Table 16.47 Distribution of Interchange Vaccine Product Cases Reported by Region (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

Region	Review period cases	% Total Cases
European Economic Area	9,927	74.5
United Kingdom	1,625	12.2
Asia	543	4.1
Australia	514	3.9
United States	486	3.6
Canada	145	1.1
Latin America	46	0.3
Switzerland	40	0.3
Middle East	3	0.0
Grand Total	**13,329**	**100**

During the reporting period, the most frequently reported preferred terms (PT) for interchange vaccines were Fatigue 4752 (7.2%), Headache 4251 (6.4%) and Injection site pain 3554 (5.4%). These are all consistent with reactogenicity reactions expected after COVID-19 immunization. The top reported PTs (>2%) during the review period for "Interchange of Vaccines Products" continue to be consistent with those seeing in the previous reporting periods as well as cumulative and are presented in Table 16.48.

Table 16.48 Top PTs (>2%) for the Interchange of Vaccines by Events (Review Period: 19 June 2022 to 17 Dec 2022) elasomeran

PT	Event Counts	% Events
Fatigue	4,752	7.2
Headache	4,251	6.4
COVID-19 immunization	3,911	5.9
Injection site pain	3,554	5.4
Pyrexia	2,906	4.4
Myalgia	2,785	4.2
Malaise	2,371	3.6
Arthralgia	1,787	2.7
Dizziness	1,653	2.5
Chills	1,573	2.4
Nausea	1,495	2.3

In the review period, while a high proportion of reported events for "Interchange of Vaccines" were after Dose 3 (12,185; 18.5%), more than half (45,424; 68.8%) of the reported events had missing dose numbers. Most of the events during the reporting period were reported as recovered/ recovering (27,633; 41.8%) at the time of the report (Table 16.49). There were 83 cases (208 events) reported with a fatal outcome (0.3%)

Table 16.49 Number and Percentage of Events Reported after Interchange of Vaccines (Heterologous Vaccination) by Dose Number, Outcome (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

	Review Period	
	Events	
	N	%
Total	66,031	100
Dose number prior to onset		
Dose 1	1,078	1.6
Dose 2	5,252	8.0
Dose 3	12,185	18.5
Dose 4	1,767	2.7
Dose 5	318	0.5
Dose 6	5	0.0
Dose 7	2	0.0

	Review Period	
	Events	
	N	%
Unknown	45,424	68.8
Outcome		
Fatal	208	0.3
Not Recovered/Not Resolved	19,718	29.9
Recovered/Resolved	16,021	24.3
Recovered/Resolved with Sequelae	1,486	2.3
Recovering/Resolving	11,612	17.6
Unknown	16,986	25.7

Overview of Heterologous Vaccines Serious Cases by Manufacturer elasomeran

Of the 13,329 cases heterologous vaccines reported in the review period, 3,097 cases (23.2%, 15,391 events) were assessed as serious and 81 (2.6%) reported serious cases had fatal outcome. Among the serious cases reported, the highest number of cases were from Pfizer-BioNTech (2,381; 76.9%), AstraZeneca (435; 14.0%), Janssen (115; 3.7%) and other manufacturers (327; 10.6%). There was a female preponderance during the review period reported in serious cases (1,881; 60.7%) than males (1,154, 37.3%), while 62 (2.0%) reported cases were missing gender data values with most cases reported in the 50-64 years age group (872; 28.2%). Of the 15,391 serious events reporting during the review period, 2,856 events (18.6%) were resolved. Most events were seen after dose 3 (3,433; 22.3%) (Table 16.51).

Age distribution among serious interchange vaccine products is presented in Table 16.50; details by MAH further are described in their respective sections below under fatalities by interchange vaccine products (MAH).

Table 16.50 Age Distribution of Serious Cases by Manufacturers (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

Age	Pfizer-BioNTech		AstraZeneca		Janssen		Other	
	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases
< 2 years	3	0.1	1	0.2	0	0.0	0	0.0
2-4 years	0	0.0	0	0.0	0	0.0	0	0.0
5-11 years	1	0.0	1	0.2	0	0.0	1	0.3
12-17 years	11	0.5	0	0.0	0	0.0	0	0.0

Age	Pfizer-BioNTech		AstraZeneca		Janssen		Other	
	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases
18-24 years	79	3.3	8	1.8	1	0.9	2	0.6
25-39 years	453	19.0	49	11.3	17	14.8	33	10.1
40-49 years	420	17.6	39	9.0	20	17.4	33	10.1
50-64 years	620	26.0	156	35.9	40	34.8	107	32.7
65-74 years	312	13.1	85	19.5	14	12.2	68	20.8
75+ years	266	11.2	60	13.8	3	2.6	60	18.4
missing	216	9.1	36	8.3	20	17.4	23	7.0
Total	**2,381**	**100.0**	**435**	**100.0**	**115**	**100.0**	**327**	**100.0**

Note: There is overlap of cases between different age groups.

Serious events for interchange vaccines by dose and outcome are presented in Table 16.51. While a high proportion of reported events for "Interchange of Vaccines" were after dose 3, (9,475; 61.6%) of the reported events had missing dose numbers. A high proportion of the reported events had not resolved at the time of the report (5,188, 33.7%).

Table 16.51 Serious Events by Dose Number and Outcome Interchange Vaccine Products (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran

	Review Period	
	Events	
	N	%
Total	15,391	100
Dose number prior to onset		
Dose 1	455	3.0
Dose 2	1,069	7.0
Dose 3	3,433	22.3
Dose 4	749	4.9
Dose 5	208	1.4
Dose 6	0	0.0
Dose 7	2	0.0
Unknown	9,475	61.6
Outcome		
Fatal	208	1.4
Not Recovered/Not Resolved	5,188	33.7
Recovered/Resolved	2,856	18.6

	Review Period	
	Events	
	N	%
Recovered/Resolved with Sequelae	740	4.8
Recovering/Resolving	2,362	15.3
Unknown	4,037	26.2

There were no differences among the serious cases, when compared to the non-serious cases, regarding the most frequently reported PT (>2%events) with fatigue (770, 5.0%), headache (587, 3.8%), dizziness (403, 2.6%) and pyrexia (388, 2.5%) being the most commonly reported PTs. Most of the events reflect common and well-described reactogenicity of ModernaTx, Inc. elasomeran and other COVID-19 vaccines and were comparable or lower than the respective percentage of these events in the general population with elasomeran. Table 16.52 presents the top serious PTs by events/cases and their percentages for the reporting period.

Table 16.52 Top Serious PTs (>2%) by Number of Serious Events and Percentages for Heterologous Interchange During the Review Period (Review Period: 19 Jun 2022 to 17 Dec 2022)

PT	Event Counts	% Events
Fatigue	770	5.0
Headache	587	3.8
COVID-19 immunization	541	3.5
Dizziness	403	2.6
Pyrexia	388	2.5
Myalgia	362	2.4
Interchange of vaccine products	360	2.3
Malaise	327	2.1

Table 16.53 presents the top five (5) events reported. Pfizer-BioNTech primary series with ModernaTx, Inc. boosters had the highest cases across all doses and higher serious cases compared to other vaccines. The trend noted is an increasing rate of serious cases with increasing dose, which tapered by dose 7. Top PTs and their reporting rates were similar across all vaccines, except for AZ which had a higher rate of COVID-19 infection.

Table 16.53 Overview of Co-Administered COVID-19 Vaccines by Top 5 Reported Preferred Terms, and Dose Number, and Number of Reported Serious Cases (Review Period 19 Jun 2022 to 17 Dec 2022) elasomeran

Heterologous Co-Suspect	Top 5 PTs (# events; %)	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Unknown	# of Serious Cases
Pfizer-BioNTech COVID-19 vaccine	COVID-19 immunization (895; 8.2%) Pyrexia (610, 5.6%) Headache (557, 5.1%) Fatigue (535; 4.9%) Myalgia (363; 3.3%)	234	1496	3120	485	73	2	1	8401	2381
AstraZeneca COVID-19 vaccine	COVID-19 (294; 23.6%) Headache (37, 3.0%) Fatigue (32, 2.6%) Pyrexia (24, 2.0%) Arthralgia (22, 1.8%)	42	45	286	121	29	0	0	922	435
Janssen COVID-19 vaccine	COVID-19 (29, 7.4%) Fatigue (18; 4.6%) Headache (12; 3.1%) Injection site pain (10; 2.5%) Myalgia (10, 2.5%) Suspected COVID-19 (10, 2.5%)	12	133	41	7	0	0	1	270	115
Other vaccine Manufacturers	Arthralgia (21, 1.9%) Headache (21; 1.9%) Fatigue (20,	29	112	133	181	68	0	0	762	327

Heterologous Co-Suspect	Top 5 PTs (# events; %)	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Unknown	# of Serious Cases
	1.8%) Myalgia (20, 1.8%) COVID-19 (18; 1.6%)									

Note: There is overlapping of cases between multiple doses for all manufacturers

Overview of Fatalities for Interchange Vaccine Products elasomeran

During this review period, a total of 81 cases (208 events) of vaccine interchange with fatal outcomes were reported. Pfizer-BioNTech interchange had the highest fatal outcome (57; 0.5%). However, the outcomes are independent of doses distributed. Table 16.54 presents interchange fatalities by manufacturer.

Table 16.54 Frequency and Number of Reported Fatal Cases by Manufacturers of COVID Vaccines (Reporting Period 19 Jun 2022 to 17 Dec 2022) elasomeran

Manufacturer/ Co-Suspect	Total Cases	Fatal Cases	% per Vaccine
Pfizer-BioNTech	10,939	57	0.5
AstraZeneca	1248	17	1.4
Janssen	393	5	1.3
Other	1130	6	0.5

Note: There is overlapping of cases between different manufacturers

Overview of Cases for Interchange Vaccine Products after Dose 3+/booster elasomeran

During the reporting period, a review of cases including events after dose 3+/booster dose reported with co-suspect manufacturers' of COVID vaccines showed that the highest events were seen in age groups 25-39 for Pfizer-BioNTech and Other vaccines; 50-64 for AZ and Janssen. This may be explained by the demographics of administration of each vaccine product. The highest reports after dose 3+/booster were reported with Pfizer-BioNTech (10,829) followed by AstraZeneca (5,078) (Table 16.55).

Table 16.55 Number of Cases after Heterologous Vaccination by Age for Dose 3+ by Manufacturers of COVID Vaccines- elasomeran

Manufacturers	Co-Suspect Subpopulations	Case Counts
Pfizer-BioNTech COVID-19 vaccine	< 2 years	6
	2-4 years	2
	5-11 years	14
	12-17 years	59
	18-24 years	545
	25-39 years	3,404
	40-49 years	2,245
	50-64 years	2,333
	65-74 years	844
	75+ years	783
	missing	594
	Total Booster/3rd +Dose	10,829
AstraZeneca COVID-19 vaccine	<2 years	1
	2-4 years	0
	5-11 years	2
	12-17 years	0
	18-24 years	74
	25-39 years	542
	40-49 years	1,142
	50-64 years	2,024
	65-74 years	574
	75+ years	245
	missing	474
	Total Booster/3rd +Dose	5,078
Janssen COVID-19 vaccine	<2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	0
	18-24 years	15
	25-39 years	53
	40-49 years	46
	50-64 years	98
	65-74 years	37

Manufacturers	Co-Suspect Subpopulations	Case Counts
	75+ years	25
	Missing	17
	Total Booster/3rd +Dose	291
Other COVID-19 vaccine	< 2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	1
	18-24 years	38
	25-39 years	345
	40-49 years	239
	50-64 years	336
	65-74 years	223
	75+ years	174
	Missing	56
	Total Booster/3rd +Dose	1,412

Heterologous Interchange Vaccine Schedule with Booster Dose elasomeran/imelasomeran - Review Period (19 Jun 2022 to 17 Dec 2022)

During the review period, there were 88 cases (295 events) reported with 43 serious cases. There was 1 case with a fatal outcome. In this case ([redacted]) involving concomitant administration of influenza vaccine, alternative etiology is suspected of the reported events of myocardial infarction and acute kidney injury, given the patients advanced age (89-year-old female patient), multiple underlying relevant comorbidities (including hypertension, breast cancer, osteoporosis; pernicious anaemia) and polypharmacy which provide a more likely explanation for the reported events potentially leading to a fatal outcome.

The majority of reported cases were by regulatory authorities (68; 77.3%); originated from the UK (61; 69.3%) followed by the Asia (13, 14.8%) (Table 16.57). A high proportion of reported cases were in females (51; 58.0%) than males (34, 38.6%) and (3, 3.4%) were reported with unknown age. The most frequent age group for reported cases in the 65-74 years (24; 27.3%). The median age of reported cases was 67 years. There were only 1 (1.1%) reported cases in the pediatric age group (less than 12 years) and no reports for adolescent subpopulations (12-17 years) (Table 16.56). Of the 295 events, 46 events (15.6%) Not recovered, 143 events (48.5%) had resolved, while 39 events (13.2%) had resolving. There were 61 (20.7%) events with unknown/missing outcome (Table 16.59).

Table 16.56 Age and Gender Distribution "Interchange of Vaccine Product" Cases (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Age Group	Review Period							
	Female		Male		Unknown		Total	
	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases
< 2 years	1	1.1	0	0.0	0	0.0	1	1.1
2-4 years	0	0.0	0	0.0	0	0.0	0	0.0
5-11 years	0	0.0	0	0.0	0	0.0	0	0.0
12-17 years	0	0.0	0	0.0	0	0.0	0	0.0
18-24 years	0	0.0	0	0.0	0	0.0	0	0.0
25-39 years	7	8.0	2	2.3	0	0.0	9	10.2
40-49 years	4	4.6	4	4.6	0	0.0	8	9.1
50-64 years	12	13.6	2	2.3	0	0.0	14	15.9
65-74 years	13	14.8	10	11.4	1	1.1	24	27.3
75+ years	9	10.2	14	15.9	0	0.0	23	26.1
missing	5	5.7	2	2.3	2	2.3	9	10.2
Grand Total	**51**	**58.0**	**34**	**38.6**	**3**	**3.4**	**88**	**100.0**

Table 16.57 Distribution of Interchange Vaccine Product Cases Reported by Region (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Region	Review period cases	% Total Cases
United Kingdom	61	69.3
Asia	13	14.8
Canada	7	8.0
European Economic Area	7	8.0
Grand Total	**88**	**100**

In the reporting period, the most frequently reported preferred terms (PT) for interchange vaccines were fatigue (21, 7.1%), headache (17, 5.8%) and limb discomfort (16, 5.4%). These are all consistent with reactogenicity reactions seen in the general population; Limb discomfort is usually associated with the vaccinated arm and may represent vaccination site pain. The top PTs (>2%) reported for "Interchange of Vaccines Products" are presented in Table 16.58.

Table 16.58 Top PTs (>2%) event counts and percentages for the Interchange of Vaccines by Events (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

PT	Event Counts	% Events
Fatigue	21	7.1
Headache	17	5.8
Limb discomfort	16	5.4
COVID-19 immunisation	11	3.7
Interchange of vaccine products	11	3.7
Arthralgia	9	3.1
Pain in extremity	9	3.1
Malaise	7	2.4
Myalgia	7	2.4
Nausea	7	2.4
Pyrexia	7	2.4

In the review period, while a high proportion of reported events for "Interchange of Vaccines" were Dose 4 (89; 30.2%), more than half (155; 52.5%) of the reported events had missing dose numbers. Of the 295 reported events, 143 (48.5%) were resolved and 46 (15.6%) were not resolved at the time of the report (Table 16.59). Some of the underlying medical conditions that were noted included rheumatoid arthritis, hypertension etc., Refer to Appendix 11.8.

Table 16.59 Number and Percentage of Events Reported after Interchange of Vaccines (Heterologous Vaccination) by Dose Number and Outcome (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

	Review Period	
	Events	
	N	%
Total	295	100
Dose number prior to onset		
Dose 1	0	0.0
Dose 2	1	0.3
Dose 3	12	4.1
Dose 4	89	30.2
Dose 5	38	12.9
Dose 6	0	0.0

	Review Period	
	Events	
	N	%
Dose 7	0	0.0
Unknown	155	52.5
Outcome		
Fatal	2	0.7
Not Recovered/Not Resolved	46	15.6
Recovered/Resolved	143	48.5
Recovered/Resolved with Sequelae	4	1.4
Recovering/Resolving	39	13.2
Unknown	61	20.7

Overview of Heterologous Vaccines Serious Cases by Manufacturer Elasomeran/imelasomeran

Of the 88 cases heterologous vaccines reported in the review period, 43 cases (48.9%; 162 events) were assessed as serious and 1 (2.3%) reported serious cases had fatal outcome. Among the serious cases reported, the highest number of cases were from Others (20, 46.5%), Pfizer-BioNTech (17; 39.5%), Astrazeneca (6; 14.0%). There was a female preponderance during the review period reported in serious cases (25; 58.1%) than males (16, 37.2) while 2 (4.7%) reported cases were missing gender data values with most cases reported in the 75+ years age group (14; 32.6%). Of the 162 serious events reporting during the review period, 73 events (45.1%) were resolved and 28 (17.3%) had unreported outcome. Most events were seen after dose 4 for the interchange of vaccine products (62; 38.3%) (Table 16.61). Almost half of the events had an unreported dose number (72, 44.4%).

Age distribution among serious interchange vaccine products is presented in Table 16.60; details by MAH further are described in their respective sections below under fatalities by interchange vaccine products (MAH).

Table 16.60 Age Distribution of Serious Cases by Manufacturers (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Age	Pfizer-BioNTech		AstraZeneca		Other	
	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases
< 2 years	0	0.0	0	0.0	1	0.0

Age	Pfizer-BioNTech		AstraZeneca		Other	
	Cases	% Of total cases	Cases	% Of total cases	Cases	% Of total cases
2-4 years	0	0.0	0	0.0	0	0.0
5-11 years	0	0.0	0	0.0	0	0.0
12-17 years	0	0.0	0	0.0	0	0.0
18-24 years	0	0.0	0	0.0	0	0.0
25-39 years	1	5.9	0	0.0	1	5.0
40-49 years	2	11.8	1	16.7	1	5.0
50-64 years	3	17.7	2	33.3	4	20.0
65-74 years	5	29.4	2	33.3	4	20.0
75+ years	5	29.4	1	16.7	8	40.0
Missing	1	5.9	0	0.0	1	5.0
Total	**17**	**100.0**	**6**	**100.0**	**20**	**100.0**

Serious events by dose and outcome are presented in Table 16.61. The outcome for serious events that resolved were 73 events (45.1%), and that were not resolved were (27; 16.7%). There were 1 (1.2%) reported cases with fatal outcomes in the review period. An overview of the fatalities is described below.

Table 16.61 Serious Events Overview by Dose Number and Outcome for Interchange Vaccine Products (Review Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

	Review Period	
	Events	
	N	%
Total	162	100
Dose number prior to onset		
Dose 1	0	0.0
Dose 2	1	0.6
Dose 3	2	1.2
Dose 4	62	38.3
Dose 5	25	15.4
Dose 6	0	0.0
Dose 7	0	0.0
Unknown	72	44.4
Outcome		
Fatal	2	1.2

	Review Period	
	Events	
	N	%
Not Recovered/Not Resolved	27	16.7
Recovered/Resolved	73	45.1
Recovered/Resolved with Sequelae	4	2.5
Recovering/Resolving	28	17.3
Unknown	28	17.3

Among the serious cases, the most frequently reported serious PT (>2%) in the group of Interchange of vaccine products were fatigue (12, 7.4%), headache (7,4.3%), myalgia (6, 3.7%) and arthralgia (5, 3.1%). Most of the events reflect common and well-described reactogenicity of ModernaTx, Inc. elasomeran/imelasomeran and other COVID-19 vaccines. The percentage of all events of fatigue, headache, pyrexia, myalgia, and arthralgia were comparable or lower than the respective percentage of these events in the general population with elasomeran/imelasomeran. Table 16.62 presents the top serious PTs by events and their percentages for the reporting period.

Table 16.62 Top Serious PTs (>2%) by Number of Events and Percentages for Heterologous Interchange During the Review Period (19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

PT	Event Counts	% Events
Fatigue	12	7.4
Headache	7	4.3
Myalgia	6	3.7
Arthralgia	5	3.1
COVID-19	5	3.1
Dizziness	5	3.1
Nausea	5	3.1
Chest Pain	4	2.5
Dyspnea	4	2.5
Malaise	4	2.5

Table 16.63 Overview of Co-Suspect Manufacturers of COVID Vaccines by Dose Number and Serious Cases (Review Period 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Heterologous Co-Suspect	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Unknown	# of Serious Cases
Pfizer-BioNTech	0	0	3	20	5	0	0	35	17

Heterologous Co-Suspect	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Unknown	# of Serious Cases
AstraZeneca COVID-19 vaccine	0	0	1	5	0	0	0	6	6
Janssen COVID-19 vaccine	0	0	0	0	0	0	0	1	0
Other Manufacturers	0	1	1	8	9	0	0	14	20

Note: There is currently insufficient data to stratify by vaccine type and corresponding PT and there can be overlap of cases between the manufacturers.

During this review period, a total of 1 case (discussed above) of vaccine interchange with fatal outcomes were reported, However, the outcomes are independent of doses distributed. Table 16.64 presents interchange fatalities by manufacturer.

Table 16.64 Frequency and Number of Reported Fatal Cases by Manufacturers of COVID Vaccines (Reporting Period 19 June 2022 to 17 Dec 2022) elasomeran/imelasomeran

Manufacturer/Co-Suspect	Total Cases	Fatal Cases	Fatal %
Pfizer-BioNTech	47	0	0.0
AstraZeneca	11	0	0.0
Janssen	1	0	0.0
Other	29	1	3.4

Note: There is overlapping of cases between different manufacturers

During the reporting period, a review of cases including events reported with co-suspect manufacturers' of COVID vaccines is presented below. The demographics of administration of each vaccine product described below (Table 16.65). The highest events were seen in age groups 65-74 for Pfizer-BioNTech and Astrazeneca; 75+ for other vaccines. This may be explained by the demographics of administration of each vaccine product. The highest reports after dose 3+/booster were reported with Pfizer-BioNTech (28) followed by Janssen (23).

Table 16.65 Cases Distribution by Age by Manufacturers of COVID Vaccines (Reporting Period: 19 Jun 2022 to 17 Dec 2022) elasomeran/imelasomeran

Manufacturers	Co-Suspect Subpopulations	Subpopulation Case Counts
Pfizer-BioNTech COVID-19 vaccine	< 2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	0

Manufacturers	Co-Suspect Subpopulations	Subpopulation Case Counts
	18-24 years	0
	25-39 years	7
	40-49 years	6
	50-64 years	3
	65-74 years	8
	75+ years	4
	missing	0
	Total Cases	28
Janssen COVID-19 vaccine	< 2 years	1
	2-4 years	0
	5-11 years	0
	12-17 years	0
	18-24 years	0
	25-39 years	5
	40-49 years	6
	50-64 years	2
	65-74 years	6
	75+ years	3
	missing	0
	Total Cases	23
AstraZeneca COVID-19 vaccine	< 2 years	0
	2-4 years	0
	5-11 years	0
	12-17 years	0
	18-24 years	0
	25-39 years	0
	40-49 years	1
	50-64 years	2
	65-74 years	3
	75+ years	0
	missing	0
	Total Cases	6
Other COVID-19 vaccine	<2 years	1
	2-4 years	0

Manufacturers	Co-Suspect Subpopulations	Subpopulation Case Counts
	5-11 years	0
	12-17 years	0
	18-24 years	0
	25-39 years	1
	40-49 years	1
	50-64 years	4
	65-74 years	3
	75+ years	7
	missing	0
	Total Cases	17

Note: There is overlap of cases between the age groups

Heterologous Interchange Vaccine Schedule with Booster Dose elasomeran/davesomeran - Review Period (19 Jun 2022 to 17 Dec 2022)

During the review period, there were 8 cases (18 events). All the reported cases were spontaneous of which 17 originated from the United States. The case distribution was higher in males (4, 50.0%) than in females (3, 37.5%). The median age of reported cases was 55.5 years. There were no cases in adolescents and pediatric patients. Of the 8 cases, 6 cases were almost evenly distributed amongst the adult age groups and for 2 case the patient age was unknown. Of the 18 events, 7 events (38.9%) were Not recovered. There were 11 (61.1%) events with unknown/missing outcome. There are no cases with fatal outcome. The reported PTs with the use of elasomeran/davesomeran contained isolated reports of each event only and no specific safety patterns were seen.

16.3.5.5.5 Discussion

The landscape of heterologous/interchange vaccine increasingly is becoming complex over time, with increasing number of booster doses administered. Overall, case reports after heterologous "Mix and Match" booster with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccine have increased globally, due to the massive scale up of COVID-19 vaccination and advocacy for boosting. Based on the currently available safety data, the AE profile reported after booster dose in vaccine interchange has been generally similar to that seen in the general population and noted to be of similar reactogenicity events compared with the safety profile established in the primary series of elasomeran.

Notably, there has been an increasing trend in the use of interchange of vaccine products (Mix &Match and booster) for the global COVID-19 mass vaccination campaign, especially for the booster or more than 2 doses. Hence, a significant proportion of reported events were noted after dose 3+. However, the most frequently reported AEs raised no notable safety concerns and did not show any specific new patterns.

The analysis of the review period safety data reported for heterologous vaccines interchange did not find any new safety issue and showed that the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran is not different when used with other heterologous vaccines.

16.3.5.5.6 Conclusion

The data provided in this PBRER sufficiently describes the review period safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when used with other heterologous vaccines.

Based on the analysis of the review period safety data available as of 17 Dec 2022 for heterologous interchange of COVID-19 vaccines, including primary series vaccination as well as boosting, the MAH considers that heterologous priming schedule/Mix & Match and boosting-related events do not presently constitute a safety issue of concern.

The benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when used with other heterologous vaccines remains favorable. The MAH will continue to evaluate heterologous priming schedule/Mix & Match and boosting-related events using routine surveillance.

16.3.5.6 Use in frail subjects with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders

16.3.5.6.1 Source of the New Information

New information presented below includes analysis performed on cases received into GSDB by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022. ModernaTx, Inc. queried the GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran.

16.3.5.6.2 Background Relevant to the Evaluation

Frail patients are considered at higher risk of complications due to coronCOVID-19 infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. Since frail subjects with unstable health conditions and comorbidities were excluded from the registration trials, ModernaTx, Inc. is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Frailty refers to a state of vulnerability to stressors characterized by a decreased physiological reserve, resulting in poor health outcomes compared to individuals of the same chronological age [119].

There is growing evidence supporting the safety profile of the COVID-19 vaccine in immunocompromised patients, such as HIV-infected patients, diabetics, and patients with cardiopulmonary diseases, is similar to that in the general population. Presently, the US Centers for Disease Control and Prevention, British Society for Immunology, and various other governmental and professional societies and organizations endorse COVID-19 vaccination in the immunocompromised population. Overall, recommendations for use in patients with immunocompromising medical conditions and immunosuppressing medications on the efficacy of the vaccine may support the extrapolation into the frail subpopulation indicating potential benefits to outweigh theoretical risks. The frail population was the first subpopulation group vaccinated with elasomeran and other COVID-19 vaccines given that this population was recognized to have the potential for more severe complications due to COVID-19 infection. This same recommendation is still in place for vaccination against SARS-CoV2 and its variants.

Lupo-Staghellini et al [120] in a prospective, multicenter, national VAX4FRAIL study (NCT04848493) which evaluated vaccines in a large trans-disease cohort of patients with solid or hematological malignancies, and/or neurological, and/or rheumatological diseases demonstrated that frail patients who are candidates for mRNA COVID-19 vaccination should be reassured about the safety profile of vaccine strategy. They noted that AEs were in line with the reporting from the healthy cohort of subjects and national observatories, no evidence of worsening of the underlying disease was reported, and no concern on the adherence to the treatment program of the disease itself emerged from the prospective multicenter national study [120].

Connolly et al [121] is an observational cohort study examining approximately 325 frail patients with rheumatic and musculoskeletal diseases and taking immunomodulatory therapy; 51% received BNT-162b2 and 49% were vaccinated with elasomeran. The most common diagnoses were inflammatory arthritis (38%), systemic lupus erythematous (28%) and overlap connective

tissue disease (19%). Observed AEs were mild local and systemic reactions consistent with expected vaccine reactogenicity and occurred at a similar frequency as in the non-frail population [121].

Cavanna et al [122] is an observational study of 257 frail participants with solid tumor malignancies who received two doses of either elasomeran or BNT-162b2; 85.21% of subjects were taking active anti-cancer therapy. Mild local or systemic reactions consistent with symptoms of reactogenicity such as weakness, headache, fever, and muscle pain were reported by 33.46% of patients, with more severe AEs after the second dose, in line with AE reports in the healthy population [122].

Thus far, there have been no specific safety concerns identified for use of elasomeran in frail subjects with unstable health conditions and comorbidities. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals after vaccination with elasomeranor elasomeran/imelasomeran or elasomeran/davesomeran and they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran.

As of the DLP of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in frail individuals. Serious events and fatalities reported after vaccination are heavily confounded or may have been caused by underlying medical conditions. Otherwise, the general pattern of commonly reported AEs in those considered frail individuals or with unstable health conditions and comorbidities is comparable to the general population.

Based on all the information provided, the MAH is requesting to discontinue presenting analysis of events in frail subjects with unstable health conditions and comorbidities in each PSUR and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in frail subjects with unstable health conditions and comorbidities as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in frail subjects with unstable health conditions and comorbidities through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/ imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.6.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for reports of frail individuals using "Frail" custom search as defined in the ModernaTx, Inc. PSSF (see Appendix 11.29), which included subjects of

all ages with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders).

Literature Review

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeranand the frail subpopulation to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 60 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran in the frail subpopulation.

16.3.5.6.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on Frail cases please refer to Appendix 11.10.

Overview of Cases

Cumulatively, as of 17 Dec 2022, a total of 54,153 cases (246,375 events) were reported in frail subjects, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these, 37,792 cases (69.8%) were medically confirmed, 19,708 (36.4%) were serious, and 2,457 cases (4.5%) had a fatal outcome. The median age of frail subjects was 61.0 years (range: less than 1 year – 121.0 years); 1,161 reports were missing age information. There was a higher proportion of cases reported in females (36,452; 67.3%) compared to males (17,330; 32.0%) and 371(0.7%) were missing gender descriptor. The majority of cases were reported by regulatory authorities (83.0%) in the United States (70.9%), followed by France (6.6%), the UK (4.5%), and Germany (2.4%).

During the reporting period, there was approximately a 19% decrease in the number of reported cases in the frail subpopulation, compared to the prior period. There was a total of 5,078 cases (21,917 events) reported, representing 6.3% of the 80,461 cases reported in all populations in this reporting period. Of these 5,078 cases, 1,382 (27.2%) were medically confirmed, 1,671 cases (32.9%) were serious, and 103 cases (2.0%) had a fatal outcome. There were disproportionately more cases reported in females (3,304; 65.1%) compared to males (1,722; 33.9%), and gender was unknown in 52 cases (1.0%). The median age was 55.0 years, ranging from 0.2 years to 99.0 years.

Most cases in this reporting interval were reported by regulatory authorities (81.1%), with the highest contributors from Sweden (25.7%), Germany (22.4%), and the United States (11.6%).

Of the 5,078 frail cases in this interval period, 1,533 cases (30.2%) were in the elderly age group 65 years and older. See Table 16.66 below for age distribution.

Table 16.66 Age Distribution of Reports in the Frail Subpopulation this Reporting Period

Age Group	Review Period	
	# Cases	% of Total Cases
<2	3	0.0
02-05	2	0.0
06-11	5	0.1
12-15	24	0.5
16-17	22	0.4
18-24	135	2.7
25-39	874	17.2
40-49	836	16.5
50-64	1,452	28.6
65-74	867	17.1
75+	666	13.1
Missing	192	3.8
Grand total	**5,078**	**100.0**

The most frequently reported events in frail subjects by PT were in line with those seen in the general population and in line with expected reactogenicity with elasomeran. The most frequently reported PTs are listed below (Table 16.67).

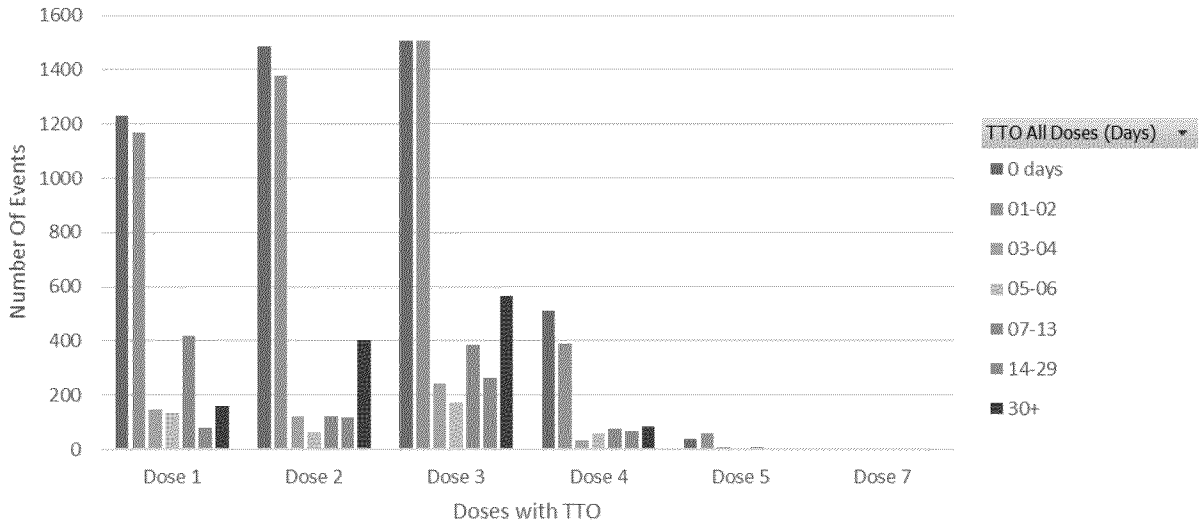
Table 16.67 Most Frequently Reported Events by Preferred Term in Frail Subjects >=2% (Review Period)

PT	# Events	% of Total Events
Fatigue	1,161	5.3
Pyrexia	1,061	4.8
Headache	1,004	4.6
Myalgia	754	3.4
Chills	696	3.2
Malaise	593	2.7
Vaccination site pain	562	2.6

PT	# Events	% of Total Events
Arthralgia	547	2.5
Nausea	530	2.4
Dizziness	528	2.4

During this review period, dose number was not reported for 40.6% of events. When reported, events were most frequently reported after dose 3 (4,643; 21.2%), followed by dose 2 (3,688; 16.8%). When TTO was known, clusters of events were frequently reported in the first two days (9,273; 42.3%) regardless of the dose number (Figure 16-9).

Figure 16-9 Number of Events by Dose Number Time to Onset in the Frail Subpopulation (Review Period)



Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard.

Outcomes

During the review period, 103 cases (2.0%) were reported with fatal outcome. When event outcomes were reported, 26.0 % (5692) of events had resolved, 16.0% (3511) events were resolving, and 32.4% (7104) events had not resolved. The outcome of 21.3% (4664) events was unknown as at the time of report. The category "Not recovered/Not resolved" is an overestimate as it reflects information submitted at the time of the report (generally without additional follow-up). Fatal cases are reviewed below.

Serious Cases in the Frail Subpopulation (Review Period)

There were 1,671 serious cases (7,438 events) in the frail subpopulation in this reporting period, of which 716 (42.9%) were medically confirmed. Serious cases in the frail subpopulation were most frequently reported in the elderly age 65 and over (39.1%), followed by in the 50 to 64-year-old age group (28.8%).

The age distribution of frail subpopulation in serious cases are presented below in Table 16.68.

Table 16.68 Age Distribution of Serious cases in the Frail Subpopulation in the Review Period

Age Group	Review Period	
	# Cases	% of Total Cases
<2	1	0.1
2-5	1	0.1
6-11	0	0
12-15	6	0.4
16-17	8	0.5
18-24	36	2.2
25-39	189	11.3
40-49	209	12.5
50-64	482	28.8
65-74	320	19.2
75+	333	19.9
Missing	86	5.1
Grand total	**1,671**	**100.0**

Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard.

Events in serious cases were missing dose or TTO information in 50.5% of instances. When known, most events were reported following the third dose (20.6%) followed by the second dose (11.9%), the first dose (7.9%) and the fourth dose (7.7%). The most frequently reported events terms in serious cases in the frail subpopulation were fatigue (3.7%), Headache (2.9%), Pyrexia (2.7%), and Dizziness and Dyspnoea (2.3% each). There were 113 events of arrhythmia (1.5% of all serious events), and 111 cases of chest pain (1.5%).

The 113 events of arrhythmia were reported in 101 cases, including one case with fatal outcome.

Gender distribution showed 65.3% of cases reported in females compared to 34.7% cases in males. The median age was 56.0 years (ranging from 27.0 years to 87.0 years). Most events of arrhythmia were reported following dose 3 (51 events), with 20 of these events occurring within 3 days of vaccination and 12 events occurring 30 or more days later. Most cases were confounded by underlying cardiovascular conditions, or respiratory disorders, type 2 diabetes, autoimmune diseases, or concomitant medications, or did not contain information regarding dose or TTO. No trends were seen with reported incidence of arrhythmia and age, dose number, or time of occurrence after vaccination.

The one case ([redacted]) with fatal outcome for arrhythmia was a report from a health authority of an 87-year-old female patient who experienced arrhythmia, bradycardia, and atrioventricular block complete after vaccination with elasomeran (TTO not known). She was previously vaccinated with tozinameran for her previous dose. The patient died within 7 days of vaccination; reported cause of death was bradycardia and cardiac arrest. No further information with regards to other medical history, concomitant medications or clinical course was provided. Case was confounded by underlying type 2 diabetes and advanced age.

Chest pain was reported in 111 events in 106 cases, including two cases with fatal outcome. Gender distribution showed slightly more cases in males (52.8%) than females (46.2%). The median age was 43.0 years (range from 13.0 years to 94.0 years). Most events of chest pain were reported following dose 3 (22 events) and dose 2 (17 events). Most events were reported within 5 days of vaccination. Cases were confounded by concomitant medications or underlying medical conditions also associated with chest pain, including cardiac disorders such as pericarditis, acute coronary syndrome, and myopathy, respiratory disorders such as asthma and COPD, chest injury, and upper gastrointestinal conditions such as gastrooesophageal reflux disease. No trends were noted among these reported cases with TTO, age, or dose number.

There were two cases with fatal outcomes reporting chest pain. One case ([redacted]) was a 53-year-old male patient with a history of myocardial infarction who experienced acute myocardial infarction, chest pain, and malaise an unknown time after a booster dose of elasomeran (as dose 3). The patient died 3 months and 17 days following vaccination. The second case ([redacted]) was reported in a 94-year-old female patient who experienced cough, pleural effusion, and chest pain 10 days after vaccination with her first dose of elasomeran. The patient died in the hospital two days later; no information was provided on course of treatment, autopsy results or cause of death. The event chest pain was confounded by the patient's advanced age and underlying hiatal hernia.

On reviewing the events outcome for serious cases in the frail subpopulation, 19.2% had resolved, 14.8% were resolving, while 34.7% had not resolved as at the time of report. Event outcome was unknown for 23.0% of events. The reported outcome "not recovered" is an overestimate as it reflects information submitted at the time of the report (generally without additional follow-up).

Fatal Cases in the Frail Subpopulation: Review Period

There were 103 cases with fatal outcome (266 events) in the frail subpopulation in this reporting period, of which 80 cases were medically confirmed, and 68.0% were in the elderly population 65 years of age or older. The median age in fatal cases was 75.5 years (range: 23.0 years - 99.0 years). Fatal cases were reported slightly higher (58.3%) in male than in females (41.7%). A high proportion of the fatal cases was reported by regulatory authorities (73.8%) in Japan (19.4%), the UK and France (11.7% each), and Germany (10.7%). The most frequently reported event terms in the fatal cases in the frail subpopulation were death (6.8%), cardiac arrest (3.8%), and COVID-19 (2.6%). Exceptionally, myocarditis was reported at a higher frequency in frail subpopulation (2.3%) compared to the general population (0.2%). Medical review of these cases of myocarditis revealed strong confounders/multiple risk factors and comorbidities, including COVID-19 infection, inflammatory diseases, and cardiovascular diseases.

Frail patients also have comorbidities or unstable health conditions which are subject to worsening and can lead to fatal outcomes. The most frequently reported concurrent diseases and concomitant medications cumulatively are presented Table 16.69 and Table 16.70. The most commonly reported concomitant medications are those that would be expected to be taken by those having the common comorbidities of cardiovascular disease and DM.

Table 16.69 Most Frequently Reported Comorbidities (Cumulative period)

Medical History	Cases	% Cases
Asthma	17,470	32
Drug hypersensitivity	15,557	28.5
Hypertension	13,911	25.5
Diabetes mellitus	10,819	19.8
Type 2 diabetes mellitus	5,274	9.7
Food allergy	4,335	7.9
Chronic obstructive pulmonary disease	4,188	7.7
Atrial fibrillation	4,011	7.3
Seasonal allergy	3,206	5.9

Medical History	Cases	% Cases
Hypothyroidism	3,082	5.6
Hypersensitivity	3,009	5.5
Gastrooesophageal reflux disease	2,913	5.3
Hyperlipidaemia	2,868	5.3
Obesity	2,411	4.4
Depression	2,291	4.2
Coronary artery disease	2,214	4.1
COVID-19	2,151	3.9
Anxiety	1,786	3.3
Multiple sclerosis	1,527	2.8
Chronic kidney disease	1,496	2.7
Arthritis	1,485	2.7
Osteoarthritis	1,465	2.7
Migraine	1,340	2.5
Rubber sensitivity	1,340	2.5

Note: Frequently reported 2.5% &above comorbidities
Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard

Table 16.70 Most Frequent Reported Concomitant medications (Cumulative period)

Concomitant Medication	Cases	Percent
ATORVASTATIN	5,882	4.4
LEVOTHYROXINE	4,554	3.4
LISINOPRIL	4,442	3.3
AMLODIPINE	3,853	2.9
METOPROLOL	3,549	2.6
CALCIUM	3,390	2.5
LOSARTAN	3,386	2.5
VITAMIN D3	3,167	2.3
METFORMIN	3,093	2.3
OMEPRAZOLE	3,065	2.3
SIMVASTATIN	2,525	1.9
MULTIVITAMIN [VITAMINS NOS]	2,375	1.8
SYNTHROID	2,297	1.7

Source: ModernaTx, Inc. GSDB - PBRER SpotFire Dashboard.

Subpopulation Analyzes: Review Period

Frail Subpopulation Children 0-5 years

During the reporting period, there were 5 cases (12 events) in the frail subpopulation in the age group 0-5 years, of which 2 cases were medically confirmed and serious, with no fatal outcomes. A slightly higher proportion 3 (60%) was reported spontaneous and 2 (40%) cases were reported by regulatory authorities. There were 3 cases reported from the United States and 1 each from Argentina and Sweden. Five events were reported following dose 1, two events after dose 2, and dose number was unknown for five events.

Two cases do not refer to children who received elasomeran but rather maternal exposure: one case ([redacted]) described a 2-month-old baby with a non-serious case of exposure via breast milk with reported diarrhea the same day as mother was vaccinated, which resolved after 3 days. The second case ([redacted]) was serious and described a congenital defect in a full-term infant, born one year and five months after mother's last dose. Mother was not pregnant at the time of the last dose of elasomeran. The other serious case ([redacted]) reported febrile convulsion in a four-year-old male child one day after his second dose. Patient symptoms were consistent with complex febrile seizures with lowered seizure threshold secondary to fever following COVID vaccination. Patient was admitted but no outcome information was available.

Frail Subpopulation Children 6-11 years

During the reporting period, in the age group 6-11 years of the frail subpopulation, there were five cases reported, of which all were medically confirmed, (16 events), none of the cases were serious or had a fatal outcome. Reported cases were predominantly in males (4; 80%); Three (60%) of these cases were reported by regulatory authorities in Argentina, and the other two cases were reported spontaneously in the United States. Four cases reported medication errors (administered to wrong age, accidental overdose, or expired vaccine given), one in which the child experienced pyrexia and diarrhea the same day as vaccination with little other information ([redacted]), one in which the concurrent non-serious events included feeling abnormal, illness, neck pain, and respiration abnormal, with no reported TTO, and a temporal relationship could not be determined ([redacted]), and two with no associated clinical AEs ([redacted]; [redacted]). The fifth case reported non-serious symptoms consistent with reactogenicity one day post-vaccination ([redacted]).

Frail Subpopulation Adolescents 12-17 years

During the reporting interval, there were 46 cases (164 events) in frail adolescents 12 – 17 years of age, of which 38 were medically confirmed, 14 were serious, and none had a fatal outcome. Similar to the 6 to 11-year-old frail age group, a large proportion of cases (56.5%) were reported from Argentina. Reported cases were similarly distributed among males and females (45.7% and 52.2% respectively). The most frequently reported medical history in these frail adolescents was asthma, reported in 34 of the 46 cases. The most frequently reported preferred terms (PTs) in frail adolescents 12 to17 years were mostly in line with expected reactogenicity for elasomeran (pyrexia, fatigue, headache etc), and similar to those seen in the general population, and in the entire frail subpopulation. Myo/pericarditis was the exception and was reported in eight of the 14 serious cases in frail adolescents (five male and three female). See Section 16.3.1.2.

Five of the six remaining serious cases were confounded by medical history/concomitant medications, describes events consistent with known reactogenicity with vaccines including elasomeran, or lack information on clinical course of treatment, outcome, or TTO.

The remaining case ([redacted]) describes a 17-year-old female patient with medical history of asthma and polycystic ovarian syndrome, no reported concomitant medications, who reportedly experienced pain, haematoma, and thrombocytopenia four days after her second dose of elasomeran. Patient was brought to the hospital after reported metrorrhagia, punctiform skin lesions in the neck and trunk, and spontaneous epistaxis. Platelet count was reported to be 50,000 (low). Patient was hospitalized and no information about ongoing clinical course of treatment or outcome of events was provided. According to the WHO-UMC causality assessment, this case is assessed as possible, based on temporal association, abnormal laboratory test, with reasonable time relationship to the product. However, information on concomitant medication is lacking.

Frail Patients After Dose 3 and above of elasomeran

During this reporting period, there was a 14% reduction in the number of cases reported after dose 3 and above, compared with the prior period. There were 1,664 cases (5,984 events, 419 (25.2%) medically confirmed), reported after dose 3 elasomeran, of which 611 cases (36.7%) were serious, and 41 cases (2.5%) had fatal outcome. Most events were reported after dose 3 (4,643; 77.6%) and dose 4 (1,217; 20.3%). Events after dose 3 and above in the frail subpopulation were most frequently reported with a TTO of less than 3 days.

The most frequently reported PTs after dose three and above in the frail subpopulation

(Table 16.71) were in line with expected reactogenicity with elasomeran and similar to those reported in the immediate period after dose 1 and 2. About 24% of reported events had resolved as at the time of reporting.

Table 16.71 Most Frequently Reported Preferred Terms after Dose 3 and above of elasomeran in the Frail Subpopulation (Review Period)

PT	# Events	% of Total Events
Fatigue	350	5.8%
Pyrexia	312	5.2%
Headache	300	5.0%
Myalgia	245	4.1%
Dizziness	205	3.4%
Chills	199	3.3%
Malaise	164	2.7%
Arthralgia	151	2.5%
Nausea	142	2.4%
Dyspnoea	130	2.2%

Source: ModernaTx, Inc. GSDB - PBRER Spotfire Dashboard.

Serious Cases After Dose 3 and above

During the review period, 611 serious cases (1507 serious events, 216 [35.4%] medically confirmed cases and 41 cases [6.7%] with fatal outcome) were reported in receipts of elasomeran dose 3 and above. A high proportion of these serious cases were reported by regulatory authorities (82.2%), mostly in Germany (31.8%), the UK (24.1%) and Japan (10.3%). There were more serious cases reported in females (55.3%), compared to males (43.5%). The median age was 63.0 years (range: 19.0 years to 99.0 years). Most serious cases were reported in elderly patients 65 years and older (275 cases; 45.0%), followed by age group 50-64 years (196 cases; 32.1%). Of the 1,507 serious events reported, a high proportion (60.1%) were after dose 3, and 32.7% after dose 4. Most events in serious cases with dose 3 and above were reported to have occurred less than 3 days post-vaccination.

Events outcomes in serious cases in the frail subpopulation were most frequently reported as "not recovered (40.1%) while 18.2% had recovered as at the time of reporting. The most frequent events reported in serious cases after dose 3 or above are more of reactogenicity that is known to be associated with elasomeran and other vaccines and are presented below (Table 16.72).

Table 16.72 Most Frequently Reported Preferred Terms (PT) in Serious Cases after Dose 3 and above elasomeran in the Frail Subpopulation (Reporting Period)

PT	# Events	% of Total Events
Fatigue	92	4.2%
Dizziness	88	4.0%
Headache	78	3.5%
Pyrexia	77	3.5%
Arrhythmia	52	2.3%
Dyspnoea	47	2.1%
Myalgia	45	2.0%
Nausea	44	2.0%
Malaise	44	2.0%

Fatal cases after booster (dose 3 or above) of elasomeran

There were 41 fatal cases (84 serious events) reported after dose 3 or above of elasomeran, of which 35 fatal cases were medically confirmed. There were more cases reported among males (68.3%) compared to females (31.7%), and most of the cases (31; 75.6%) occurred in elderly 65 years and older. The median age of reported fatal cases after dose 3 and above was 77.5 years (range: 23.0 years – 99.0 years). The most frequently reported events in these fatal cases were death (8 events; 9.5%), cardiac arrest (4; 4.8%), cardiorespiratory arrest, respiratory arrest, pyrexia, and sudden death (3 events; 3.6% each). The same number of events in these fatal cases occurred after dose 3 and dose 4 (41 events each), with two cases reported with dose 5. Fatal cases after dose 3 and above were strongly confounded by comorbidities (including DM, neoplasms/cancers, cardiovascular diseases, and COPD), and concomitant medications, such as anti-cancer therapies.

Overview of Cases in the Frail Subpopulation After Receiving Booster Dose with elasomeran/imelasomeran

During this reporting period, 305 cases (1,128 events, of which 396 were serious) were reported in the frail subpopulation with elasomern/imelasomeran, of which 166 cases (54.4%) were assessed as serious, 75 (24.6%) cases were medically confirmed, and 10 cases (3.3%) reported fatal outcomes. Cases were disproportionately reported in females compared to males (57.7% vs 40.3%, respectively) and were most frequently reported via regulatory authority (85.9%) from the UK (42.0%) and the Netherlands (39.0%). These cases reported a median age of 67.0 years (range from 0.0 to 99.0 years).

In this reporting interval, TTO was not reported for 58.1% of events. Of all 1,128 events, most were reported after the fourth and fifth dose (240 cases and 106 cases, respectively). This is expected as most patients receiving the bivalent booster have already received three or four previous doses. Most events were reported within less than 3 days post-vaccination, regardless of vaccine dose.

Case reports in the frail subpopulation represented 5.8% of all elasomern/imelasomeran cases (5,230 cases) across all populations in this reporting period, and serious cases in the frail subpopulation comprised 42.1% of all elasomeran/imelasomeran serious cases (940 cases) in all age groups during the reporting period.

The most frequently reported events in the frail subpopulation who received elasomern/imelasomeran were representative of expected reactogenicity (such as headache, fatigue, malaise, and chills) and were similar to those reported after elasomeran and in the general population.

Serious Cases After Receiving Booster Dose with elasomern/imelasomeran)

In this review period, 166 serious cases (396 serious events) were reported in frail patients receiving a booster dose with elasomern/imelasomeran. Of these 166 serious cases, 47 (28.3%) cases were medically confirmed, and ten cases (6.0%) had fatal outcomes. There were more cases reported in females (90; 54.2%) than in males (73; 44.0%), and three cases had missing gender information. These serious cases reported a median age of 69.0 years (ranging from 23.0 years to 99.0 years).

The PTs reported most frequently in serious cases after booster elasomeran dose(s) in the frail subpopulation were largely consistent with symptoms of expected reactogenicity, except for 15 events of dyspnoea, all of which reported confounding medical history of respiratory or cardiac disorders.

Among serious cases during the reporting period, events were most frequently reported after dose 4 (150 events; 37.9%), followed by dose 5 (64 events; 16.2%), and dose 3 (6 events;1.5%). Events in these serious cases occurred on average within three days of vaccination.

Overview of Fatal Cases with elasomern/imelasomeran

During the reporting interval, there were 10 cases with fatal outcomes (20 serious events) reported among frail recipients of elasomern/imelasomeran. The majority of these cases were medically confirmed (80.0%) and reported by regulatory authorities (80.0%). Most fatal cases were from

Taiwan (60.0%). Of the 20 events reported in fatal cases, nine events were reported after dose 5 and six events after dose 4, with an additional 5 events not reporting dose number. Time to onset for fatal cases with elasomern/imelasomeran varied from 1 to 18 days post-vaccination; average TTO was 6.7 days (SD 6.3).

A review of the 10 fatal cases reported in the frail subpopulation found them all to be strongly confounded by medical history of respiratory disorders, such as pulmonary fibrosis and COPD, cardiovascular disorders, including atrial fibrillation, acute coronary syndrome, CAD, and hypertension, diabetes, and renal disorders. There was no safety concern observed for reported events in fatal cases after administration of elasomern/imelasomeran in the frail subpopulation.

Overview of Cases in the Frail Subpopulation After Receiving Booster Dose with elasomern/davesomeran

During this reporting period, 120 cases (531 events, of which 41 were serious) were reported in the frail subpopulation after vaccination with elasomeran/davesomeran, of which 25 (20.8%) were assessed as serious, 54 (45.0%) cases were medically confirmed, and one case (0.8%) reported a fatal outcome. Cases were disproportionately reported in females compared to males (58.3% vs 39.2%, respectively), and a majority were reported spontaneous (99.2%), in the United States (91.7%), and fewer cases were reported in Puerto Rico (6.7%), with one case each reported in Canada and Japan. A higher proportion of cases were reported in females than males (58.3% vs 39.2% respectively). These cases reported a median age of 71.0 years, with a range from 4.0 years to 100.0 years.

In this reporting interval, most events were reported after dose 5 (130 events; 24.5%) and dose 4 (94 events; 17.7%). This is expected, as most patients receiving the bivalent booster .222 have already received three or four previous doses. Events were most frequently reported within 3 days of vaccination, regardless of dose number. Case reports in the frail subpopulation represented 5.1% of all elasomeran/davesomeran cases (2,348 cases) across all populations in this reporting period, and serious cases in frail patients comprised 21.0% of all elasomeran/davesomeran serious cases (119 cases) in all populations during the reporting period.

The most frequently reported events in the frail subpopulation who received elasomeran/davesomeran were representative of expected reactogenicity and were similar to those reported after elasomeran and in the general population. As elasomeran/davesomeran was more recently authorized, the data are limited.

Serious Cases After Receiving Booster Dose with elasomeran/davesomeran

In this review period, 25 serious cases (41 serious events) were reported in frail patients receiving a booster dose with elasomeran/davesomeran. Of these 25 serious cases, 48.0% of cases were medically confirmed, and one case reported a fatal outcome. A similar number of cases was reported in females (12 cases) and males (13 cases), though overall case counts were low. These serious cases reported a median age of 74.0 years (ranging from 42.0 years to 90.0 years).

The event terms reported most frequently in serious cases in the frail subpopulation after elasomeran/davesomeran were consistent with expected reactogenicity, except for atrial fibrillation (4 events), insomnia (3 events), and peripheral swelling (3 events) Most of these cases are confounded by reported underlying comorbidities, concomitant medications, and advanced age (average age of patients experiencing these three events was 75.5 years). There was no trend noted with dose number or temporal relationship. Medical review of the cases including events of atrial fibrillation found the events to be confounded by the patients' advanced age and underlying cardiovascular disease, including one patient with a history of atrial fibrillation. The three cases of insomnia refer to subjective "trouble sleeping" in relation to other reported events, such as Bell's palsy, abdominal pain, vertigo, and myalgia. All cases of peripheral swelling were confounded by multiple comorbidities and multiple concomitant medications.

Among serious cases during the reporting period, more events were reported after dose 5 (38 events) than dose 4 (22 events). An additional 79 cases were missing dose information. Events in serious cases occurred most frequently within two days of vaccination, as is the general trend with most doses.

Overview of Fatal Cases with elasomeran/davesomeran)

During the reporting interval, there was one case with a fatal outcome reported among frail recipients of elasomeran/davesomeran, reported spontaneously in the United States and was not medically confirmed. This case ([redacted]) was strongly confounded by comorbidities, including CAD with bypass and diabetes, and is discussed in detail in Section 16.3.6.7.6.

16.3.5.6.5 Discussion

The general pattern of commonly reported AEs in the frail subpopulation is consistent with expected elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran reactogenicity and comparable to those events observed in the general population and in patients with these

underlying conditions, especially the elderly. This is to be expected, as the elderly comprise 30.2% of the frail subpopulation in the reporting period.

As expected with the time course of reactogenicity events observed in the general population, event clustering in the frail subpopulation was observed in the three-day window after vaccination, irrespective of dose number.

Notably, reports of event term COVID-19 infection were much less prevalent in serious cases in the frail subpopulation (1.3%) compared to the general population (2.0%). This is likely due to the preferential roll out of boosters to this frail subpopulation in many countries. The most frequently reported event terms in serious cases in the frail subpopulation closely match those seen both in the elderly population and in the general population as a whole. Fatal cases in the frail subpopulation in the reporting period (2.0%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, which compromise a little less than a third of the frail subgroup.

Case reports across all available vaccines after doses 3 and above have increased as expected with uptake of booster doses administered in many countries. The total number of cases in doses 3 and above for elasomeran has dropped slightly, which is expected given the emergence of the bivalent boosters, as they are established as the preferred vaccine used for doses after the primary two dose series. With this increase in booster dosing, more events were reported after dose 3 than any other dose in this reporting period. The AE profile observed after booster doses in the frail subpopulation is similar to that seen in the general population, notably as reactogenicity events with similar TTO for dose 3 as after dose 1 and dose 2.

The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of

elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Use in frail individuals with unstable health conditions and comorbidities the benefit-risk profile for elasomeran remains favorable.

The MAH has monitored Use in frail subjects with unstable health conditions and comorbidities in each MSSRs as well as PSURs since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found:

Review of the safety data in frail subjects with unstable health conditions and comorbidities reported in the GSDB indicates that the general pattern of commonly reported AEs in those frail subjects with unstable health conditions and comorbidities is comparable to the general population, rather than as a result of vaccine exposure.

The MAH continues to evaluate Use in frail subjects with unstable health conditions and comorbidities in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies.

Use of elasomeran in frail subjects with unstable health conditions and comorbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines and no longer constitutes missing information in the safety profile of elasomeran.

Rationale for removal:

Extensive use of the elasomeran vaccines (>800 million individuals vaccinated with at least one dose), including in frail subjects with unstable health conditions and comorbidities, has provided extensive safety information in this subpopulation group to support its removal as missing information.

There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of elasomeran with respect to 'Use in frail subjects with unstable health conditions and comorbidities' as long-term safety is being kept as missing information.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in frail subjects with unstable health conditions and comorbidities in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in frail subjects with unstable health conditions and comorbidities as Missing Information from the EU-RMP, and to continue monitoring use in frail subjects with unstable health conditions and comorbidities through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.6.6 Conclusion

Based on the analysis of all the safety data received during the reporting period and cumulatively, ModernaTx, Inc. considers that events in the frail subpopulation occurring after the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran did not raise any safety issue of concern. ModernaTx, Inc. will continue to monitor events in the frail subpopulation using routine surveillance. The benefit-risk evaluation remains positive.

16.3.5.7 Use in subjects with Autoimmune and Inflammatory Disorders

16.3.5.7.1 Source of the New Information

Information presented below includes analyzes performed on cases from the subpopulation with known history of autoimmune and inflammatory disorders (MedHx AI/ID) received by ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022.

16.3.5.7.2 Background Relevant to the Evaluation

Use of elasomeran in individuals with AI/ID is an area of missing information in the RMP. Because there was limited data from CTs on the use of elasomeran in individuals with AI/ID, the MAH has been closely monitoring the safety profile of elasomeran in this population through routine pharmacovigilance.

Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for

immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, countries are recommending a booster dose (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in immunocompromised individuals, especially now with the bivalent vaccines. The third dose of elasomeran recommended for immunocompromised patients is 100 ug dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 ug dose.

In general, public health and professional groups recommend COVID vaccination for patients with AI/ID. These recommendations highlight the likely potential benefits of COVID vaccines in this population with the potential risk of more severe COVID infections, sequelae, and impact on underlying immune-mediated diseases [104-107]. Of note, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine and may be a risk factor for more severe COVID-19 disease [123,124]. Note, those AI/ID cases of patients who are on immunosuppressive therapy included in this section, are also included and overlap with the immunocompromised section of this PBRER (See the Section-Immunocompromised on "Use in Immunocompromised Subjects" and Section-Vaccine Failure "Vaccine Failure").

As it has been described before in previous PBRER, exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID vaccines [125-127]. While decreased immunogenicity for those on immunosuppressive therapies (IST) and the hypothetical risk of disease exacerbation have been recognized by professional and public health organizations, given the risk of the more severe COVID-19 and sequelae, vaccination is generally recommended with monitoring and management of any potential flare or exacerbation after vaccination.

Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran [120,128-130]. No SAEs were reported. Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in

individuals with autoimmune/ inflammatory conditions in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of Use in individuals with AI/ID as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals with AI/ID through routine surveillance. elasomeran. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.7.3 Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for valid, clinical, and spontaneous case reports for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran in people with a medical history of autoimmune and/or inflammatory disease (hereafter referred to as "MedHx AI/ID"), received from health-care providers, HAs, consumers, and literature, for the review period (19 Jun 2022–17 Dec 2022) and cumulatively (18 Dec 2020–17 Dec 2022).

Reports from individuals with a MedHx AI/ID were identified from ModernaTx, Inc. GSDB using the Immune-mediated/autoimmune disorders Standard MedDRA Query (SMQ) "Immune-mediated/autoimmune disorders SMQ" PTs identified in past medical history.

Data for this MedHx AI/ID subpopulation was also compared to the general population. The "General Population" (all elasomeran data in the ModernaTx, Inc. GSDB) refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the elasomeran GSDB.

Subsections describe MedHx AI/ID data for all, serious and fatal cases, as well as for adolescents and those who received Dose 3 or more than three doses. Serious events must be interpreted with caution, and many are not events meeting the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases.

To identify cases of potential flares after vaccination among cases with MedHx AI/ID, cases with MedHx AI/ID that also have: 1) events with PT captured in SMQ AI/ID or 2) PTs of "condition aggravated", "disease progression", or "disease exacerbation" were assessed. Medical review of the narratives of these cases revealed three scenarios: 1) flares of pre-existing AI/ID conditions; 2) new onset of an AI/ID condition in the setting of a different pre-existing AI/ID condition (i.e., an

individual may have several AI/ID conditions); 3) lastly, coding errors where MedHx PTs are misclassified as AI/ID conditions, or vice versa. ModernaTx, Inc. included an in-depth review of potential flares in PBRER#2, DLP 31 Dec 2021, and in-depth cumulative review of myasthenia gravis during PBRER#3.

Literature Methodology:

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelaosmeran and elasomeran/davesomeranand AI/ID using multiple search strategies to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 1,495 unique literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran.

16.3.5.7.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on cases involving autoimmune or inflammatory disorders please refer to Appendix 11.11.

Overview of MedHx AI/ID Cases Reported for elasomeran:

Cumulatively, there have been 22,478 cases (7,552 serious and 287 fatal) with 104,597 events (26,030 serious) among people with MedHx AI/ID; 12,660 cases were medically confirmed.

During this reporting period, there were 3,048 (1,083 serious, 14 fatal) cases with MedHx AI/ID with 13,299 events (2,931 serious) among people with MedHx AI/ID. Of the 3,048 cases, 600 were medically confirmed. Table 16.73 displays the MedHx AI/ID cases by review period and case seriousness.

Table 16.73 Cases With MedHx AI/ID by Seriousness - elasomeran

Case Seriousness	Prior to Review Period		Review Period		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Non-Serious	13,021	66.5%	1,965	64.5%	14,926	66.4%
Serious	6,563	33.5%	1,083	35.5%	7,552	33.6%

Case Seriousness	Prior to Review Period		Review Period		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Grand total	19,584	100.0%	3,048	100.0%	22,478	100.0%

During the reporting period, as in previous reporting periods, there were more reports involving females 76.8% (2,342; 76.8%) than males (654; 21.5%) with few reports missing gender information (52; 1.7%). The mean age was 51.7 years (SD 14.8), and the median age was 52.0 (range 0.2-93); Table 16.74 presents gender and age group distribution of the cases during the reporting period.

Table 16.74 Gender and Age Distribution of Cases with MedHx AI/ID, Reporting Period - elasomeran

Age Group	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
(0-5 Mths)[1]	0	0	0	0	1	0.0%	1	0.0%
06-11Y[2]	2	0.1%	0	0	0	0	2	0.1%
12-15Y[3]	4	0.1%	3	0.1%	0	0	7	0.2%
16-17Y[3]	5	0.2%	2	0.1%	0	0	7	0.2%
18-24Y	35	1.1%	15	0.5%	0	0	50	1.6%
25-39Y	485	15.9%	121	4.0%	2	0.1%	608	19.9%
40-49Y	508	16.7%	105	3.4%	5	0.2%	618	20.3%
50-64Y	750	24.6%	206	6.8%	8	0.3%	964	31.6%
65-74Y	313	10.3%	104	3.4%	9	0.3%	426	14.0%
75Y+	123	4.0%	68	2.2%	3	0.1%	194	6.4%
Missing	117	3.8%	30	1.0%	24	0.8%	171	5.6%
Grand total	**2,342**	**76.8%**	**654**	**21.5%**	**52**	**1.7%**	**3,048**	**100.0%**

[1]1 case noted for children 0-5 months pertains to exposure via breastfeeding; please refer to the Subsection on Children <12 years of age.
[2] Please refer to the Subsection on Children <12 years of age.
[3] Please refer to the Subsection on Adolescents 12-17 years of age.

[Note that cumulatively, a total of 2,020 cases (867 serious and 38 fatal) overlaps between the MedHx AI/ID and the immunocompromised/immunosuppressed populations, as many people with AI/ID are taking IST. During the review period, 238 cases (133 serious and 1 fatal) overlapped. (Please also refer to the Section 16.3.5.4 on Use in immunocompromised patients)].

During this reporting period, most of the cases were received from the EEA (1,943; 63.7%), followed by the United States (602; 19.8%). The cumulative gender, age and geographic distribution of cases is comparable to that in the reporting period.

Many of the most frequently reported events (pyrexia [4.6%], fatigue [5.0%], headache [4.9%], chills [3.1%], myalgia [3.1%], nausea [2.5%], and arthralgia [2.7%]) in the review period represent expected reactogenicity following elasomeran. The types and distribution of the most frequently reported events during this review period is generally similar to the distribution observed for the cumulative period, and when compared to the general population.

A difference from the previous reporting period, during this review period, more events were reported after Dose 3 (2,389; 18.0%) compared to cumulative reporting for these doses in MedHx AI/ID population; this is likely reflective of the general trend of increased uptake of booster doses. When time to onset was known, the same pattern observed in the previous reporting period continued with more cases reporting a TTO within less than 7 days after vaccination (6,339; 47.7%), and mostly within 0 to 2 days (5,690; 42.8%) after vaccination, regardless of dose number. Same reporting trend was observed for cumulative reports (0 to 6 days: 62,036; 59.3%; 0 to 2 days: 54,776; 52.4%).

Serious Cases and Events - elasomeran)

Cumulatively, there have been 7,552 serious cases (26,030 serious events) after elasomeran among people with MedHx AI/ID; 4,135 cases were medically confirmed.

During the review period, 1,083 serious cases (2,931 serious events) with MedHx AI/ID (14 cases reported a fatal outcome) were reported. Of the 1,083 serious cases, 303 were medically confirmed. Same reporting pattern was observed for serious cases regarding reported gender, with more cases involving females (775; 71.6%) than males (280;25.9%), there were 28 reports (2.6%) with missing gender information. The mean age was 54.9 years (SD 14.8), the median age was 55.0 years (range, 7.0 to 93.0) and 5.7% (62) cases were missing age information. The gender and age

distribution for the cumulative period is similar to the reporting period.

The most frequently reported serious events by cases with MedHx AI/ID during this review period as well as cumulatively, reflect expected reactogenicity events, such as fatigue, headache, pyrexia, myalgia, arthralgia, dyspnoea, nausea, and chills. The types and distributions of the events were generally similar to the most frequently reported serious events cumulatively in cases with MedHx AI/ID as well as in the general population.

Fatal Reports - elasomeran)

During the reporting period, 14 cases (31 events) with MedHx AI/ID had a fatal outcome; 10 fatal cases were medically confirmed. There were no important differences for the cases reporting a fatal outcome regarding gender, with 6 cases (42.9%) involving males, and 7 (50.5%) cases involving females. There was 1 (7.1%) report with missing gender information. The mean age for these reports was 66.2 years (SD: 24.5) and median age was 75.5 years (range 13.0-89.0) and 14.2% (2/14) were missing age data.

During the reporting period, out of the 14 fatal cases reported, there were 9 (64.3%) cases that are considered "frail" persons defined by comorbidities and age. These cases included comorbid conditions such as hypertension, Type 2 DM, COPD, arteriolosclerosis, hyperlipidemia, and chronic kidney disease. The median TTO was 3 days (range 1-181) during the reporting period.

All cases reporting a fatal outcome during the reporting period are heavily confounded by concurrent medical history and according to the reported cause of death, most of them are considered unlikely related to vaccination (Natural causes, Prostate cancer, COVID-19 infection, HV infection and chronic kidney disease stage 3, SLE, etc.). A medical review of all fatal cases in MedHx AI/ID cases received during the review period is presented in Appendix 11.11. Refer to Section 16.3.6.7.6 (Elderly), and Section 16.3.5.6 (Frail).

Use Among Persons with MedHx AI/ID Who Received a 3rd or Booster Dose of elasomeran

Cumulatively, there have been 2,594 (9,464 events) cases with MedHx of AI/ID after a 3rd Dose or booster dose, with 591 cases medically confirmed. There were 1,273 serious cases (3,928 serious events) with 23 cases reporting a fatal outcome. There were more reports involving females (1,997; 77.0%) than males (558; 21.5%), with 39 reports (1.5%) missing gender information.

During the reporting period, there were 881 (3,140 events) cases with MedHx AI/ID after Dose 3 or a booster with 119 cases medically confirmed. There were 337 (735 serious events) serious

cases with 3 fatal reports. Following the same trend observed cumulative, there were more reports involving females (680; 77.2%) than males (191; 21.7%), with 10 reports (1.1%) with missing gender data.

There were no differences of the most frequently reported PTs during the review period, for cases with MedHx AI/ID regardless of the dose number. Table 16.75 presents cumulative distribution of most frequently reported PTs among MedHx AI/ID cases receiving elasomeran (combined data for all doses of elasomeran) versus Dose 3 or booster doses of elasomeran.

Table 16.75 Most Frequently Reported PTs Among MedHx AI/ID Cases Receiving elasomeran Cumulative versus ≥ 3 Doses of elasomeran

elasomeran All doses			elasomeran 3 or more Doses		
PT	**# Events**	**% Events**	**PT**	**# Events**	**% Events**
Headache	4,587	4.4	Headache	480	5.1
Fatigue	4,524	4.3	Fatigue	456	4.8
Pyrexia	4,194	4.0	Pyrexia	457	4.8
Chills	2,998	2.9	Chills	301	3.2
Nausea	2,686	2.6	Myalgia	294	3.1
Pain	2,567	2.5	Nausea	272	2.9
Pain in extremity	2,450	2.3	Arthralgia	221	2.3
Myalgia	2,343	2.2	Pain in extremity	212	2.2
Arthralgia	2,242	2.1	Dizziness	204	2.2
Dizziness	1,878	1.8	Vomiting	121	1.3

During the reporting period, TTO of events reported by cases with MedHx AI/ID after Dose 3 or booster was mostly within 2 days (64.0%) after vaccination. The median TTO was 1.0 day (range 0-565). This is comparable to the cumulative data from cases with MedHx AI/ID who received Dose 3 or booster

Serious Cases and Events Among Persons with MedHx AI/ID Who Received Dose 3 or Booster of elasomeran)

Cumulatively, there have been 1,273 (3,928 serious events) serious cases with MedHx of AI/ID who received Dose 3 or a booster dose with 591 cases medically confirmed. During the reporting period, 337 (735 serious events) serious cases with MedHx AI/ID who received Dose 3 or a booster were reported. There were 119 serious cases medically confirmed.

There were no differences in the gender distribution of the serious cases reported after a Dose 3 or

booster, when compared with the cumulative reports and non-serious reports, with more reports involving females (680; 77.2%) than males (191; 21.7%) with 10 reports (1.1%) missing gender data. Mean age of these cases was 54.0 years (SD: 13.5), median age of 53.5 years (range 22.0 to 88.0), with 2.8% (5) cases missing age information.

There were no observed differences in the PTs associated with the reported serious events in individuals receiving a 3rd dose or a booster dose, when compared to the rest of the reports received from individuals with MedHx of AI/ID, both during the reporting period or cumulative.

Fatal Events Among Persons with MedHx AI/ID Who Received 3 or more doses - elasomeran

During the review period, 3 cases reported a fatal outcome. All three reports involved males, two cases 83 years of age, and another one 86 years old. All 3 reports are considered unlikely related to the vaccine due to the associated risk factors, comorbidities and clinical course describe in the reported events.

Use Among Children (< 12 Years of Age) With MedHx AI/ID-elasomeran

Cumulatively, 6 cases have been reported in the age group of <12 years old: 1 non-serious case ([redacted]) was reported in a child 0-5 months old, and 1 serious case ([redacted]) in a child 6-months to 2 years old, both these cases pertained to exposure via breastfeeding following maternal vaccination; 1 non-serious case ([redacted]) was reported in a child with history of Coeliac disease in the age group of 2-5 years of age; 3 cases were reported in children 6-11 years old with history of Psoriasis ([redacted]), Crohn's disease ([redacted] and Kawasaki's disease ([redacted]). These include 3 reports received during the reporting period ([redacted], [redacted], **and** [redacted]). The medical review of the 2 serious cases received during this reporting period ([redacted], [redacted]) in children in the age group of 6-11 years is presented below:

[redacted]**:** This is a regulatory case concerning a 7-year-old female patient with the concurrent medical conditions of Crohn's disease and hypertension and medical history of knee pain, urinary tract disorder, and skin eruption, who experienced eczema, on the same day after an unspecified dose of elasomeran. The event was described as extensive eczematous rash of both forearms that persisted for 2 months. Concurrent medical condition of Crohn's disease and hypertension in addition to medical history of skin eruption plus the use of concomitant medications (reported as Bisoprolol; Candesartan; Esomeprazole; Loperamide; Loperamide) remains as confounders/co-suspects. This case is considered possible given that there is not enough

information regarding the reported medical history of skin eruption and whether or not that is related to the reported extensive rash developed by the patient.

[redacted]: This is a regulatory authority case concerning a 7-year-old, female patient with concurrent medical condition of Kawasaki's disease. The patient experienced the event of acute lymphangitis of face the same day of the second dose of elsomeran vaccine administration. The patient developed swelling in the vaccinated region with dizziness, headache, fever, lack of energy, facial numbness, inability to move and chest pain. The patient sought emergency consult and was diagnosed with bilateral lymphadenitis and was subsequently admitted. It was also reported that several lymph nodes in the oral cavity were swollen. The symptoms were largely relieved with an inpatient drip treatment which was unspecified although several lymph nodes in the oral cavity remained swollen. The follow-up reported that the patient's oral condition was recovering, and that patient experienced occasional heart throbbing pain. The outcome of the event was reported as resolving. The concurrent medical condition of Kawasaki's disease remains a confounder for the symptoms of headache, fever, lack of energy, swollen lymph nodes in oral cavity and chest pain. This case is considered possible given that there is important missing information related to the concurrent medical history reported by the patient.

Use Among Adolescent (12-17 years) With MedHx AI/ID - elasomeran

Cumulatively, there have been 57 (120 events) cases reported in children 12 to 17 years of age, with 18 serious (29 serious events) cases and 1 case reporting a fatal outcome; 48 cases were medically confirmed. There were more reports involving females (35; 61.4%) than males (22; 38.6%). The mean age was 15.9 years (SD 1.4), with a median age of 16.0 years (range 12.0 to 17.0); 28.1% (16) of cases were 12-15-year-olds, and 71.9% (41) are 16-17-year-olds. Most of the cases were from the United States (52.6%), followed by the EEA (19.3%).

During the review period, 14 (23 events) cases among adolescents with MedHx AI/ID was reported with 6 serious (7 serious events) cases, and there were no fatal cases during the reporting period; 12 cases were medically confirmed.

Table 16.76 summarizes the distribution of autoimmune conditions in the past medical history in the adolescent population with AI/ID.

Table 16.76 AI/ID Medical Conditions Among MedHx AI/ID 12-17-year-old Subpopulation–elasomeran, Cumulative

Medical History	# Cases
Diabetes mellitus (DM) [Type 1 DM (n=8), and DM/autoimmune disorder (n=2)]	10
Autoimmune disorder	9
Coeliac disease	8
Crohn's disease	4
Rheumatoid arthritis	4
Systemic lupus erythematosus	4
Autoimmune thyroiditis	3
Colitis ulcerative	3
Kawasaki's disease	3
Psoriasis	2
Raynaud's phenomenon	2
Antiphospholipid syndrome	1
Autoimmune thyroiditisFH	1
Autoinflammatory disease	1
Behcet's syndrome	1
Immune system disorder	1
Immune thrombocytopenia	1
Juvenile idiopathic arthritis	1
Myasthenia gravis	1
Polyarthritis	1
Sjogren's syndrome	1

All serious cases reported during the review period were medically reviewed and no unexpected patterns were observed. During the review period, one case, [redacted] of myocarditis/pericarditis in adolescents with MedHx AI/ID was reported; please see Section 16.3.1.2 for more information on this case.

Autoimmune and Inflammatory Conditions Aggravated/ Potential Flares

As described in Section 16.3.5.7.3 using the applied strategy to identify cases of potential flares after vaccination requires caution in interpretation and medical review of the narrative to identify reports of flares in the MedHx AI/ID subpopulation. Given the nature of spontaneous reporting and insufficient information in some reports, it is sometimes difficult to differentiate expected reactogenicity from a true flare, or to confirm if the reported events are a true flare as often,

pre-vaccination disease state/stage, clinical course, diagnostics, treatment and outcome are not reported. Additionally, the number of individuals with potential flares might be an overestimate, because each episode of a flare for an individual might be reported as a separate case (e.g., if an individual reports a flare after Dose 1 and Dose 2, two reports with unique case IDs could be created [one for each episode of a reported flare]).

Cumulatively, 2,437 cases (13,800 events) of potential flares have been reported with 1,779 considered serious cases (6,037 serious events); there were 39 fatal reports. There were 1,321 cases were medically confirmed.

During the reporting period, 420 cases (1,806 events) of potential flares were reported with 306 serious cases (675 serious events), and 3 cases reporting a fatal outcome; there were 155 cases medically confirmed. There were more reports of flares involving females (293; 69.8%) than males (115; 27.4%), with 12 reports (2.9%) missing gender information. The average age was 55.0 years (SD 14.3) and median age was 55.0 (range 15.0-93.0). The cumulative gender and age distribution was comparable to that in the review period.

During the reporting period there were more reports of flares after dose 3 (206; 11.4%), and after dose 2 (185; 10.2%). When TTO was reported, most of the reports had a TTO within less than 7 days (405; 22.4%), the same trend has been observed cumulative (5,470; 39.6%).

Five of the frequently reported types of potential AI/ID flares (rheumatoid arthritis, multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, and ulcerative colitis/inflammatory bowel disease) continue to be among the most frequently reported AI/ID conditions cumulatively and were presented in-depth in previous PBRER. Preferred Terms of Autoimmune/Inflammatory Disorder SMQ in reports with past medical history of AI/ID, representing a subset of potential flares are presented in Appendix 11.11.

To date, no cases of potential flares have been reported in children younger than 12 years of age. Cumulatively, 7 cases (7 events) of potential flares have been reported in adolescents 12-17 years of age, with 5 cases considered serious. There have not been any fatal reports cumulatively. During the reporting period there were 2 cases (1 serious) reported, with one of them being serious.

Use in Patients with Autoimmune or Inflammatory Disorders Receiving Booster Dose with elasomeran/imelasomeran

Cumulatively, 146 cases (593 events) have been reported for elasomeran/imelasomeran; there were71 serious cases and 4 that reported a fatal outcome, and 24 cases were medically confirmed;

all these reports were received during the reporting period of this PBRER. Same trend was observed for reported gender, with more reports involving females (108; 74.0%) than males (35; 24.0%), there were 3 reports (2.1%) missing gender information. The mean age was 62.7 years (SD 14.7) and median age was 63.5 years (range 23.0-89.0).

The most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among MedHx AI/ID cases receiving elasomeran/imelasomeran represent expected reactogenicity. The types and distribution of the most frequently reported events is comparable to those observed with vaccination with elasomeran in MedHx AI/ID cases. Table 16.77 presents cumulative distribution of most frequently reported PTs in MedHx AI/ID cases by vaccine (elasomeran vs elasomeran/imelasomeran).

Table 16.77 Most Frequently Reported Events by Preferred Term (PT) Among Cases with MedHx AI/ID Receiving elasomeran elasomeran/imelasomeran, Cumulative

elasomeran			elasomeran/imelasomeran		
PT	**# Events**	**% of Total Events**	**PT**	**# Events**	**% of Total Events**
Headache	4,587	4.4	Headache	46	7.8
Fatigue	4,524	4.3	Fatigue	42	7.1
Pyrexia	4,194	4.0	Pyrexia	30	5.1
Chills	2,998	2.9	Nausea	29	4.9
Nausea	2,686	2.6	Arthralgia	28	4.7
Pain	2,567	2.5	Chills	28	4.7
Pain in extremity	2,450	2.3	Malaise	27	4.6
Myalgia	2,343	2.2	Myalgia	26	4.4
Arthralgia	2,242	2.1	Injection site pain	19	3.2
Dizziness	1,878	1.8	Vomiting	12	2.0

The most frequently reported serious events of cases with MedHx AI/ID receiving elasomeran/imelasomeran were not different from the ones observed for non-serious cases reflecting expected reactogenicity events, such as fatigue, headache, pyrexia, myalgia, arthralgia, nausea, and chills.

Cumulatively, 4 fatal cases were reported for elasomeran/imelasomeran. All cases were considered unlikely related to the vaccine due to the associated comorbidities included in the reports (cancer, kidney disease and peritoneal dialysis, acute hemolytic anemia, SLE; Peritoneal dialysis; Hypertension; Pulmonary hypertension; Sjogren's syndrome, among others).

Use in Patients with Autoimmune or Inflammatory Disorders Receiving Booster Dose with elasomeran/davesomeran

Cumulatively, 58 cases (214 events) have been reported for elasomeran/davesomeran; there were 16 serious cases (28 serious events) and no cases reporting a fatal outcome; there were 9 cases medically confirmed. All these reports were received during the reporting period. Same observed pattern for gender reports was observed for reports after elasomeran/davesomeran, with more cases involving females (42; 72.4%) than males (16; 27.6%). The mean age was 60.9 years (SD 14.5) and median age was 64.0 years (range 25.0-90.0).

The most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among MedHx AI/ID cases receiving elasomeran/davesomeran represent expected reactogenicity. The types and distribution of the most frequently reported events is similar to those observed with elasomeran in MedHx AI/ID cases and the general population receiving elasomeran/davesomeran. Table 16.78 presents the cumulative distribution of most frequently reported PTs in MedHx AI/ID cases by vaccine (elasomeran vs. elasomeran/imelasomeran).

Table 16.78. Most Frequently Reported Events by Preferred Term (PT) Among Cases with MedHx AI/ID Receiving elasomeran or elasomeran/davesomeran, Cumulative

Elasomeran			Elasomeran/davesomeran		
PT	**# Events**	**% of Total Events**	**PT**	**# Events**	**% of Total Events**
Headache	4,587	4.4	Pyrexia	11	5.1
Fatigue	4,524	4.3	Pain	8	3.7
Pyrexia	4,194	4.0	COVID-19	7	3.3
Chills	2,998	2.9	Headache	7	3.3
Nausea	2,686	2.6	Illness	7	3.3
Pain	2,567	2.5	Myalgia	7	3.3
Pain in extremity	2,450	2.3	Chills	6	2.8
Myalgia	2,343	2.2	Pain in extremity	6	2.8
Arthralgia	2,242	2.1	Vaccination site pain	6	2.8
Dizziness	1,878	1.8	Arthralgia	5	2.3

There have been no MedHx AI/ID cases with fatal outcome reported for elasomeran/davesomeran.

Cumulatively, there were 9 cases (9 events) of which 6 were serious, of potential AI/ID flares in MedHx AI/ID after vaccination with elasomeran/davesomeran.

Literature Findings

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and AI/ID MedHx to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved.

A total of 1,495 literature articles were retrieved using these search criteria. These literature search results were medically/scientifically reviewed and are discussed above, under section Background Relevant to the Evaluation. There was no additional published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran.

16.3.5.7.5 Discussion

In the review period for PBRER#4 and cumulatively, the most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among MedHx AI/ID cases receiving elasomeran, elasomeran/imelasomeran and elasomeran/davesomearn represent expected reactogenicity. The types and distribution of the most frequently reported events is comparable to those observed with elasomeran in MedHx AI/ID cases and those receiving elasomeran/imelasomeran or elasomeran/davesomeran.

During this reporting period, Dose 3 and Dose 4/5/6/7 cases constituted 9.5% and 2.1%, respectively of all cases with MedHx AI/ID in the safety database.

Cumulatively, there were 6 reports received for children under 12 years of age and 57 cases of adolescents 12-17 years of age with MedHx AI/ID.

During this reporting period, the 442 potential cases of exacerbation of underlying AI/ID reported after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran may have limited information and lack a description of the baseline disease status or historic pattern of flares, the clinical course, diagnostics/labs/imaging, treatment, outcome, clear TTO and/or dose number. Those reports also include signs and symptoms of reactogenicity that could mimic signs and symptoms of autoimmune disease (such as fever, myalgia, fatigue, arthralgia, headache), and thus it may be difficult to fully differentiate transient reactogenicity from AI/ID reactivation/flare.

Given the natural waxing and waning course of AI/ID, and that there are no reliable reference data of the background rates of respective flares, the modest number of cases do not represent a safety

concern at this time. There have been reports of flares after many vaccines, including various COVID vaccines. Both health-care providers and patients acknowledge the potential risk of flares after any vaccination, yet flares are not specifically described in any vaccine labels. At present, the global consensus is that the benefit of vaccination outweighs the potential risks of flares but should be discussed between patient and HCP.

Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran [120,128-130]. Relevant literature findings during the reporting period provides support to the observed safety and benefit/risk profile of COVID vaccination among individuals with AI/ID. Findings from these articles during this reporting period did not provide new substantive data to impact the benefit-risk profile of the use of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran among persons with MedHx AI/ID. Published studies continue to demonstrate that elasomeran is safe and well tolerated in individuals with MedHx AI/ID. Although, the incidence of flare rates noted in published studies had a wide range for multiple COVID vaccine types and varied AI/ID conditions, the studies consistently showed that flares were transient, typically mild and self-limited. Additionally, the studies that included an unvaccinated arm or captured information on the background flare rates of vaccinated cohort, have not shown a significant difference in the flare rates between vaccinated and unvaccinated individuals or pre and post-vaccination.

Given that each AI/ID has a different immune pathophysiology, makes it difficult to generalize observed flare rates across different AI/ID conditions. Despite the limitations noted above, study findings indicate that the safety profile of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran among individuals with AI/ID is reassuring and disease flares are limited. The published literature continues to support the benefit-risk profile of the use of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran in individuals with autoimmune and inflammatory diseases.

As of the DLP of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in individuals with AI/ID. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. In addition, there have been non-serious, serious and fatal reports of COVID-19 in this subpopulation, perhaps reflective of reduced

immunogenicity/effectiveness of the vaccine in this population, the surges of variants and subvariants, waning immunity, and policy and behavior changes. Otherwise, the general pattern of commonly reported AEs in those with a medical history of AI/ID is comparable to the general population.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of use in individuals with AI/ID, the benefit-risk profile for elasomeran remains favorable.

The MAH has monitored use in individuals with AI/ID in each MSSRs as well as PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data individuals with AI/ID reported in the GSDB indicates that the general pattern of commonly reported AEs in those with a medical history of autoimmune/ inflammatory disorder is comparable to the general population, rather than as a result of vaccine exposure.
- Exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID vaccines. This has been recognized by professional and public health organizations; yet, given the risk of the potential consequences of COVID infection, some are recommending vaccination with monitoring and management of any potential flare or exacerbation occurring after vaccination. In addition, those individuals with AI/ID may be on immunosuppressive

medications, which may reduce the immunogenicity and efficacy of the vaccine, and/or make them more susceptible to infections.

- Use of elasomeran in individuals with AI/ID is embedded in clinical practice and included in the elasomeran SmPC, CCDS and relevant health guidelines.
- The MAH continues to evaluate Use in individuals with AI/ID in reports of elasomeran (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorization safety studies.

Rationale for removal:

- Extended use of the elasomeran vaccines (>800 million individuals vaccinated with at least one dose) has provided extensive safety information including individuals with AI/ID to support the removal of this population as missing information.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to individuals with AI/ID.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events in individuals with AI/ID conditions in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of use in individuals with AI/ID as Missing Information from the Spikevax EU-RMP, and to continue monitoring use in individuals with AI/ID through routine surveillance. An updated Spikevax RMP for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran will be submitted along with this PSUR procedure.

16.3.5.7.6 Conclusion

Based on the analysis of all the safety data received during the reporting period and cumulatively in the AI/ID subpopulation, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The MAH will continue to monitor AEs in individual with AI/ID using routine surveillance.

16.3.6 Adverse Events of Special Interest

16.3.6.1 Cardiac Disorders

16.3.6.1.1 Arrhythmias

16.3.6.1.1.1 Source of the New Information

New information presented below includes analysis performed on new cases received by MAH cumulatively for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022.

16.3.6.1.1.2. Background Relevant to the Evaluation

The MAH received a health authority request to perform a cumulative review of all cases concerning elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran associated with arrhythmias from all sources, including any relevant articles from literature. Cumulatively, as of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. Cumulatively, as of the end of the reporting period, 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

Cardiac arrhythmia is characterized by irregular rhythm of heartbeat, which could be either too slow (<60 beats/min) or too fast (>100 beats/min) and can happen at any age [131]. Cardiac arrhythmias can be classified according to the site of origin (atria, atrioventricular junction, or ventricles) and whether the response is abnormally fast and early (tachycardia or premature beats), or abnormally slow and delayed (bradycardia or escape beats) [132]. Cardiac arrhythmias are prevalent among humans across all age ranges and may occur in the setting of underlying heart disease as well as in structurally normal hearts. While arrhythmias are widely varied in their clinical presentations, they may possess shared electrophysiologic properties at the cellular level. The 3 main mechanisms responsible for cardiac arrhythmias are automaticity, triggered activity, and re-entry [133]. COVID-19 infection is associated with many different systemic complications.

Among these, cardiovascular system complications are particularly important as these can be associated with significant mortality. There are many different subgroups of cardiovascular complications, including arrhythmias. Arrhythmias are especially important as there is a substantial percentage of patients who have arrhythmia after a COVID-19 infection, and these patients have been noted to have an increased mortality rate [134]. An important aspect with regard to arrhythmias in the context of vaccination is the well-described "immunization stress-related response" (ISRR) that is used to describe the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom. Individual responses to stress vary from person to person and may change according to time or context. According to WHO, ISRR may manifest as acute stress responses, vasovagal reactions or dissociative neurological symptom reactions [135]. Stress can contribute to heart rhythm disorders (arrhythmias) such as atrial fibrillation. Some studies suggest that stress and mental health issues may cause atrial fibrillation symptoms to worsen. High levels of stress may also be linked to other health problems. An acute stress response is an internal physiological response to a perceived threat in all mammals and is often referred to as a "fight or flight" response. It may manifest with variable severity of symptoms and may range from mild feelings of worry and "butterflies" in the stomach to sympathetic stimulation: increased heart rate, palpitations, difficulty in breathing or rapid breathing (hyperventilation). It results from activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenocortical axis, which increases blood flow to the brain, heart, lungs and skeletal muscles and reduces the blood flow to less critical body areas.

Relevant Background Literature

The study conducted by Patone et al., is a self-controlled case series study of people aged 16 or older vaccinated for COVID-19 in England between 1 Dec 2020 and 24 Aug 2021 using the English National Immunization Database of COVID-19 vaccination, which includes data on vaccine type, and date of doses for all vaccinated people in England [136]. This information was linked, at individual patient level, to national data for mortality, hospital admissions and SARS-CoV-2 infection data to examine the associations between the first and second dose of ChAdOx1, BNT162b2 or elasomeran vaccines and cardiac AEs including myocarditis, pericarditis or cardiac arrhythmias. They also investigated the associations between a positive SARS-CoV-2 test (before or after vaccination) as a secondary exposure and the same cardiac AEs. Hospital admission or death due to myocarditis, pericarditis and cardiac arrhythmias were investigated in the 1–28 days following adenovirus (ChAdOx1, n = 20,615,911) or messenger RNA-based (BNT162b2, n =

16,993,389; elasomeran, n = 1,006,191) vaccines or a severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) positive test (n = 3,028,867).

Of the 38,615,491 vaccinated individuals included in the study, 385,508 (1.0%) were admitted to hospital with or died with an ICD code related to cardiac arrhythmia at any time in the study period (either before or after vaccination); 86,754 (0.2%) of these occurred in the 1-28 days after any dose of vaccine. Of those who were admitted or died 39,897 (10.3%) had a SARS-CoV-2 positive test, with 29,694 (7.7%) having a positive test before vaccination. There were 7,795 deaths with cardiac arrhythmia recorded as the cause of death (1,108 had a SARS-CoV-2 positive test). There were no deaths associated with cardiac arrythmias and vaccination with elasomeran.

Over the 1–28 days post-vaccination, the authors found:

- A decreased risk of cardiac arrhythmia associated with a first dose of ChAdOx1 (IRR 0.94, 95% CI 0.93, 0.96) and BNT162b2 (IRR 0.89, 95% CI 0.87, 0.90) and following a second dose of ChAdOx1 (IRR 0.95, 95% CI 0.94, 0.96); and BNT162b2 (IRR 0.95, 95% CI 0.93, 0.96)
- No significant increase in the risk of arrythmias for elasomeran first dose (IRR 0.90, 95% CI 0.76, 1.06). (Incidence rate ratios (IRR 95% CI) for single outcomes in pre-defined risk periods immediately before and after exposure to vaccination, adjusted for calendar time from 01 Dec 2020 to 24 Aug 2021).
- An increased risk of cardiac arrhythmia following a second dose of elasomeran (IRR 1.46, 95% CI, 1.08, 1.98), with 24,335 (95% CI 15,547 – 103,369) individuals needed to be exposed to a second dose of elasomeran to cause one excess event.
- An even higher increased risk of cardiac arrythmias for individuals with SARS-CoV-2 positive test (IRR 5.35, 95% CI 5.21, 5.50) with only 416 (95% CI 414 – 419) individuals needed to have a SARS-CoV-2 infection in order to cause one excess event.

Cardiac arrhythmias (n = 385,508) were categorized as atrial fibrillation or flutter (n = 229,248, 59.4%), atrio-ventricular block and related conduction disorders (n = 114,701, 29.7%), ventricular tachycardia (n = 8,211, 2.1%), ventricular fibrillation (n = 2,910, 0.7%) and other, including supraventricular tachycardia (n = 130,485, 33.8%).

According to this categorization, over the 1–28 days postexposure, the authors observed an increased risk of:

- Atrial fibrillation or flutter arrhythmia at 15–21 days following a first dose of elasomeran vaccine (IRR 2.06, 95% CI 1.11, 3.82)
- Ventricular fibrillation at 22–28 days following a second dose of ChAdOx1 vaccine (IRR 1.35, 95% CI 1.05, 1.74)
- Other cardiac arrhythmia at 1–7 days following a second dose of elasomeran vaccine (IRR 2.32, 95% CI 1.49, 3.62).

In those patients with a positive SARS-CoV-2 test there was a higher increased on the risk of all cardiac arrhythmia subgroups in the 1–28 days (IRR 21.35, 95% CI 18.37, 24.80). Important to note that the IRR for elasomeran regarding the occurrence of cardiac arrythmias is very similar after the first dose over 1 to 28 days after vaccination when compared to the other two evaluated vaccines.

Patone et al., [136] acknowledge important limitations of their study. First, their finding cannot determine causal associations. Second, their study relied on hospital admission codes to define the outcome measures, and therefore they do not represent confirmed diagnoses; for example, codes for arrythmia may simply represent "rule out" diagnoses. Third, the elasomeran roll out in the UK occurred toward the end of the study period, and thus the number of immunizations with this vaccine was low. Consequently, the proportion of first doses in the study that involved elasomeran was only 2.6%, and the corresponding proportion for second doses was even lower (1.1%). For elasomeran, the number of first doses was approximately 1.0 million, and second doses were 0.37 million. Thus, in the data analyzed, only 37% of first dose vaccinees received a second dose. For ChAdOx1 and BNT162b2, the corresponding proportions were 96% and 71%. That the number of elasomeran vaccinees was so low raises the possibility that there may have been under-ascertainment of vaccination and that the recording of second doses might have occurred preferentially in association with an AE; this would introduce bias in the results. Illustrative of this dosing disparity, the assessment of risk (IRR) of arrhythmia 1 to 28 days after the second dose of elasomeran (1.46; 95% CI 1.08-1.98) was based on only 48 events, whereas for ChAdOx1 and BNT162b2 there were, respectively, 23,019 and 20,947 events.

Fourth, the authors acknowledge that they are "unclear" about the biologic plausibility of their findings of some reduced risks of arrhythmia and pericarditis linked to vaccination, and they stated that these findings should be interpreted with caution; analogous caution could similarly be applied to their other findings. Fifth, the authors performed numerous statistical comparisons using 95%

confidence intervals, not considering multiple testing which, as the authors state "may lead to some erroneous inferences."

Another limitation of the Patone et al [136] study relates to the fact that the elasomeran vaccine was introduced in England on 13 Apr 2021, whereas the vaccination campaign with BNT162b2 began 08 Dec 2020, and the ChAdOx1 vaccination campaign commenced on 04 Jan 2021. On 17 May 2021, the CDC announced cases of myocarditis following mRNA vaccines. In contrast to timing for the other two vaccines, which had been in use for 4 to 5 months, this CDC announcement occurred around the time that the earliest elasomeran vaccinees were receiving their second doses. Thus, in contrast to the other vaccines, nearly the entire dose 2 observation period for elasomeran occurred after the CDC alert, which could potentially bias the findings by heightening awareness of cardiac symptoms and their investigation.

With regards to the outcome arrhythmia, the Patone et al [136] study identified this outcome by collecting 46 different ICD-10 codes, including some that are non-specific such as *palpitations* (R002), *abnormalities of heartbeat* (R00), and *other and unspecified abnormalities of heartbeat* (R008). It is possible that some of these and other ICD-10 codes may have represented "rule out" diagnoses or simply symptoms associated with common vaccine reactogenicity, rather than true ECG-diagnosed arrhythmias.

A large epidemiological study by Dickerman et al., [137] was led by researchers from Harvard University and used data from the US Veterans Affairs Healthcare system to compare the safety of BNT162b2 and elasomeran in a nationwide cohort of US veterans [137]. With regard to arrhythmia, this study's findings do not confirm the findings of Patone et al. In fact, the risk of arrhythmia was higher for BNT162b2 than for elasomeran, as described below.

The Dickerman et al [137] study was designed to emulate target trials. From a base population of 6,226,326 veterans, the investigators identified 3,465,065 who were vaccinated before 21 Sep 2021. Then the investigators excluded veterans with prior documented SARS-CoV-2 infection, with interaction with the health-care system less than or equal to 3 days before vaccination, with no residential address or were in long-term care, with no use of VA health-care system in last year, with no recent body mass index or smoking status data, with incomplete COVID-19 vaccination record. Then, for study inclusion, the veterans had to be vaccinated in a VA station that administered both elasomeran and BNT162b2 vaccines, with a second dose scheduled 21 days later (BNT162b2) or 28 days later (elasomeran); in contrast with the Patone et al study, 98% of vaccinees received a second dose. Finally, there was careful 1:1 matching for

216,836 pairs (433,672 persons); recipients of each vaccine were matched in a 1:1 ratio according to risk factors using the following variables: calendar date, age, sex, race, urbanicity of residence, and geographic location coded as categories of Veterans Integrated Services Network. In another contrast to the study by Patone et al, non-specific ICD codes such as *palpitations* (R002), *abnormalities of heartbeat* (R00) and other and *unspecified abnormalities of heartbeat* (R008) were not counted as arrhythmia events. The main potential limitation of the Dickerman et al study was that it was mostly made up of men (93%) and older individuals (90% were >50 years of age) which may limit generalizability.

The 38-week risk of arrhythmia was 277.6 per 10,000 persons for BNT162b2, and 251.4 per 10,000 persons for elasomeran. The risk ratio was 1.1 (95% CI:1.00 to 1.15). The authors concluded: "there were few differences in risk of AEs within 14 days of the first dose of either the BNT162b2 or the elasomeran vaccine and small-magnitude differences within 42 days of the first dose. The 38-week risks of AEs were low in both vaccine groups, although risks were lower for recipients of the elasomeran vaccine than for recipients of the BNT162b2 vaccine".

A study by Montano [138] aimed to assess AEs related to AstraZeneca, Janssen, ModernaTx, Inc., and Pfizer-BioNTech COVID-19 vaccines. The study used EudraVigilance and VAERS data from 2020 to Oct 2021. More than 7.8 million AEs in 1.6 million persons were included; among studies assessing AE reports of arrhythmia from these databases, this study included the largest number of AE reports and thus is the one described here, to avoid multiple reports of the same data. The ARs were classified with the Common Toxicity Criteria categories. Using AEs reported between Dec 2020 and Oct 2021, reporting rates of vaccines against COVID-19 were compared to corresponding rates for influenza. The population level vaccine exposures to COVID-19 and influenza vaccines comprised about 451 million and 437 million exposures, respectively. The study calculated reporting rates (that they called risks) for several vaccines against COVID-19. Montano then calculated reporting rate ratios (that they called relative risks) for each COVID-19 vaccine by dividing its reporting rate by the reporting rate for a composite of influenza vaccines; this was done for each of a broad range of AEs that also included arrhythmia for the EU (using EudraVigilance) and US (using VAERS) populations aged 18 years and older. Reporting rate ratios from EudraVigilance were AstraZeneca (ChAdOx1) 27.43 [95% CI: 23.17–32.48], Janssen 2.25 [1.88–2.69], ModernaTx, Inc. 15.22 [12.85–18.04], Pfizer-BioNTech 42.91 [36.25–50.79]. Reported reporting rate ratios from VAERS were: Janssen 17.77 [15.48–20.39], ModernaTx, Inc. 56.87 [49.77–64.99], Pfizer-BioNTech 70.80 [61.98–80.88]. It is interesting to note that in these studies the ModernaTx, Inc. vaccine had lower reporting rate ratios than both the Pfizer-BioNTech

and the ChAdOx1 vaccines. Three of the important study limitations that Montano acknowledged are: 1) there is not conclusive evidence of a causal association; 2) the reported health events are unverified; 3) there may be under- or over-reporting bias.

16.3.6.1.1.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively to 17 Dec 2022 for valid case reports of arrhythmia received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following MedDRA PTs: "SMQ Cardiac Arrhythmia (Narrow scope)".

There is no SPEAC or Brighton Collaboration case definition available for arrhythmias, however individual arrhythmias have their own criteria of diagnosis.

The MAH has created the case definition for evaluation of the arrhythmia cases.

Cardiac arrhythmia is characterized by abnormal or irregular rhythm of heartbeat which could be either too slow (<60 beats/min) or too fast (>100 beats/min) and can happen at any age [131]. Cardiac arrhythmias can be classified according to the site of origin (atria, atrioventricular junction, or ventricles) and whether the response is abnormally fast and early (tachycardia or premature beats), or abnormally slow and delayed (bradycardia or escape beats) [132].

Identified cases were classified into four categories as:

1. **Confirmed case**: has less than 60 beats/min (Bradycardia) or more than 100 beats per min (tachycardia) and ECG identifying irregular heart rhythm
2. **Possible Case**: Only has information on the irregular rhythm or number of beats per minute (pulse rate, heart rate) and no diagnostic confirmation (no info on ECG)
3. **Not a case**: Case has normal rhythm
4. **Unassessable**: Has no information on heart rate or pulse rate or ECG

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Methodology Implemented to Review the Post-marketing Data

The MAH performed the cumulative search as of 17 Dec 2022 in the GSDB, using the MedDRA (v 25.1) SMQ "Cardiac arrhythmias" (Narrow scope), the search retrieved 8,803 cases. These

8,803 cases were screened for the information on ECG, which identified 1,832 cases. These 1,832 cases were further analyzed for Arrhythmia-related information with the following key words (*Bradycardia, Heartbeat, Irregular heartbeat, Tachycardia, irregular rhythm, ventricles, Premature beats, and Atrioventricular junction*). The review of 1,832 cases with the key terms showed 693 cases. Of these 693 cases, all Tachycardia confirmed cases (475) with no other associated symptom were eliminated (Tachycardia is an increased heart rate for any reason. It can be a usual rise in heart rate caused by exercise or a stress response (sinus tachycardia). Sinus tachycardia is considered a symptom, not a disease) and of the remaining 218 cases (134 serious and 84 non-serious), the serious cases (134) were further reviewed in detail, to identify a true case of Arrhythmia. Details of these reviews are presented below in Post-Authorization Data section.

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and Cardiac arrhythmia to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 596 literature articles were retrieved using these search criteria. These literature search results were medically/scientifically reviewed, and informative articles are discussed above, under section Background Relevant to the Evaluation. There was no additional published clinical literature that described new and potentially important safety information on the safety profile of elasomeran/imelasomeran and elasomeran/davesomeran).

16.3.6.1.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed Vs Expected Analysis

See Appendix 11.3.

Clinical Trial Data

The topic of arrhythmia was cumulatively reviewed in the clinical trial datasets, within the following studies of P301 study (ages ≥18 years; DLP: 04 May 2021), P203 study (ages 12-17 Years; DLP: 27 Jan 2022) and P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022), for any PT (listed below) included in the SOC cardiac disorders (MedDRA version was 23.0 and 24.0).

P301 Study

The P301 (randomized, stratified, observer-blind, placebo-controlled study) included healthy adults ≥ 18 years of age, at appreciable risk of SARS-CoV-2 infection, with no known history of SARS-CoV-2 infection. There were approximately 30,000 participants randomized in 1:1 ratio to dose groups placebo (n = 15,000) and mRNA-1273 100 µg (n = 15,000) with vaccine schedule of 2 IM doses, 28 days apart. The frequency of arrhythmia events in the clinical trial data showed that the placebo group was comparable to that in the vaccine group as shown in the table below, which is excerpted from the clinical dataset (Table 16.79 and Table 16.80).

Table 16.79 Reported Incidence of Serious Treatment-Emergent Adverse Events of Arrhythmia by Preferred Term Throughout the Entire Duration of mRNA-1273-P301 (Safety Set)

PT	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)
Atrial fibrillation	10 (<0.1)	6 (<0.1)
Atrial flutter	2 (<0.1)	2 (<0.1)
Bradycardia	0	1 (<0.1)
Supraventricular tachycardia	0	1 (<0.1)
Ventricular extrasystoles	0	1 (<0.1)
Arrhythmia	1 (<0.1)	0
Atrioventricular block complete	1 (<0.1)	0
Atrioventricular block second degree	1 (<0.1)	0
Paroxysmal arrhythmia	1 (<0.1)	0
Sinus tachycardia	2 (<0.1)	0

Table 16.80 Subject Incidence of Unsolicited Non-Serious TEAE of Arrhythmias by Preferred Term up to 28 Days After Any Injection Safety Set – mRNA-1273-P301

PT	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)
Tachycardia	9 (<0.1)	15 (<0.1)
Bradycardia	16 (0.1)	13 (<0.1)
Atrial fibrillation	9 (<0.1)	9 (<0.1)
Arrhythmia	10 (<0.1)	6 (<0.1)
Sinus tachycardia	2 (<0.1)	3 (<0.1)

PT	Placebo (N=15162) n (%)	100 µg mRNA-1273 (N=15184) n (%)
Atrial flutter	1 (<0.1)	0
Atrial tachycardia	1 (<0.1)	0
Ventricular fibrillation	1 (<0.1)	0

P203 Study

The P203 (Phase 2/3, randomized, observer-blind, and placebo-controlled) included healthy adolescents in age group 12 to < 18 years. There were approximately 3,000 participants randomized in 2:1 ratio with a vaccine schedule of 100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart. As shown in Table 16.81 below, the observed incidence of arrhythmia terms was comparable in the long-term follow-up of the placebo and active arms of the clinical study.

Table 16.81 Subject Incidence of Unsolicited TEAE by Preferred Term in Long-term Analysis Safety Set - mRNA-1273-P203

Preferred Term	Placebo-mRNA-1273 (N=1243) n (%)	mRNA-1273 (N=2489) n (%)
Sinus bradycardia	1 (0.1)	8 (0.3)
Tachycardia	0	2 (0.1)
Bundle branch block	0	1 (<0.1)
Postural orthostatic tachycardia syndrome	0	1 (<0.1)
Supraventricular tachycardia	0	1 (<0.1)
Tachyarrhythmia	1 (0.1)	0

P204 Study

The P204 (Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation, and randomized, observer-blind, placebo-controlled expansion) included healthy pediatrics between 6 months to < 12 years. There were approximately 750 to 4500 participants indifferent age groups randomized in 3:1 ratio with a vaccine schedule of 25 ug, 50 ug, 100 µg mRNA-1273 (25 µg only for 6 months to < 2 years age group) or placebo (3:1) 2 IM doses, 28 days apart. The safety data set for this study did not identify any events of arrhythmia.

Post-Authorization Data

Post-Authorization Safety Study Analysis

A Late-Breaking News request was received on 16 Jan 2022 from a health authority to perform a self-control risk interval (SCRI) analysis of arrhythmia for adults as well as the pediatric population from the Post Authorization Safety Studies (PASS) mRNA-1273-P903 and provide the results as part of the cumulative review in the PSUR. Analysis of the data from mRNA-1273-P903 addressing the request from the health authority is presented in Section 16.3.6.1.1.

Overview of Cases for elasomeran (Cumulatively through 17 Dec 2022)

Cumulatively, a total of 8,803 cases (10,044 events) of arrhythmia-related PTs were identified for elasomeran (Appendix 11.12). Of the 8,803 cases, 6,197 (6,672 serious events) were considered serious with 246 cases (279 events) with a fatal outcome reported. There were 4,193 (47.6%) cases medically confirmed.

Most of the events with reported outcomes were resolved/ resolving (4,080; 40.6%), with 3,738 events (37.2%) reported as not resolved. There were 279 (2.8%) fatal events. There were more reports involving females (5,068; 57.6 %) compared to males (3,604; 40.9 %), and 131 (1.5 %) cases did not specify gender. The largest proportion of the reports were in individuals ≥50-64 years of age (1,686; 27.2%) The median age of reported cases was 56.0 years (min 0.1/ max 121.0 years) with a mean age of 55.0 years (SD: 17.6). For the cumulative listings with 8,803 cases.

Based on the methodology described above in section Methods of Evaluation, of these 8,803 cumulative cases (10,044 events), 218 Cases (319 events) were considered as possible cases of arrhythmia for analysis. Of these 218 cases, there were 134 serious cases (213 events) and 84 non-serious cases (106 events). These 134 serious cases (213 serious events) were further considered for detailed review for Arrhythmia. These 134 serious cases are described in detail from this point forward in this medical evaluation of Arrhythmia.

Overview of Cases for elasomeran that Qualified for Arrhythmia Review (Cumulatively till 17 Dec 2022)

Cumulatively a total 134 serious cases (213 serious events) with arrhythmia-related PTs were identified for elasomeran. The distribution of the reports was equal in females (66; 49.3%) and males (66; 49.3%), two (1.5%) had unknown gender. Most of the events were in individuals >50 years of age (79;59.0%) (Table 16.82).

Table 16.82. Age and Gender Distribution of Serious cases that Qualified for Arrhythmia Review (Cumulatively through 17 Dec 2022 - elasomeran)

Age Group	Female		Male		Unknown		Grand total # of Cases	Grand Total % Cases
	# Of Cases	% Of Cases	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
18-24Y	2	1.5	6	4.5	0	0	8	6.0
25-39Y	15	11.2	12	9.0	0	0	27	20.1
40-49Y	10	7.5	6	4.5	0	0	16	11.9
50-64Y	20	14.9	16	11.9	0	0	36	26.9
65-74Y	9	6.7	16	11.9	0	0	25	18.7
75Y+	7	5.2	10	7.5	1	0.7	18	13.4
Missing	3	2.2	0	0	1	0.7	4	3.0
Grand total	**66**	**49.3**	**66**	**49.3**	**2**	**1.5**	**134**	**100.0**

The most frequently reported PT for serious cases were Atrial fibrillation (37; 18.5%), arrhythmia (32; 16.0%), and Heart rate irregular (10.0%). The top 10 PTs reported from the 213 serious events of "Arrhythmia" related are presented in Table 16.83.

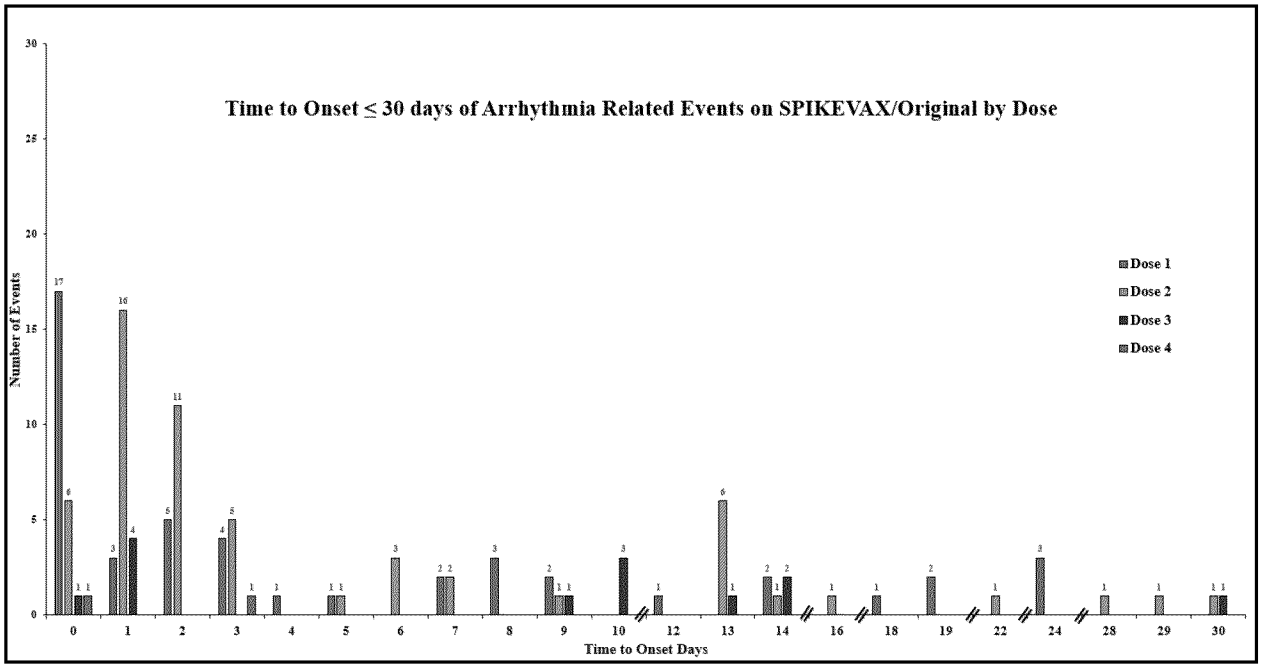
Table 16.83. Top 10 PTs for the Serious Events that Qualified for Arrhythmia Review Reported following elasomeran (Cumulatively through 17 Dec 2022)

PT	Grand total # of Serious Events	Grand total % of Serious Events
Atrial fibrillation	37	18.5
Arrhythmia	32	16.0
Heart rate irregular	20	10.0
Extrasystoles	17	8.5
Sinus bradycardia	12	6.0
Cardiac flutter	11	5.5
Atrioventricular block	7	3.5
Supraventricular tachycardia	7	3.5
Ventricular extrasystoles	7	3.5
Bundle branch block right	6	3.0

When evaluating serious events of arrhythmia by time to onset (TTO), highest number of events were observed after Dose 2 (81;40.1%), and regardless of dose number, most of the events reported a TTO ≤14 days (89;44.5%). When TTO was known, 124 of 213 events were reported within 30 days, and these are presented in Figure 16-10. Additionally, there were 43 events reported with

TTOs spread out between 31 to 300 days after vaccination. The graphic pattern is generally similar to that of all AEs reported following elasomeran immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination (reactogenicity events, ISRRs events) or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. Currently, with the limited number of reports, the finding is an observation, as there is no clear biological explanation.

Figure 16-10. Number of Serious Events that Qualified for Arrhythmia Review by Dose Number and Time to Onset of elasomeran (Cumulatively through 17 Dec 2022)



Evaluation of the serious arrhythmia-related events showed that many of the reports were in patients with concurrent medical history that can be considered a risk factor/ confounder to the occurrence of arrhythmia. A history of Drug hypersensitivity, Hypertension and Hypersensitivity was reported frequently. It is possible that hypersensitivity or hypertension may contribute to the occurrence of arrhythmias. See Table 16.84.

Table 16.84. Top 10 Medical History* Terms Noted in Reports that Qualified for Arrhythmia Review, by MedDRA PT (Cumulative through 17 Dec 2022) - elasomeran

Medical History	# of Cases	% of Cases
Drug hypersensitivity	89	66.4
Hypertension	24	17.9
Hypersensitivity	19	14.2
Food allergy	11	8.2
Hyperlipidaemia	10	7.5
Cardiac pacemaker insertion	9	6.7
Diabetes mellitus	9	6.7
Osteoarthritis	8	6.0
Asthma	8	6.0
Seasonal allergy	8	6.0

*Include current and past medical history

The incidence of certain clinical arrhythmias varies between men and women. Clinical and experimental observations suggest the existence of true differences in electrophysiologic properties between the sexes [139]. Some of these differences are related to known variations in the frequency of underlying organic heart disease, such as coronary artery disease (CAD) and associated ventricular arrhythmias [140]. Among the 134 serious cases, there were two fatalities reported following elasomeran, details of these cases are summarized below.

1. [redacted] **(WW Identifier: US-**[redacted] This case involved a 66-year-old man without reported medical history, who was taking two medications (hydrochlorothiazide and lisinopril) for hypertension, as well as albuterol. He experienced syncope at home 19 days after dose 1, Emergency medical services was called, and the patient was hospitalized but was not stabilized. Patient died the day following hospital admission. Patient diagnosed with ST Elevation Myocardial Infarction-myocardial infarction with ST Elevation. ST Elevation Myocardial Infarction is the likely direct cause of the agonal rhythm and bradycardia noted, rather than elasomeran. WHO Causality for arrhythmia: Unlikely.
2. [redacted] **(WW Identifier: US-**[redacted]**):** This 71-year-old male patient died from acute hypoxemic respiratory failure secondary to COVID-19 pneumonia._The patient's noted arrhythmias likely resulted from multi-organ

failure and metabolic derangements due to this fatal infection, rather than from elasomeran. WHO Causality: Unlikely. This case is a duplicate of [redacted].

Arrhythmia in Children (<12 Years of Age) (Cumulatively to 17 Dec 2022) elasomeran

There were no cases of arrhythmia in children <12 years of age.

Arrhythmia in Adolescents (12-17 Years of Age) (Cumulatively to 17 Dec 2022) elasomeran

There were no cases of adolescents identified in the list of 134 cases that were reviewed to identify a true case of Arrhythmia.

Serious Cases Qualified for Arrhythmia Review in Patients After a Third Dose or Booster Dose of elasomeran (Cumulatively to 17 Dec 2022)

The review of the cumulative data as of 17 Dec 2022, identified 134 cases for detailed review, of which, a total of 16 serious cases (22 events [*of which 21 serious*]), were reported in the GSDB after a booster dose (defined as the third dose or higher) of elasomeran. Of these 16 serious cases, 6 were medically confirmed and 0 fatal cases were reported. There were more reports involving females (11; 68.8%) than males (4; 25.0%) with 1 (6.3 %) report with missing gender information, and the median age was 54.0 years (min 23.0/ max 85.0 years) with a mean age of 54.8 years (SD: 18.0). (Table 16.85)

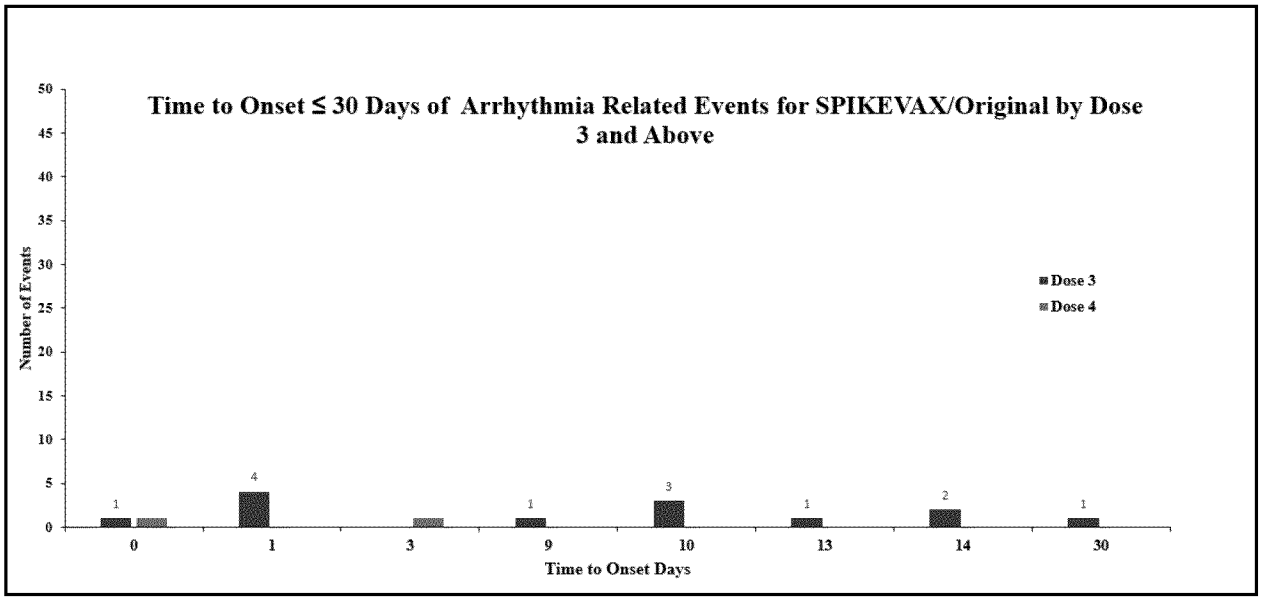
Table 16.85. Age and Gender Distribution Serious Cases Qualified for Arrhythmia Review following booster Dose (Cumulatively through 17 Dec 2022) elasomeran

Age Group	Female		Male		Unknown		Grand total # Of Cases	Grand total % of Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-24Y	0	0	1	6.3	0	0	1	6.3
25-39Y	4	25.0	0	0	0	0	4	25.0
40-49Y	2	12.5	0	0	0	0	2	12.5
50-64Y	2	12.5	1	6.3	0	0	3	18.8
65-74Y	2	12.5	1	6.3	0	0	3	18.8
75Y+	1	6.3	1	6.3	1	6.3	3	18.8
Grand total	**11**	**68.8**	**4**	**25.0**	**1**	**6.3**	**16**	**100.0**

There were 22 events reported on Dose 3 and above; of these 15 events were reported with a TTO of ≤ 30 days. Time to onset and dose for serious events received after dose 3 or more are depicted

graphically below (Figure 16-11). Additionally, there were 7 events reported after day 30 until day 129.

Figure 16-11. Number and Percentage of Serious Arrhythmia Cases by Dose Number and Time to Onset after Dose 3 and Booster dose (Cumulatively through 17 Dec 2022)



Fatal Cases After a Third Dose or Booster Dose of elasomeran (Cumulatively through 17 Dec 2022)

Cumulative, no fatal reports were reported in patients receiving dose 3 or above from the list of 134 cases that were reviewed to identify a true case of for Arrhythmia.

Cases that Qualified for Arrhythmia Review After Receiving Booster Dose with elasomeran/imelasomeran) (Cumulatively through 17 Dec 2022)

Cumulatively, there were no reports that qualified for arrhythmia review in patients vaccinated in elasomeran/imelasomeran.

Fatal Cases After Receiving Booster Dose with elasomeran/imelasomeran) (Cumulatively through 17 Dec 2022)

Cumulative, no fatal reports were reported in patients vaccinated in elasomeran/imelasomeran from the list of 134 cases that were reviewed to identify a true case of for Arrhythmia.

Cases that Qualified for Arrhythmia After Receiving Booster Dose with elasomeran/davesomeran (Cumulatively till 17 Dec 2022)

Cumulatively, there was one report that qualified for arrhythmia review in patients vaccinated with elasomeran/davesomeran. Details of this case is as follow:

[redacted] (*WW Identifier:* [redacted]): This spontaneous case reported by a patient, concerns a 74-year-old male with history of Syncope, Right Bundle Branch Block, Obstructive sleep apnea syndrome. He had a prior ECG with atrial fibrillation noted 14.5 months before this reported event. This reported event concerns the unexpected, serious (medically significant) AESI Atrial fibrillation a few hours after receiving the 5th dose of elasomeran/davesomeran as fifth dose in the COVID-19 vaccine series. The patient experienced sudden onset atrial fibrillation post-vaccination notified to him by a device. He was advised by his cardiologist to visit the ED for evaluation. His ECG showed atrial fibrillation, Troponin was 11 ng/L (Unknown-20 ng/L) The patient was started on Eliquis(apixaban) and was eventually discharged. The patient had another episode of atrial fibrillation approximately a month after the initial incident and was scheduled for ancillary procedures the next month. Further details on the clinical course and additional treatment were not provided. The patient's advanced age, medical history of Right bundle branch block and concurrent obesity, hypertension, and high cholesterol may be considered as confounders for this atrial fibrillation; therefore, this this report is assessed as WHO-UMC Causality possible primarily due to temporal association.

Fatal cases After Receiving Booster Dose with elasomeran/davesomeran (Cumulatively till 17 Dec 2022)

There were no fatal reports reported after elasomeran/davesomeran.

Case Evaluation for Cases meeting Arrhythmia's Case Definition

As described in the Post-Authorization Data section, there were 134 serious cases that met the case definition for Arrhythmia. Of these 134 serious cases, seven (7) were classified as unassessable due to lack of information including ECG results; 37 cases were classified as possible cases and 90 cases were classified as confirmed cases. (Table 16.86). Information of those cases is included in Appendix 11.12.

Table 16.86. Number of cases of Arrythmia According to Case Definition

Classification by Case Definition of Arrhythmia	Number of Cases	% Of cases
Confirmed	90	67.2
Possible	37	27.6
Unassessable	7	5.2
Total	**134**	**100**

According to the WHO causality assessment the 134 serious that were classified as cases of arrhythmia, were assessed as follows: 20 cases were Unassessable, due to the lack of information including medical history, clinical course, among others and 22 case were unlikely. The remaining (92) cases were assessed as possible, since the time course was consistent, however adequate information to evaluate the underlying cause of the reported events was not generally available. In several cases, there was history of atrial fibrillation or therapy with thyroid hormone replacement, which may have provided alternative explanation for the reported events. In some reports the arrhythmias were reported in the context of myocarditis, which is known to be associated with the product. Details of these cases are included in Appendix 11.12.

Review of External Databases

- VAERS and EVDAS were reviewed for SMQ Arrhythmia and EVDAS showed disproportionality of ROR for PTs "Agonal rhythm", "Arrhythmia", "Extrasystoles", "Atrial fibrillation" and "Heart rate irregular" (Table 16.87) (Appendix 11.12).
- **VAERS:** No Disproportionate Reporting of Arrhythmia-related Events Using EB05 >2 (elasomeran versus All vaccines in adults) in VAERS through 17 Dec 2022 was observed.
- **EVDAS:** Amongst the PTs of SMQ Arrhythmia, the PTs "Agonal rhythm", "Arrhythmia", "Extrasystoles", "Atrial fibrillation" and "Heart rate irregular" showed disproportionality.

Table 16.87. EVDAS Disproportionality Analysis

MedDRA PTs	ROR (-) All (31 Dec 2021- 31 Dec 2022)
Arrhythmia	2.13
Extrasystoles	2.03
Atrial fibrillation	1.05
Heart rate irregular	1.4

16.3.6.1.1.5. Discussion

Cardiac arrhythmia is a clinically and etiologically heterogenous entity. In the data presented above, no particular type of arrhythmia predominated. Importantly, the pivotal CTs performed in adults, adolescents and children found similar frequency of various arrhythmias in the elasomeran and placebo control arms. Such clinical trial findings provide the most rigorous medical-scientific findings, although they may not detect very rare AEs.

Epidemiological studies, although less rigorous than CTs, may provide useful information; however, their findings should be carefully scrutinized for potential bias, confounding, lack of generalizability and other methodological limitations. Two large epidemiological studies were described above that had different findings with regard to the risk of arrhythmia after elasomeran. The study by Patone et al, [136] with some findings associating elasomeran with arrhythmia described in detail above, had important limitations including: 1) the referral bias acknowledged by the authors; 2) nearly all of the elasomeran second doses were administered after the CDC myocarditis warning that raised awareness of cardiac symptoms; 3) only 37% of elsomeran vaccinees were reported to have received a second dose, raising the possibility that reporting of the second dose was linked to arrhythmia (bias); 4) the assessment of risk (IRR) of arrhythmia 1 to 28 days after the second dose of mRNA-1273 (1.46; 95% CI 1.08-1.98) was based on only 48 events, whereas for ChAdOx1 and BNT162b2 their corresponding risks were based, respectively, on 23,019 and 20,947 events. 5) some arrhythmia events may have represented "rule out" diagnoses or simply vaccine reactogenicity; 6) the "unclear" biological plausibility acknowledged by the authors for some of their cardioprotective findings of vaccination, and the authors' suggestion that these findings should be interpreted with caution likely applies to all their findings.

In contrast to the Patone et al study, the Dickerman et al study [136,137] described above employed a study design to emulate target trials, and their finding did not confirm those of Patone et al. Dickerman et al [136,137] included 433,672 US veterans who were matched 1:1 according to calendar date, age, sex, race, urbanicity of residence, and geographic location; one member of each pair received BNT162b2 and the other elasomeran. The 38-week risk of arrhythmia after vaccination was 277.6 per 10,000 persons for BNT162b2, and 251.4 per 10,000 persons for elasomeran. The risk ratio was 1.1 (95% CI:1.00 to 1.15). The authors concluded: "there were few differences in risk of AEs within 14 days of the first dose of either the BNT162b2 or the elasomeran vaccine and small-magnitude differences within 42 days of the first dose. The 38-week risks of AEs were low in both vaccine groups, although risks were lower for recipients of the elasomeran vaccine than for recipients of the BNT162b2 vaccine". In summary, the two epidemiological

studies had divergent findings with respect to arrhythmia, and the Patone et al study had important methodologic limitations; an association of elasomeran with arrhythmia has not been shown epidemiologically.

Medical care and study of arrhythmias require clinical diagnostic testing. The cases in the post-marketing database were screened for the reports that had information on electrocardiogram together with abnormal heart rate, and the cases meeting these criteria were medically reviewed. The medical review showed that most case reports lacked adequately detailed information on the workup to assess the possible etiology of the reported arrhythmia event.

16.3.6.1.1.6 Conclusion

The data provided in this PBRER describe sufficiently the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in the reporting period and cumulatively. The safety profile of the vaccine and the benefit-risk evaluation remain positive.

Based on the analysis of all safety data available as of 17 Dec 2022, the MAH considers that for cases included under the arrhythmia-related PTs, information does not substantiate convincing evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and arrhythmia, and the published epidemiologic studies also do not consistently show an increase in arrhythmia in association with vaccine administration. The MAH will continue to monitor events of arrhythmia using routine surveillance.

16.3.6.2 Hematologic Disorders

16.3.6.2.1 Thrombosis with Thrombocytopenia syndrome (TTS)

16.3.6.2.1.1 Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTx, Inc. for the review period, from 19 Jun 2022 to 17 Dec 2022 for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.2.1.2. Background Relevant to the Evaluation

Thrombosis with Thrombocytopenia syndrome, also known as Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or vaccine-induced immune thrombotic thrombocytopenia (VITT), is a rare and newly identified syndrome which has been reported in people who have received adenoviral vector COVID-19 [141]. This syndrome is characterized by venous or arterial thrombosis, mild to severe thrombocytopenia, and positive PF4-heparin Enzyme-Linked

Immunosorbent Assay (ELISA) ('heparin-induced thrombocytopenia [HIT]" ELISA). These clinical and laboratory features are similar to rare cases of HIT-like autoimmune thrombosis with thrombocytopenia, previously described following surgery, certain medications or infections in patients not receiving heparin. The pathogenesis of vaccine-induced thrombotic thrombocytopenia is not known at this time. However, given its clinical presentation and biochemical similarities to heparin-induced thrombocytopenia, which is a prothrombotic and potentially life-threatening condition, a similar immune-mediated response induced by these adenoviral vector vaccines has been postulated as immune complexes with a mixture of antibody specificities similar to HIT was noted in the serum of patients who developed this syndrome [142]. Symptoms on presentation may include intense headache, abdominal pain, back pain, nausea and vomiting, vision changes, change in mental status, shortness of breath, leg pain and swelling, and/or bleeding/petechiae. Patients may complain of severe, recurrent, or persistent symptoms from 4 to 42 days following COVID-19 vaccination, with the peak time period for initial symptoms falling between days 6 to 14 [143]. The MAH has agreed to continue to closely evaluate events of "Thrombosis with Thrombocytopenia related events".

16.3.6.2.1.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB for the reporting period of 19 Jun 2022 to 17 Dec 2022 for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The search strategy included using a customized list of MedDRA PTs from the SMQ-Embolic and thrombotic events-narrow, to identify cases with a reported thromboembolic event, which were then cross-checked for any of the following thrombocytopenia related PTs: Acquired amegakaryocytic thrombocytopenia; Megakaryocytes decreased; Platelet count decreased; Platelet maturation arrest; Platelet production decreased; Platelet toxicity; Thrombocytopenia; Megakaryocytes abnormal; Platelet count abnormal; Platelet disorder; Plateletcrit abnormal; Plateletcrit decreased; Immune thrombocytopenia; hemolysis, elevated liver enzymes, and low platelets syndrome; Thrombotic thrombocytopenic purpura; Thrombocytopenic purpura, Platelet transfusion, Petechiae, Ecchymosis, and Purpura.

All cases identified were reviewed and classified using both the CDC working definition and the Brighton Collaboration interim case definition for TTS.

The **CDC classification** for possible cases of TTS [18] divides cases into 2 tiers based on the location of thrombosis and severity of symptoms, with Tier 1 being associated with higher

morbidity and mortality. Reported cases of possible TTS with insufficient evidence or information to be classified according to either of the case definitions were classified as "unassessable"; and cases with evidence that parameters were not met for either case definition were classified as "Not a TTS case".

The **Brighton Collaboration case definition** for TTS [144] divides cases into 5 levels:

- Level 1 – Definite Case
- Level 2 – Probable Case
- Level 3 – Possible Case
- Level 4 – Not enough information
- Level 5 – Not a case of TTS

For those cases that are classifiable according to the CDC or Brighton Collaboration definitions, the Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Appendix 11.13 includes the reporting period information for all TTS-related case reports according to the Brighton collaboration case definitions for TTS, the CDC working case definition for TTS, and case causality assessments according to the WHO-UMC standardized case causality assessment.

16.3.6.2.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected

See Appendix 11.3.

Overview of Cases

For more details on TTS cases please refer to Appendix 11.13.

Cumulative Review (cumulative to 17 Dec 2022)

Cumulatively, through 17 Dec 2022, a total of 230 cases (and 224 events) were identified with Thrombosis with Thrombocytopenia related events, of which 224 cases were assessed as serious and 31 cases had a fatal outcome. Of the 230 cases, 194 (84.3%) were medically confirmed. When

dose number and TTO was reported, events most frequently were reported after Dose 2 (29.2%) and within 7 to >30 days (96; 38.4%) after vaccination.

There was no major difference observed in cases reported in males (117; 50.9%) compared to females (107; 46.5%); gender information was not reported for 6 cases (2.6%). The mean age was 59.5 years (SD19.0); median age was 63.0 years (min. 15/max. 96); 7 cases were missing age data. Reports most frequently originated from the United States (82; 35.7%), followed by European Economic Area (EEA) (69; 30.0%) and the Asia (50; 21.7%), and were received most frequently from regulatory authorities (184; 80.0%).

Report Period Review (19 Jun 2022 to 17 Dec 2022)

During the reporting period, there were 33 cases (35 events) of Thrombosis with Thrombocytopenia related events, of which 32 cases were serious, and 5 cases had a fatal outcome. During the review period, there were more cases of TTS- related events reported in males (19 cases [57.6%]) than in females (13 cases [39.4%]), with one report with unknown gender (3.0%). The mean age was 60.8 years (SD: 18.5); median age was 67.0 years (min. 18.0/ max. 88.0).

Similar to previous report periods, the majority of reports were received from regulatory authorities (16; 48.5%). The majority of case reports during the reporting period continues to occur in individuals aged ≥ 50 years of age (21; 63.6%). During this reporting period there were no cases of TTS-related events reported in individuals <12 years of age (Table 16.88).

Table 16.88. Number and Percentage of Thrombosis with Thrombocytopenia Related Cases by Age group - Review Period 19 Jun 2022 to 17 Dec 2022

Age Group	Prior to Review Period		Review Period		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	2	1.0	0	0	2	0.9
18-24Y	10	5.1	1	3.0	11	4.8
25-39Y	22	11.2	3	9.1	25	10.9
40-49Y	22	11.2	5	15.2	27	11.7
50-64Y	46	23.4	5	15.2	51	22.2
65-74Y	47	23.9	10	30.3	57	24.8
75Y+	44	22.3	6	18.2	50	21.7
Missing	4	2.0	3	9.1	7	3.0
Grand total	**197**	**100.0**	**33**	**100.0**	**230**	**100.0**

During the reporting period most of TTS-related events were reported as occurring after Dose 3

(7; 21.0%), a notable change from the prior review period in which events occurred most frequently after Dose 2 (65.0%). There is no notable temporal pattern in the TTO reported following each of the respective doses. The relatively greater number of reports received following Dose 3 could be attributed to the increasing number of Dose 3 elasomeran administrations during this report period (Table 16.89).

Table 16.89. Number and Percentage of Thrombosis with Thrombocytopenia Related Events by Dose* and Time to Onset - Review Period 19 Jun 2022 to 17 Dec 2022

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total of # Events	Grand total of % of Total Events
		# Events	% of Total Events	# Events	% of Total Events		
Dose 1	Subtotal	51	23.7	4	11.4	55	22.0
	0 days	3	1.4	0	0	3	1.2
	01-02	6	2.8	1	2.9	7	2.8
	03-04	5	2.3	0	0	5	2.0
	05-06	1	0.5	0	0	1	0.4
	07-13	13	6.0	3	8.6	16	6.4
	14-29	17	7.9	0	0	17	6.8
	30+	6	2.8	0	0	6	2.4
Dose 2	Subtotal	72	33.5	1	2.9	73	29.2
	0 days	4	1.9	0	0	4	1.6
	01-02	14	6.5	0	0	14	5.6
	03-04	8	3.7	0	0	8	3.2
	05-06	2	0.9	1	2.9	3	1.2
	07-13	12	5.6	0	0	12	4.8
	14-29	12	5.6	0	0	12	4.8
	30+	20	9.3	0	0	20	8.0
Dose 3	Subtotal	11	5.1	7	20.0	18	7.2
	0 days	1	0.5	1	2.9	2	0.8
	01-02	2	0.9	2	5.7	4	1.6
	07-13	2	0.9	0	0	2	0.8
	14-29	4	1.9	0	0	4	1.6
	30+	2	0.9	4	11.4	6	2.4
Dose 4	Subtotal	0	0	4	11.4	4	1.6

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total of # Events	Grand total of % of Total Events
		# Events	% of Total Events	# Events	% of Total Events		
	0 days	0	0	2	5.7	2	0.8
	01-02	0	0	1	2.9	1	0.4
	14-29	0	0	1	2.9	1	0.4
Unknown	Subtotal	81	37.7	19	54.3	100	40.0
	0 days	5	2.3	0	0	5	2.0
	01-02	8	3.7	0	0	8	3.2
	03-04	2	0.9	0	0	2	0.8
	05-06	6	2.8	0	0	6	2.4
	07-13	3	1.4	3	8.6	6	2.4
	14-29	5	2.3	0	0	5	2.0
	30+	3	1.4	0	0	3	1.2
	Missing	49	22.8	16	45.7	65	26.0
Grand total		**215**	**100.0**	**35**	**100.0**	**250**	**100.0**

During the review period, similar to the cumulative period, the most frequently reported PT were Thrombocytopenia (10; 28.6%), Thrombotic thrombocytopenic purpura (10; 28.6%) and TTS (7; 20.0%). The most frequently reported PTs during the reporting period were in line with those seen in the prior to review period. (Table 16.90).

Table 16.90. Number and Percentage of Reported MedDRA PTs in Cases of Thrombosis with Thrombocytopenia Related Events - Review Period 19 Jun 2022 to 17 Dec 2022

PT	Prior to Review Period		Review Period		Total # Events	% Events
	# Events	% Events	# Events	% Events		
Thrombocytopenia	104	48.4	10	28.6	114	45.6
Thrombotic thrombocytopenic purpura	38	17.7	10	28.6	48	19.2
Thrombosis with thrombocytopenia syndrome	26	12.1	7	20.0	33	13.2
Platelet count decreased	22	10.2	1	2.9	23	9.2
Petechiae	8	3.7	5	14.3	13	5.2
Immune thrombocytopenia	9	4.2	0	0	9	3.6

PT	Prior to Review Period		Review Period		Total # Events	% Events
	# Events	% Events	# Events	% Events		
Purpura	3	1.4	1	2.9	4	1.6
Platelet disorder	3	1.4	0	0	3	1.2
Ecchymosis	1	0.5	0	0	1	0.4
Platelet transfusion	1	0.5	0	0	1	0.4
Thrombocytopenic purpura	0	0	1	2.9	1	0.4

During this reporting period, similar proportions were observed in Not recovered (9; 25.7%) and recovered or recovering (10; 28.6%) categories. Fatal outcomes were reported for 5 cases (5 events; 14.3%) (Table 16.91). Of these 5 cases, there were no specific trends observed, other than most of the cases (3 out of 5 cases) were from ≥70 years of age population. Four (4) out of 5 cases were considered of Brighton Collaboration Level-4 or 5, and 1 case was of Level-1 per Brighton Collaboration definitions of Level of Certainty.

Table 16.91. Summary of Outcomes of Thrombosis with Thrombocytopenia Related Events - Review Period 19 Jun 2022 to 17 Dec 2022

Event Outcome	Prior to Review Period		Review Period		Total # Events	% of Events
	# Events	% Total Events	# Events	% Total Events		
Fatal	32	14.9	5	14.3	37	14.8
Not Recovered/Not Resolved	44	20.5	9	25.7	53	21.2
Recovered/Resolved	35	16.3	3	8.6	38	15.2
Recovered/Resolved with Sequelae	7	3.3	0	0	7	2.8
Recovering/Resolving	28	13.0	7	20.0	35	14.0
Unknown	69	32.1	11	31.4	80	32.0
Grand total	**215**	**100.0**	**35**	**100.0**	**250**	**100.0**

Adolescents aged 12-17 years

Cumulatively there were two cases which were presented in PBRER#3. There were no reports of cases with TTS-related events received by the MAH in adolescents (12-17 years) during the reporting period.

Children aged <12 years

There were no reports of cases with TTS-related events received by the MAH through 17 Dec 2022 of TTS-related events in children <12 years of age.

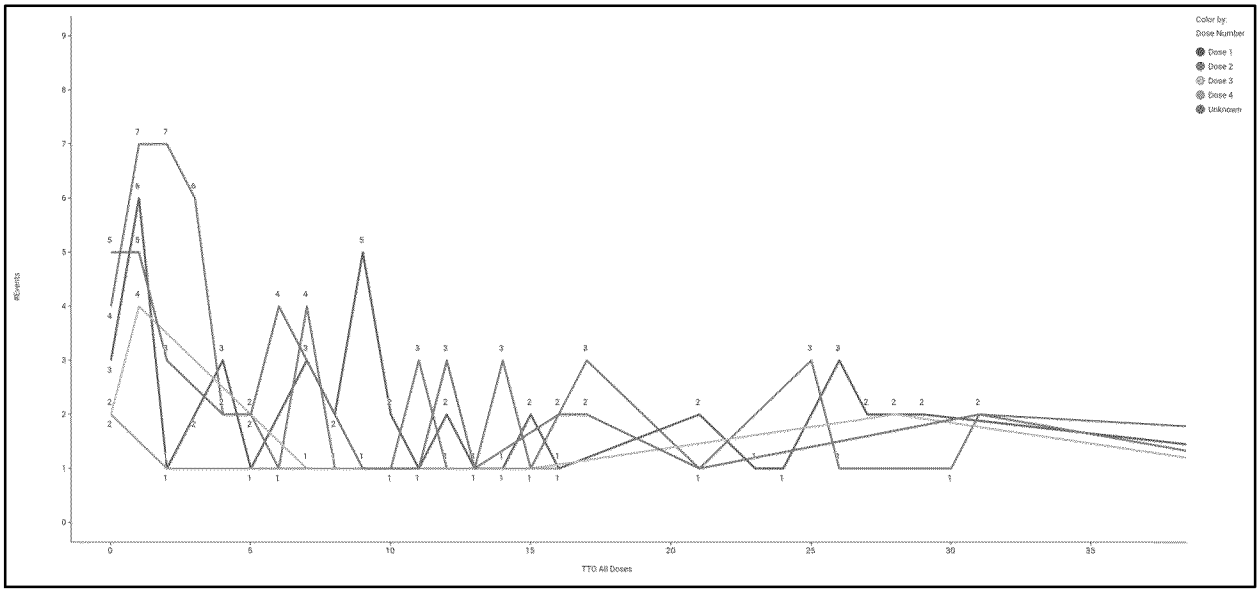
Thrombosis with Thrombocytopenia Syndrome (TTS) Cases After Dose 3 or Booster Dose

Cumulatively, there were 20 cases of thrombosis with thrombocytopenia related events reported following Dose 3 or greater. Of these 10 cases, 3 were fatal reports, received during the reporting period of this PBRER. Details of these cases, including the fatal report, received during the current reporting period are presented in Appendix 11.13.

Health authority request: *The MAH should also address the following issues in the next PSUR: Thrombosis with Thrombocytopenia Syndrome (TTS): The MAH is requested, in the next PSUR, to provide a discussion on the pattern of TTO in TTS, and whether there are differences in TTO according to dose number.*

Response: A cumulative review of all reported cases of TTS-related events (230 cases) by dose number and TTO, did not show any reporting trend or notable temporal pattern in the TTO reported after any dose. As Figure 16-12 shows random peaks are observed for all doses; with most events observed after Dose-1 and Dose-2. This observation may be due to the current trend of more individuals receiving the first two doses than boosters.

Figure 16-12 Time to Onset of Events by Dose Number



Brighton Collaboration/ CDC Working Case Definition/ WHO Causality Assessment

During the reporting period, evaluation of 33 cases identified with thrombosis and thrombocytopenia related events using the Brighton Collaboration case definition for TTS [144]

showed that there were One (1) report classified as Level 1–Definitive case, No reports classified as (Level-2 and Level-3) – Possible case, 15 reports classified as Level 4 - Not enough information, and 17 reports classified as Level 5 - Not a case of TTS.

According to the CDC working case definition for TTS, there were 3 reports classified as Tier 1, One (1) report classified as Tier 2 and 6 reports were unassessable due to the lack of information, including platelets levels; and 23 reports were classified as Not a case of TTS based on the report not meeting the case definition or on information available that provided a different clinical explanation for the classification of the events.

According to the WHO causality assessment, there were 5 reports classified as possible based solely on temporal association between the use of the product and the start of the events; however, a causal relationship cannot be excluded due to the lack of supporting information, including medical history, concomitant medications, clinical course, laboratory information, etc. There was 1 report considered conditional, 7 reports were considered as unassessable due to the lack of information, and there were 3 reports that were considered unlikely to be related to the vaccine due to prolonged TTO as well as comorbidities present in some of these patients that provide a more plausible explanation for the occurrence of the events, and there were 16 events that were not provided a causality assessment as they were not a cases of TTS-related events.

Thrombosis with Thrombocytopenia Syndrome After Receiving Booster Dose with elasomeran/imelasomeran

No reports were received as of 17 Dec 2022 for individual receiving the elasomeran/ imelasomeran booster.

Thrombosis with Thrombocytopenia Syndrome After Receiving Booster Dose with elasomeran/davesomeran

No reports were received as of 17 Dec 2022 for individuals receiving the elasomeran/davesomeran booster.

16.3.6.2.1.5. Discussion

Thrombosis with thrombocytopenia syndrome is a potentially life-threatening condition associated with adenoviral-vectored COVID-19 vaccination.

Cases of cerebral venous sinus thrombosis after vaccination with the Ad26.COV2.S COVID-19 vaccine have previously been described Case patients receiving a COVID-19 vaccine from 14 Dec 2020 through 17 Dec 2022 with thrombocytopenia and thrombosis (excluding isolated

ischemic stroke or myocardial infarction) were reported to the VAERS. Reporting rates for TTS were 3.83 per million vaccine doses (Ad26.COV2.S) and 0.00855 per million vaccine doses (mRNA-based COVID-19 vaccines) [145]. Analysis of the data reported during this reporting period does not provide evidence to support a causal association between TTS and elasomeran. Multiple reports lacked laboratory results and imaging test findings, moreover, number of reports were missing level of platelets or results of heparin-PF4 ELISA HIT antibody test. Cumulatively, the reporting rate of TTS for elasomeran is substantially lower than one report per million doses. In addition, in this reporting period most of the reports met neither the CDC nor Brighton definition for TTS, and of those that met the criteria for CDC or Brighton Collaboration definitions, the majority of the cases were considered unlikely related to the vaccine based on the WHO standardize case causality assessment guidance.

Review of the reported TTS-related events by TTO and dose did not show any trending in the occurrence of these events, with a higher number of the events reported after dose 1 and dose, indicating a higher volume of individuals receiving the initial primary series vaccination, but with no evidence of reports happening within any specific risk window.

The MAH will continue to monitor the occurrence of TTS with elasomeran or elasomeran/imelasomeran or elasomeran/davesomeran) and in all populations via routine pharmacovigilance and will be discussed in future reports.

16.3.6.2.1.6 Conclusion

The data provided in this PBRER describe sufficiently the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran cumulatively and during the reporting period. The benefit-risk evaluation remains positive. After careful review of all new safety data received during the reporting period, (19 Jun 2022 to 17 Dec 2022) for the risk of thrombocytopenia and thrombosis, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The risk of thrombocytopenia and thrombosis will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.3 Nervous System Disorders

16.3.6.3.1 Guillain-Barre Syndrome (GBS)

16.3.6.3.1.1 Source of the New Information

New information presented below includes analysis performed on new cases received by MAH from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed covers the period from the 18 Dec 2020 to 17 Dec 2022.

16.3.6.3.1.2. Background Relevant to the Evaluation

Several reports of Guillain-Barre syndrome (GBS) have been received by the Centers for Disease Control and Prevention (CDC) in the Vaccine Adverse Event Reporting System (VAERS) (CDC-Advisory Committee on Immunization Practices 2021) with the use of adenovirus vectored COVID-19 vaccines.

Guillain-Barre syndrome is an acquired degenerative, demyelinating neurological disorder classically characterized by progressive, symmetrical ascending paralysis. Absent muscle reflexes and loss of sensation are also commonly associated. The etiology remains unclear, but onset has been associated with viral illness, most commonly an upper respiratory infection (URI), next most commonly by gastrointestinal illness. Campylobacter jejuni and Haemophilus influenzae are the most commonly involved bacterial pathogens [146].

Miller Fisher syndrome (MFS) is a rare variant of GBS, observed in only about 1-5% of all cases of GBS in Western countries. In other geographic regions such as Taiwan and Japan, the proportion is higher, 19% and 25%, respectively. Miller Fisher syndrome presents with a clinical finding of ataxia, areflexia, and ophthalmoplegia. One of the main differences between MFS and more common variants of GBS is that the first nerve groups to demyelinate are commonly located in the cranium. This results in difficulties with balance and coordination, ocular muscle movement and vision impairment, and neuronal reflexes. Miller Fisher syndrome is a clinical diagnosis that often goes undiagnosed due to the low prevalence. Miller Fisher syndrome is a clinical diagnosis that can be confirmed serologically with positive anti-ganglioside GQ1b antibodies [147].

Guillain-Barre syndrome is believed to be an immune-mediated disorder resulting from the generation of autoimmune antibodies that cross-react with epitopes on peripheral nerves, leading to nerve damage. Auto-antibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infections. About two-thirds of GBS cases occur several days or weeks after an

apparent infectious illness, commonly a diarrheal illness or upper respiratory tract infection. The gastrointestinal bacterium Campylobacter jejuni has been found to stimulate cross reactive antibodies that can result in GBS, particularly acute motor axonal neuropathy. Other infectious agents that have been temporally associated with GBS include influenza viruses, Mycoplasma pneumoniae, HIV, Epstein-Barr virus, cytomegalovirus, and the vaccinia virus used in smallpox vaccines. Other exposures that appear to be temporally associated with GBS include surgical procedures and some malignancies, particularly Hodgkin's disease and other lymphomas. Various vaccines have also been temporally associated with GBS [148]. The only vaccines that have demonstrated elevated risk are influenza vaccines. Reviews of reports following use of the swine flu vaccine (1976) suggested a slightly increased risk for GBS (approximately one case per 100,000 vaccine recipients). Since then, increased risks for GBS associated seasonal influenza vaccines wax and wane; when risks are elevated, they are estimated to be approximately 1-2 cases/million doses administered (https://www.cdc.gov/ vaccine safety/concerns/guillain-barre-syndrome.html).

A recent review using data from the US VSD suggested that the risk for GBS following receipt of COVID-19 mRNA vaccines in the period 1-21 days following vaccination was no different than the background rate [149].

16.3.6.3.1.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulative to 17 Dec 2022 for valid case reports of GBS received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following MedDRA PTs: "Acute motor axonal neuropathy, Acute motor-sensory axonal neuropathy, Bickerstaff's encephalitis, Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Miller Fisher syndrome, and Subacute inflammatory demyelinating polyneuropathy".

Cases were classified into one of five categories, following the Brighton Collaboration case definitions (CD) for GBS, which also includes evaluation for possible MFS. Both GBS and MFS have 3 levels of diagnostic certainty and the lowest, level 3, is limited to clinical findings. Critical for a report of GBS to meet CD level 3, is demonstration of absent or decreased deep tendon reflexes in the same limbs that are weak. Without this, it cannot meet any level of certainty. GBS/MFS overlap syndromes may occur, where there is weakness and features of MFS. In such

cases the level of certainty should be based on the GBS criteria, but it can also be described as GBS/MF overlap syndrome [150]:

- Level 1 (Definitive case)
- Level 2 (Probable case)
- Level 3 (Positive case)
- Level 4 is a reported event of GBS/MFS with insufficient evidence to meet level 1, 2 or 3 of the CD
- Level 5 (Not a case)

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Appendix 11.14 includes detailed summary of reporting period cases that met Brighton Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

16.3.6.3.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed Vs Expected Analysis

See Appendix 11.3.

Overview of Cases

Cumulative Review (GBS, cumulative to 17 Dec 2022)

Cumulatively, a total of 683 cases of GBS and related PTs were identified for elasomeran. Of the 683 cases, 673 were serious and 10 cases had fatal outcomes. The 683 cases of GBS yielded 713 events, of which 700 were serious. Of the 683 cumulative cases of GBS, 524 cases (76.7 %) were medically confirmed. Most of the cases were received from regulatory agencies (555; 81.3%).

Cumulatively, the 683 cases reported under the GBS-related terms showed that distribution in males (349; 51.1%) was higher than in females (319; 46.7%), and in 15 cases;(2.2%) gender was not known. The majority of events were reported in patients >50 years of age, with a median patient age of 57.0 years (range 13 to 120 years of age) (Table 16.92).

Table 16.92 Number and Percentage of Guillain-Barre related Cases for elasomeran by Age and Gender-Cumulative to 17 Dec 2022

Age Group (Years)	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	1	0.1	1	0.1	0	0.0	2	0.3
16-17	3	0.4	0	0.0	0	0.0	3	0.4
18-24	16	2.3	19	2.8	0	0.0	35	5.1
25-39	58	8.5	33	4.8	0	0.0	91	13.3
40-49	57	8.3	50	7.3	0	0.0	107	15.7
50-64	89	13.0	107	15.7	0	0.0	196	28.7
65-74	52	7.6	75	11.0	3	0.4	130	19.0
75+	36	5.3	53	7.8	0	0.0	89	13.0
Missing	7	1.0	11	1.6	12	1.8	30	4.4
Grand total	**319**	**46.7**	**349**	**51.1**	**15**	**2.2**	**683**	**100.0**

The majority of GBS associated events, 82.3% were captured as PT "Guillain-Barre syndrome" (Table 16.93).

Table 16.93 Number and Percentage of Guillain-Barre related Preferred terms for elasomeran -Cumulative to 17 Dec 2022

PT	# Events	% Total Events
Guillain-Barre syndrome	587	82.3
Chronic inflammatory demyelinating polyradiculoneuropathy	57	8.0
Miller Fisher syndrome	25	3.5
Demyelinating polyneuropathy	24	3.4
Acute motor axonal neuropathy	6	0.8
Acute motor-sensory axonal neuropathy	6	0.8
Bickerstaff's encephalitis	4	0.6
Ascending flaccid paralysis	2	0.3
Subacute inflammatory demyelinating polyneuropathy	2	0.3
Grand total	**713**	**100.0**

Cumulatively, when dose number and time to onset could be determined, the TTO of GBS events after Dose 1 (173; 24.3%) or Dose 2 (169, 23.7%) was comparable with a drop-off after subsequent vaccinations (Table 16.94).

Table 16.94 Number of Guillain-Barre related Events for elasomeran by Dose Number, and Time to Onset (TTO)-Cumulative to 17 Dec 2022

Dose Number	TTO (Days)	Total # Events	% Events
Dose 1	**Subtotal**	**173**	**24.3**
	0 days	11	1.5
	01-02	26	3.6
	03-04	9	1.3
	05-06	14	2.0
	07-13	42	5.9
	14-29	44	6.2
	30+	27	3.8
Dose 2	**Subtotal**	**169**	**23.7**
	0 days	13	1.8
	01-02	17	2.4
	03-04	15	2.1
	05-06	4	0.6
	07-13	27	3.8
	14-29	41	5.8
	30+	52	7.3
Dose 3	**Subtotal**	**76**	**10.7**
	0 days	2	0.3
	01-02	7	1.0
	03-04	8	1.1
	05-06	2	0.3
	07-13	20	2.8
	14-29	15	2.1
	30+	22	3.1
Dose 4	**Subtotal**	**6**	**0.8**
	0 days	1	0.1
	07-13	1	0.1
	14-29	2	0.3

Dose Number	TTO (Days)	Total # Events	% Events
	30+	2	0.3
Unknown	**Subtotal**	**289**	**40.5**
	0 days	11	1.5
	01-02	19	2.7
	03-04	10	1.4
	05-06	6	0.8
	07-13	25	3.5
	14-29	23	3.2
	30+	33	4.6
	Missing	162	22.7
Grand Total		**713**	**100.0**

GBS in Children (<12 Years of Age) (Cumulative as of 17 Dec 2022)

There were no reports of GBS-related events for children < 12 years of age cumulatively through 17 Dec 2022.

GBS in Adolescents (12-17 Years of Age) (Cumulative as of 17 Dec 2022)

Cumulatively, a total of 5 cases of GBS-related PTs were reported for adolescents. All five cases were serious, and none had fatal outcome. Of the 5 cumulative cases, 4 cases were medically confirmed. More cases were reported in females (4 cases; 80%) compared to males (1 case; 20%). All 5 cases were received from regulatory authorities: one case each from Argentina, France, Germany, Japan, and Spain. Of the 5 events, 3 events had not recovered/ not resolved, and 2 events were recovering/resolving.

GBS in Patients After a Third Dose or Booster Dose of elasomeran (Cumulative as of 17 Dec 2022)

Cumulatively 81 cases (80 serious; one fatal case) of GBS-related PTs occurred after Dose 3 or a booster dose of elasomeran was administered. The 81 cases included 82 events (81 serious events). There were 58 medically confirmed reports of GBS in patients receiving a Dose 3 or a booster dose of elasomeran.

Reporting Period 19 Jun 2022 to 17 Dec 2022

During the reporting period, a total of 72 cases of GBS-related PTs were identified for elasomeran. Of the 72 cases, 71 were serious with three cases having a fatal outcome. Of the 72 cases, 50 (69.4%) were medically confirmed.

The event outcomes reported were as follows: 18 (25.0%) events were not recovered/ not resolved, 17 (23.6%) events were recovering/resolving, 13 (18.1%) events recovered/resolved with sequela, 8 (11.1%) events had recovered/resolved, 3 (4.2%) fatal events, and 13 (18.1%) events did not have a reported outcome. The distribution of cases was higher in males (42; 58.3%) compared to that in females (27; 37.5%), and (3; 4.2 %) cases did not specify gender. Most of the reports described patients ≥50 years of age (47; 65.3%) (Table 16.95).

Table 16.95 Number of Guillain-Barre related Case Reports for elasomeran by Gender and Age Group (19 Jun 2022 to 17 Dec 2022)

Age Group (Years)	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total cases	# Cases	% Total Cases		
12-15	0	0.0	0	0.0	0	0.0	0	0.0
16-17	0	0.0	0	0.0	0	0.0	0	0.0
18-24	2	2.8	3	4.2	0	0.0	5	6.9
25-39	3	4.2	3	4.2	0	0.0	6	8.3
40-49	3	4.2	7	9.7	0	0.0	10	13.9
50-64	11	15.3	13	18.1	0	0.0	24	33.3
65-74	4	5.6	9	12.5	0	0.0	13	18.1
75+	3	4.2	7	9.7	0	0.0	10	13.9
Missing	1	1.4	0	0.0	3	4.2	4	5.6
Grand total	**27**	**37.5**	**42**	**58.3**	**3**	**4.2**	**72**	**100.0**

Fatal Case Summary (Review Period 19 Jun 2022 to 17 Dec 2022)

During this reporting period, 3 cases ([redacted]) with fatal outcomes were received. These reports did not meet Brighton Collaboration Level 1-3 of diagnostic certainty for GBS and are not discussed further here.

Brighton Case Collaboration Case Definition.

Evaluation of the 72 cases received in the reporting period was conducted using the Brighton Collaboration case definition for Guillain-Barre and MFSs.

A review of Level 1-3 cases received during the reporting period was performed. A total of 9 cases meeting Level 1-3 Brighton Collaboration case definition for Guillain-Barre were reported. Three cases met Level 1 case definition of diagnostic certainty, four cases met Level 2 case definition, and two cases met Level 3 case definition.

An analysis of these cases by Brighton Collaboration criteria requires clinical interpretation and judgement. Often, there is a significant level of uncertainty due to missing information. For instance, WHO causality is informed by TTO and temporal relationship, which largely guides the assessment of the reviewer. Dose number and time to onset from vaccine administration were often unavailable. Concomitant medications, comorbid medical conditions and treatment for the event were also infrequently described. Very importantly, key information necessary to apply the Brighton GBS case definition and determine the level of diagnostic certainty such as flaccidity and presence/absence of reflexes, results of cerebrospinal fluid analysis, electrophysiologic studies or other investigations were often not provided. The absence such evidence affects the reviewer's ability to determine the level of diagnostic certainty.

GBS in Children (<12 Years of Age) (Reporting Period-19 Jun 2022 to 17 Dec 2022)

There were no reports of GBS-related events for children < 12 years of age during the reporting period.

GBS in Adolescents (12-17 Years of Age) (Reporting Period - 19 Jun 2022 to 17 Dec 2022)

There were no reports of GBS-related events for Adolescents (12-17 years of age) during the reporting period.

GBS in Patients After a Third Dose or Booster Dose of elasomeran) (Reporting Period-19 Jun 2022 to 17 Dec 2022)

During the review period, there were 26 cases (26 serious; one fatal case) of GBS and GBS-related PTs reported following the administration of Dose 3 and above of elasomeran. Of the 26 cases, 20 cases were medically confirmed.

A total of 5 cases meeting Level 1-3 Brighton Collaboration case definition for Guillain-Barre were reported after Dose 3. One case met Level 1 case definition of diagnostic certainty, two cases met Level 2 case definition, and two cases met Level 3 case definition.

Guillain-Barre Syndrome After Receiving Booster Dose with elasomeran/imelasomeran

During this reporting period MAH received one case ([redacted]) of GBS-related PTs occurring after receiving elasomeran/imelasomeran. The health authority report concerned a 31-year-old female patient with Urinary and respiratory tract infection approximately 10 days prior to vaccination, no concomitant medications reported, who experienced GBS 1-2 days after elasomeran/imelasomeran as dose 3 with no information provided describing vaccine doses 1 and 2. Patient had symptoms consistent with GBS, and CSF revealed protein-cell dissociation. Nerve conduction study was unremarkable.

MAH comment: Based on the clinical presentation and diagnostic evaluation revealing protein-cell dissociation and unremarkable nerve conduction study, this report is classified as Brighton Collaboration level 2 for GBS and WHO-UMC causality is assessed as possible with recent upper respiratory tract infection noted as possible confounder.

Guillain-Barre Syndrome After Receiving Booster Dose with elasomeran/davesomeran

During this reporting period MAH received one case ([redacted]) of GBS-related PTs occurring after receiving elasomeran/davesomeran. The HCP report concerned a 72-year-old man who experienced GBS 2-3 weeks after receiving elasomeran/davesomeran as dose 5 and the influenza vaccine. The patient reportedly experienced symptoms including severe pain in "both deltoid arms where he got the injections" for days, imbalance that went to his legs and difficulty walking. He was seen in the ED where a lumbar puncture showed protein and confirmed GBS after which the patient was admitted and had plasmapheresis. The pain still persists as shooting/poking discomfort.

MAH comment: The information provided yields insufficient clinical or objective laboratory evidence to meet any level of the case definition for GBS.

16.3.6.3.1.5. Discussion

Out of the 72 cases identified in the reporting period (19 Jun 2022 to 17 Dec 2022), 71 were serious with 9 of those cases evaluated as Level 1-3 according to the Brighton Collaboration case definition discussed above. Cases meeting Brighton Collaboration Level 4 and 5 were generally poorly described and most of those cases did not meet overall criteria for diagnostic certainty because they lacked clinical presentation and laboratory confirmation with evidence of decreased nerve conduction and cytoalbuminologic dissociation. Some cases provided alternative etiologies for the events.

During the reporting period, most cases (including events from Level 4 and Level 5), were consumer reports or reports received from regulatory authorities. These types of reports limit the reviewer's ability to obtain further follow-up information and/or obtain medical confirmation which hinders overall efforts to provide a proper assessment of causality.

There were 2 reports (one each) of patients who received Spikevax bivalent (elasomeran/imelasomeran and elasomeran/davesomeran vaccines, neither of which were informative to furthering the safety understanding of GBS with the bivalent vaccines.

The clinical spectrum of events in this reporting period was similar to that reported in the previous PBRER. Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported GBS, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.3.1.6 Conclusion

After careful review of all new safety data received cumulatively and during the reporting period in reports of GBS, the MAH considers there is no evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and GBS, and the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. ModernaTx, Inc. will continue to monitor events of GBS using routine surveillance.

16.3.6.4 Immune System Disorders

16.3.6.4.1 Multisystem Inflammatory Syndrome (MIS-C and MIS-A)

16.3.6.4.1.1 Source of the New Information

Information presented below includes analysis performed on cases received and entered into the GSDB of ModernaTx, Inc. from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.4.1.2. Background Relevant to the Evaluation

Multisystem Inflammatory Syndrome in Children (MIS-C) was first recognized in the UK in Apr 2020, in a fraction of children who develop a life-threatening hyperinflammatory state 4–6 weeks after infection with primary COVID-19 in the pandemic. A similar condition has also been reported as a rare complication of COVID-19 in adults (MIS-A). It is currently unknown if MIS-

C/A might follow immunization against SARS-CoV-2, therefore, a need exists to define this potential entity for monitoring as an AE following immunization.

Children who develop MIS-C are generally previously healthy individuals. The primary COVID-19 infection in these patients is almost universally mild or asymptomatic. They typically present to medical attention on day 3–5 after developing a persistent fever associated with gastrointestinal symptoms (pain, vomiting, diarrhea), evidence of mucocutaneous inflammation (rash, conjunctivitis, oromucosal changes), lymphopenia, and high levels of circulating inflammation (for examples, Elevated CRP, erythrocyte sedimentation rate [ESR], ferritin, or procalcitonin). A subset of MIS-C patients develops severe disease including hypotension/shock and evidence of cardiac involvement including myocarditis, myocardial dysfunction, and coronary artery changes. Immune modulation has been used with best supportive care to treat MIS-C, leading in most cases to prompt resolution of the inflammation. Fatal cases are rare. Given the emerging nature of this disorder, long-term outcomes are unknown, but the overwhelming majority of children appear to return to their pre-morbid baseline with respect to cardiac status.

From early in the pandemic, it was clear that a subset of adult patients experiences a severe hyperinflammatory response during primary SARS-CoV-2 infection. After MIS-C was recognized, a similar presentation in adult patients, MIS-A, was appreciated as a distinct clinical entity. MIS-A has been recognized as a severe illness requiring hospitalization in a person aged >21 years, with laboratory evidence of current or previous (within 12 weeks) SARS-CoV-2 infection, severe extrapulmonary organ dysfunction (including thrombosis), laboratory evidence of severe inflammation, and absence of severe respiratory disease. Patients with MIS-A have been reported up to age 50 years and, compared to MIS-C, are more likely to have underlying health conditions and experience an identifiable antecedent respiratory illness. MIS-A patients otherwise have remarkably overlapped clinical features with MIS-C, although the severity of cardiac dysfunction, the incidence of thrombosis and the mortality of MIS-A may be higher. The prevalence of MIS-C in communities experiencing widespread COVID-19 infections is unclear but has been estimated at 2/100,000 children. MIS-A appears to have an even less clear prevalence [151].

During the reporting period, there was no new information on epidemiology or CD available. The Brighton Collaboration Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) defines MIS-C as < 21 years and MIS-A ≥ 21 years. Based on the presentation and duration of fever, presentation of clinical features, for example, signs of mucocutaneous involvement (erythema, nonexudative conjunctivitis, et al), gastrointestinal involvement (abdominal pain,

vomiting, diarrhea, et al), presence of shock/hypotension, and or neurologic involvement (altered mental status, paresthesia, et al); Laboratory evidence of inflammation such as elevated CRP, ESR, ferritin, or procalcitonin; measures of disease activity such as elevated BNP, NT-proBNP, troponin, neutrophilia, lymphopenia, thrombocytopenia, evidence of cardiac involvement by echocardiography or physical stigmata of heart failure, ECG changes consistent with myocarditis or myo-pericarditis; and following COVID-19 infection or vaccination; a MIS-C/A may be classified into one of five levels of diagnostic certainty, refer to the section below.

16.3.6.4.1.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The ModernaTx, Inc. GSDB was queried for valid case reports of MIS-related events received from HCP, HA, consumers, and literature, worldwide, for the elasomeran, elasomeran/imelaosomeran and elasomeran/davesomeran using the MedDRA PTs of Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, and Systemic inflammatory response syndrome.

Identified cases were evaluated following the Brighton Collaboration Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A): Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data, and were classified into one of five levels of diagnostic certainty:

- Level 1 - Definitive case
- Level 2 - Probable case (Divided into Levels 2a and 2b)
- Level 3 - Possible case (Divided into Levels 3a and 3b)
- Level 4 - Insufficient Evidence
- Level 5 - Not a case of MIS-C/A

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [65].

16.3.6.4.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on MIS cases please refer to Appendix 11.15.

Observed vs Expected Analysis

See Appendix 11.3.

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and Multisystem Inflammatory Syndrome to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved.

A total of 352 literature articles were retrieved using these search criteria for the review period. The literature search results were medically/scientifically reviewed. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Overview of Cases

Cumulatively, through 17 Dec 2022, a total of 166 cases (167 events) with MIS-related terms have been reported, with 159 serious cases (95.8%) and 143 cases medically confirmed. There were 7 cases (4.2%) with fatal outcomes.

There were 70 cases (42.2%) that involved male patients, 94 cases (56.6%) that involved female patients and 2 (1.2%) cases with unknown genders. The mean patient age was 54.2 years (SD 19.5), with a median age of 58 years (min 12 /max 86); 9 cases were missing age data. Majority of cases were from the United States (62.7%) followed by the EEA (21.1%).

Multisystem Inflammatory Syndrome (Reporting Period – 19 Jun 2022 to 17 Dec 2022)

During the reporting period, a total of 20 cases (20 events) containing MIS-related events were reported, and 14 cases medically confirmed. All cases were serious with 1 case (1 event) with a fatal outcome. There were 7 (35%) cases that involved male patients, 12 cases (60%) involved female patients; and 1 (5%) with unknown gender. The mean patient age was 44.9 years (SD: 18), with a median age of 47 years (min: 19 /max: 69); 1 case was missing age data. There were 5 cases (25%) reported in the 18–24-year-old and 65–74-year-old age group. Other age groups were reported somewhat less frequently (Table 16.96)

Table 16.96 Number and Percentage of Cases Reporting MIS-related Events by Age and Gender-Reporting Period 19 Jun to 17 Dec 2022

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15Y	0	0.0	0	0.0	0	0.0	0	0
18-24Y	2	10.0	3	15.0	0	0.0	5	25.0
25-39Y	1	5.0	1	5.0	0	0.0	2	10.0
40-49Y	3	15.0	0	0.0	0	0.0	3	15.0
50-64Y	2	10.0	2	10.0	0	0.0	4	20.0
65-74Y	4	20.0	1	5.0	0	0.0	5	25.0
75Y+	0	0.0	0	0.0	0	0.0	0	0
Missing	0	0.0	0	0.0	1	5.0	1	5.0
Grand total	**12**	**60.0**	**7**	**35.0**	**1**	**5.0**	**20**	**100**

The two most reported MIS-related events were Multisystem inflammatory syndrome (6; 30%); and Systematic inflammatory response syndrome (5, 25.0%) (Table 16.97)

Table 16.97 Number and Percentage of MIS-related Events by PT-Reporting Period 19 Jun to 17 Dec 2022

PT	# Events	% Total Events
Multisystem inflammatory syndrome	6	30.0
Systemic inflammatory response syndrome	5	25.0
Cytokine storm	3	15.0
Multisystem inflammatory syndrome in adults	3	15.0
Cytokine release syndrome	3	15.0
Grand total	**20**	**100.0**

There were 16 events (80%) with insufficient data to calculate TTO, and 16 events (80%) had missing dose information. There were no events following dose 1, 2 events (10%) following dose 2, and 1 event (5%) following dose 3 and 4. (Table 16.98). The average TTO of the reported events was 5.8 days (SD: 11.9) and the median was 1 day (min: 0/max: 27). All events except one (19; 95%) were reported in less than 7 days after vaccination.

Table 16.98 Number and Percentage of MIS-related Events by Dose Number and Time to Onset (TTO)–Reporting Period 19 Jun to 17 Dec 2022

Dose Number	TTO (Days)	# Events	% Total Events
Dose 1	***Subtotal***	***0***	***0***

Dose Number	TTO (Days)	# Events	% Total Events
Dose 2	***Subtotal***	***2***	***10.0***
	01-02	2	10.0
Dose 3	***Subtotal***	***1***	***5.0***
	0 days	1	5.0
Dose 4	***Subtotal***	***1***	***5.0***
	0 days	1	5.0
Unknown	***Subtotal***	***16***	***80.0***
	14-29	*1*	*5.0*
	Missing	15	75.0
Grand total		**20**	**100.0**

Fatal Case Summaries

There was 1 case (1 event) with a fatal outcome received during this reporting period. Case summarized below.

[redacted] **(WWID: US-**[redacted]**):** This is a Literature non-study case concerning a 23-year-old male patient, with no medical history reported, who experienced Multisystem inflammatory syndrome in adults (MIS-A), Toxic epidermal necrolysis, events of Ventricular fibrillation and Cardiac arrest. Patient presented to the emergency room with fever, cough, shortness of breath, fatigue and painful rashes all over his body. Patient was diagnosed with COVID-19 three weeks prior which resolved after 3 days. He had received 2 doses of elasomeran vaccine 6 months prior. Physical exam revealed macular erythematous rash in his trunk and extremities. Leukocyte count was 4 k/uL, hemoglobin 15.5 g/dL, platelets 99 k/uL, sodium 126 mmol/L, bicarbonate 20mmol/L, blood urea nitrogen 30 mg/dL, creatinine 2.2 mg/dL, lactate 5.1 mmol/L, ferritin >7500 ng/mL, total bilirubin 7.6 mg/dL, AST 298 U/L, ALT 291 U/L, ALP 106 U/L, procalcitonin 14.71 ng/mL, D-dimer 11.98FEUug/mL. Troponin-I peaked at 1359 pg/ml. CT angiography of the chest, venous doppler and echocardiogram were normal. An extensive infectious disease workup was negative. He was suspected to have MIS-A from recent COVID-19. He was started on methylprednisolone 1g/day, intravenous immunoglobulin, anakinra and empiric antibiotics. Over the next 2 days, there was progression of rash with sloughing of skin in his trunk, back and extremities with bullae on his legs, and thigh sparing the face. Skin biopsy revealed Toxic Epidermal Necrolysis. On day 3, patient had a cardiac arrest from ventricular fibrillation, but was successfully resuscitated. Subsequently, he was intubated and required escalating vasopressor support for shock. On day 5, patient developed non-purulent conjunctivitis,

and was transferred to a higher center with a burn's unit on day 6. However, despite aggressive supportive measures he succumbed to refractory shock the following day.

Company Assessment: The authors of the article wrote that the patient fit the criteria for MIS outlined by CDC, including fevers, rash with non-purulent conjunctivitis, hypotension and thrombocytopenia, several laboratory criteria, negative infectious workup with a history of recent COVID-19 disease 3 weeks prior. However, the only temperature record was 97.3 F normal, and Blood record showed 116/78 mmHg no hypotension. The clinical presentation seems more to relate to the confirmed Toxic Epidermal Necrolysis (TEN), in which liver injury is common and thrombocytopenia is usually linked to a bad prognosis. Unfortunately, concomitant medications were not reported which will allow to provide more information on the diagnosis of TEN. Shock and system organ failure may well be the primary causes of death in TEN. The case is considered level 5 for MIS-A, due to the alternative etiology of TEN. The WHO causality thus is not applicable for MIS-A.

Multisystem Inflammatory Syndrome (MIS) in Children (<12 years old)–Reporting Period 19 Jun 2022 to 17 Dec 2022

During this reporting period, there were no cases received by the MAH of MIS-related events in children less than 12 years old.

Multisystem Inflammatory Syndrome (MIS) in Children (MIS-C) (Including Adolescents (12 to 17-years-old) and 18 to 20 years old according to case definition)–Reporting Period (19 Jun 2022 to 17 Dec 2022)

There were no cases in the 12-17 adolescent age group. However, during this reporting period, there were 1 case (1 event) reporting MIS-C related events in 18–20-year-olds. The case involved a 19-year-old male whose event outcome is listed as recovered.

Multisystem Inflammatory Syndrome in Patients After a Third Dose or Booster Dose of elasomeran –Reporting Period 19 Jun 2022 to 17 Dec 2022

During the reporting period, there were two cases in female patients, both medically confirmed received by the MAH of MIS-related events occurring on the same day following a 3rd or booster dose of elasomeran.

Brighton Collaboration Case Definition Evaluation/ WHO Causality Assessment

A review of MIS-C/A related cases with diagnostic certainty level 1–3 according to the Brighton Collaboration case definition including WHO causality assessment was performed. The following were the findings from the analysis:

There was 1 report classified as Level 1, 2 report as Level 2b, and no reports as Level 3a or 3b.

In 2 of those 3 MIS-C/A related cases with diagnostic certainty level 1–2 according to the Brighton Collaboration case definition, WHO standardized causality assessment, was classified as possible based on temporal association between the use of the product and the start of the events, and a causal relationship cannot be excluded due to the lack of other information.

There was 1 report that was considered unlikely to be related to the vaccine, due to the presence of comorbidities that provided a more plausible explanation for the occurrence of the events and over 9 months after last vaccination.

Multisystem Inflammatory Syndrome After Receiving Booster Dose with elasomeran/imelasomeran

There are no cases of MIS-related events received by the MAH after receiving booster dose with elasomeran/imelasomeran during this reporting period.

Multisystem Inflammatory Syndrome After Receiving Booster Dose with elasomeran/davesomeran

There are no cases of MIS- related events received by the MAH after receiving booster dose with elasomeran/davesomeran during this reporting period.

16.3.6.4.1.5. Discussion

Based on the analysis of all the safety data available reported during this reporting interval, the MAH considers that the majority of cases included under the AESI of MIS-C/A provided insufficient information for medical assessment or were confounded due to the reported events including TEN, COVID-19 infection, cytokine storm related events and others in the period right after vaccination.

16.3.6.4.1.6 Conclusion

A review of the data received during this reporting period showed that there is currently insufficient evidence to suggest a causal relationship between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and MIS-C/A at this point.

Based on the analysis of all the safety data received during the reporting period and cumulatively, the MAH considers that cases included under the AESI of MIS-C/A, reported in temporal

association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety issue of concern and the information provided is inadequate to provide evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and MIS-C/A. ModernaTx, Inc. will continue to monitor events for MIS-C/A using routine surveillance. A follow-up questionnaire was implemented to obtain additional information for cases reporting MIS-related events. The questionnaire has not increased the reporting of essential details. The benefit-risk evaluation remains positive.

16.3.6.5 Skin and Subcutaneous Tissue Disorders

16.3.6.5.1 Mechanical urticaria/Dermatography

16.3.6.5.1.1 Source of the New Information

The information presented below includes an analysis performed on cases received by ModernaTx, Inc. cumulatively (18 Dec 2020 to 17 Dec 2022) and during the reporting period (19 Jun 2022 to 17 Dec 2022) for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran for cases of mechanical urticaria as per a health authority request.

16.3.6.5.1.2. Background Relevant to the Evaluation

A health authority request was received by the MAH during the reporting period of this PBRER to perform a cumulative review of all cases of elasomeran associated with mechanical urticaria/dermatographism, and should the pattern indicate a co-occurrence of mechanical urticaria and chronic urticaria (CU), also include a review of CU.

- The MAH has previously conducted several comprehensive reviews of safety reports from the GSDB on the topic of urticaria and CU. The MAH determined that the signal of urticaria was considered an identified risk (not important), leading to an update to the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran CCDS.
- On 02 Aug 2022, the MAH updated the elasomeran CCDS ***Section 4.8 Undesirable effects, Table 1*** by adding "acute and delayed urticaria" as distinct terms to the ***Skin and Subcutaneous Tissue Disorders SOC*** and removing the reference "includes urticaria" from the ***Immune System Disorders SOC*** based on the evolving understanding of the types of urticaria reported with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.
- The SmPC for elasomeran and Spikevax bivalents was also updated, including under

Section 4.8 Undesirable effects, Table 3. Adverse reactions from elasomeran clinical studies and post-authorization experience in children and individuals 6 months of age and older in the ***Skin and Subcutaneous Tissue Disorders SOC*** to include the ADR term "Urticaria", with an uncommon frequency (≥1/1 000 to <1/100), including a footnote indicating: "*Urticaria has been observed with either acute onset (within a few days after vaccination) or delayed onset (up to approximately two weeks after vaccination)*".

According to the Dermatology Section of the European Academy of Allergology and Clinical Immunology, the EU-founded network of excellence, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization (WAO) developed consensus guidelines for the definition, classification, diagnosis, and management of urticaria.

Urticaria is defined as a condition characterized by the development of wheals (hives), angioedema, or both [152]. Urtiaria is a common dermatologic condition, typified by "intensely pruritic, well-circumscribed, raised wheals ranging from several millimeters to several centimeters or larger in size". Urticaria can occur with or without angioedema, which is defined as a painful, localized, warm, nonpitting oedema of the subcutaneous or interstitial tissue. The intensity of the pruritus can cause significant discomfort and impairment of daily functioning and disrupt normal sleep.

The current guidelines classified urticaria based on the clinical manifestation of urticaria which are broad, and patients may exhibit two or more subtypes at one time [153]. In this classification, the term CU is strictly reserved for spontaneous appearance of wheals, but this does not mean that the physical subtypes of urticaria are not chronic; in these cases, symptoms are not chronic but only visible when physical stimuli are present [154].

Urticaria subtypes-classification

Type	Subtype	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema <6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema >6 weeks
Physical urticaria	Cold contact urticaria	Elicited by cold objects, air, fluids, or wind
	Delayed pressure urticaria	Elicited by vertical pressure, wheals arising after 3-12 h
	Heat contact urticaria	Elicited by localized heat exposure
	Solar urticaria	Elicited by UV and/or visible light
	Dermographic urticaria (urticaria factitia)	Elicited by mechanical shearing forces, wheals arising after 1-5 min
	Vibratory urticaria/angioedema	Elicited by vibration, for example, jackhammer
Other types of urticaria	Aquagenic urticaria	Elicited by water
	Cholinergic urticaria	Elicited by increase in core body temperature, for example, exercise
	Contact urticaria	Elicited by contact with triggering substance
	Exercise-induced anaphylaxis/urticaria	Elicited by physical exercise

Source: Classification of urticaria2. Zuberbier T. Classification of Urticaria. Indian J Dermatol. 2013;58(3):208–10.

Chronic urticaria is defined by "the presence of recurrent urticaria, angioedema, or both, for a period of more than 6 weeks" whereas acute urticaria has a duration of ≤ 6 weeks [155]. Urticaria has a lifetime prevalence of about 20%, whereas CU has a lifetime prevalence of approximately 0.5% to 5%. The estimated point prevalence of CU is 0.1 to less than 1% globally [152]. Acute urticaria is typically benign and self-limited and resolves with avoidance of triggers. Chronic urticaria is often spontaneous (formerly termed "idiopathic", with no identifiable triggers), only 15% have clear inducible urticaria (where triggers are known and consistent), and many people have episodes of both induced and spontaneous flares. Chronic spontaneous urticaria is an episodic and self-limited disorder in most patients, and for 80% of patients CU resolves within a year, however, >10% may have a duration 5 years or longer. Chronic urticaria is twice as frequent in females compared to males, and most often occurs over the age of 20, and can be triggered or flared by non-steroidal inflammatory drugs [152]. A proportion of patients diagnosed with CU have physical urticaria, also referred to as chronic inducible urticaria, which is urticaria incited by a physical stimulus, such as mechanical (friction, vibration, pressure) urticaria, thermal (heat or cold) urticaria, solar urticaria, and symptomatic dermatographism [156]. Dermographism is the most common form of physical or chronic inducible urticaria. It is also called dermatographia and dermographic urticaria [157]. Mechanical urticaria is the most common of the inducible urticarias and is present in 20 to 30 percent of adults with CU and also occurs in children, although there are fewer reports regarding this population [158].

Etiology

Urticaria is believed to be caused by "immunoglobulin E- and non–immunoglobulin E-mediated release of histamine and other inflammatory mediators from mast cells and basophils" [159] [159] [159]. This may be due to immune activation in response to certain viral, bacterial, or parasitic infections; IgE-mediated allergic reactions; direct mast cell activation; NSAIDs (pseudo-allergic or allergic reactions); or physical factors such as cold exposure or exposure to sunlight [160][160][160]. Although urticaria has always been considered a mast cell-driven disease, it is now known that it involves dysregulation of both mast cell and basophils with their subsequent activation and degranulation as well as the participation of other cells, e.g., eosinophils, T and B lymphocytes, epithelial, and endothelial cells. Up to 80-90% of cases of CU are idiopathic [159][159][159]. The pathogenesis of chronic spontaneous urticaria has not been established and potential hypotheses include autoimmunity mediated by functional auto-antibodies directed against IgE or the high-affinity IgE receptor, cellular defect theories and serum or plasma factors that directly or indirectly activate mast cells or basophils.

16.3.6.5.1.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively (18 Dec 2020 – 17 Dec 2022) and for the reporting period (19 Jun 2022 – 17 Dec 2022), for valid case reports received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The search strategy used to identify cases of mechanical urticaria included the MedDRA PT "Mechanical urticaria". Within the retrieved cases, those that included medical history PT "Urticaria chronic" or PT "Urticaria" were further evaluated by medical review for co-occurrence of mechanical urticaria and CU.

There are no recognized CD for mechanical urticaria and reports where PT "Mechanical urticaria" was captured were evaluated based on the WHO-UMC system for causality assessment.

Literature Search Methodology:

The MAH performed a focused search of PubMed for elasomeran and mechanical urticaria to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 363 literature articles were retrieved using these search criteria. The literature search strategy was broad, capturing mainly published literature regarding COVID-19 vaccine-induced and COVID-19 infection-induced cutaneous manifestations. Of these 161 articles, there were no published clinical literature specific to vaccination induced mechanical urticaria that conclusively describe mechanism of action or new and potentially important safety information regarding the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.5.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases with Exposure to elasomeran

Cumulatively, through 17 Dec 2022, a total of 466 cases of mechanical urticaria were reported (including 395 non-serious events of mechanical urticaria and 76 serious events of mechanical urticaria) in individuals who received elasomeran. Of the 466 cumulative cases, 184 (39.5%) were medically confirmed and no case reported a fatal outcome.

Regions with the greatest number of cases were EEA (172 cases, 36.9%) Switzerland (155 cases, 33.3%), United States (101 cases, 21.7%) and the UK (30 cases, 6.4%)

During this PBRER interval, a total of 71 cases of mechanical urticaria were reported (including 61 non-serious events of mechanical urticaria and 10 serious events of mechanical urticaria) in individuals who received elasomeran. Of the 71 interval cases, 31 (43.7%) were medically confirmed and no case reported a fatal outcome.

Regions with the greatest number of cases were EEA (49 cases, 69.0%), Switzerland (8 cases, 11.3%), United States (7 cases, 9.9%), and the UK (3 cases, 4.2%).

Event Time to Onset by Dose

Cumulatively, when dose and TTO were reported, the majority (246, 52.2%) of mechanical urticaria events were reported after Dose 3 of elasomeran. Of those 246 events, 186 (75.6%) events had a delayed TTO ranging from 7 to 13 days post-vaccination. This pattern is similar to what has been observed in previous evaluations of urticaria.

During the reporting period, a similar pattern was observed for events of mechanical urticaria. Of the 71 events of mechanical urticaria reported during the reporting period, 35 (49.3%) events were reported after Dose 3 of elasomeran). Of those 35 events, 26 (74.3%) events had a delayed TTO ranging from 7 to 13 days post-vaccination.

This is notable given the relatively fewer number of individuals who have received a third dose of the vaccine compared to Dose 1 and 2. Please see Figure 16-13 and Table 16.99 for a comparison of mechanical urticaria events by dose and TTO for the prior reporting period and current reporting period.

Figure 16-13. Percentage of Mechanical Urticaria Events by TTO and Dose Number, Prior Reporting Period vs. Reporting Period – elasomeran

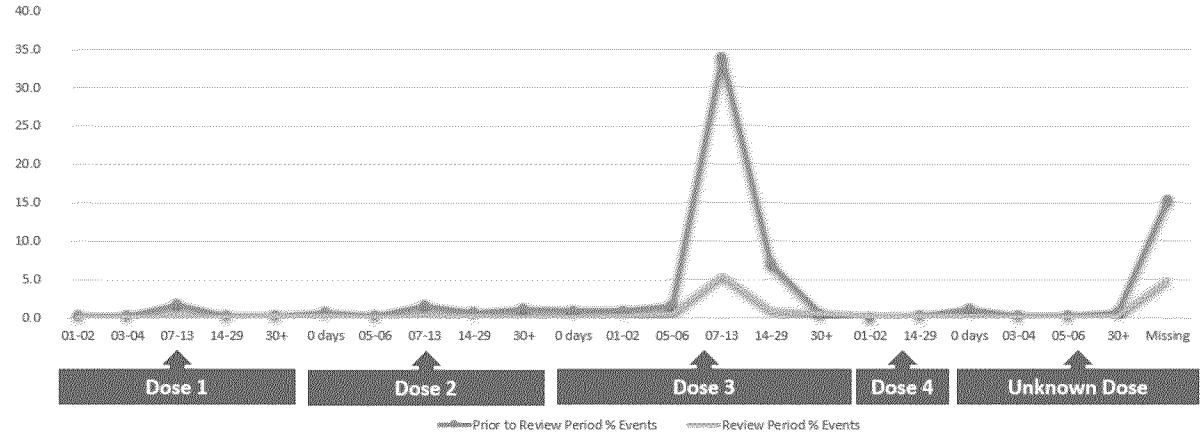


Table 16.99 Latency of Mechanical Urticaria Events by TTO and Dose Number-elasomeran, Cumulative

Dose Number	TTO (Days)	Prior to Review Period		Review Period[1]		# Events	% Events
		# Events	% Events	# Events	% Events		
Dose 1	Subtotal	14	3.0	2	0.4	16	3.4
	0 days	2	0.4	0	0	2	0.4
	01-02	1	0.2	0	0	1	0.2
	03-04	1	0.2	0	0	1	0.2
	07-13	8	1.7	1	0.2	9	1.9
	14-29	1	0.2	0	0	1	0.2
	30+	1	0.2	1	0.2	2	0.4
Dose 2	Subtotal	21	4.5	3	0.6	24	5.1
	0 days	3	0.6	1	0.2	4	0.8
	01-02	2	0.4	0	0	2	0.4
	05-06	1	0.2	0	0	1	0.2
	07-13	7	1.5	1	0.2	8	1.7
	14-29	3	0.6	1	0.2	4	0.8
	30+	5	1.1	0	0	5	1.1

Dose Number	TTO (Days)	Prior to Review Period		Review Period[1]		# Events	% Events
		# Events	% Events	# Events	% Events		
Dose 3	Subtotal	211	44.8	35	7.4	246	52.2
	0 days	4	0.8	0	0	4	0.8
	01-02	4	0.8	1	0.2	5	1.1
	03-04	1	0.2	0	0	1	0.2
	05-06	7	1.5	2	0.4	9	1.9
	07-13	160	34.0	26	5.5	186	39.5
	14-29	33	7.0	4	0.8	37	7.9
	30+	2	0.4	2	0.4	4	0.8
Dose 4	Subtotal	1	0.2	2	0.4	3	0.6
	01-02	0	0	1	0.2	1	0.2
	14-29	1	0.2	1	0.2	2	0.4
Unknown	Subtotal	153	32.5	29	6.2	182	38.6
	0 days	5	1.1	1	0.2	6	1.3
	01-02	5	1.1	0	0	5	1.1
	03-04	1	0.2	0	0	1	0.2
	05-06	1	0.2	0	0	1	0.2
	07-13	54	11.5	4	0.8	58	12.3
	14-29	12	2.5	0	0	12	2.5
	30+	3	0.6	1	0.2	4	0.8
	Missing	72	15.8	23	4.9	95	20.2
Grand total		**400**	**84.9**	**71**	**15.1**	**471**	**100.0**

[1]Please note: Events reported during the reporting period should be interpreted with caution. The majority of individuals reporting events during the reporting period received their primary series of vaccinations prior to the reporting period. The majority of events reported during this reporting period were among individuals receiving 3 or more doses of elasomeran.

Demographics

Cumulatively, there were more cases reported in females (248; 53.2%) compared to males (211; 45.3%) with 7 (1.5%) reports that did not report gender. Patient age ranged from 13 years-old to 77 years-old, with a mean age 36.6 years-old and a median age of 35.0 years-old. Of the 466 cases, 389 (83.5%) cases were reported in individuals 18-49-years of age while the majority (253, 54.3%) of cases were reported in individuals 25-39 -years of age.

During the reporting period, fewer cases were reported, and no conclusions can be drawn with regards to gender imbalance with 32 reports involving females, 37 reports involving males, and 2 reports which did not report gender. Patient age ranged from 17 years-old to 74 years-old, with

a mean age of 33.2 years-old, and a median age of 32.0 years-old. Of the 71 cases, 64 (90.1%) cases were reported in individuals 18-49-years of age while the majority (49, 69.0%) of cases were reported in individuals 25-39-years of age. For a summary of cases by age group, gender, and review period please see Table 16.100 below.

Table 16.100 Cases of Mechanical Urticaria by Age Group, Gender, and Review Period – elasomeran

Age Group (years)	Prior to Review Period						Review Period						# of Total Cases	% of Total Cases
	Female		Male		Unknown		Female		Male		Unknown			
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15	1	0.2	0	0	0	0	0	0	0	0	0	0	1	0.2
16-17	0	0	0	0	0	0	0	0	1	0.2	0	0	1	0.2
18-24	12	2.6	29	6.2	0	0	6	1.3	3	0.6	0	0	50	10.7
25-39	107	23.0	95	20.4	2	0.4	22	4.7	26	5.6	1	0.2	253	54.3
40-49	60	12.9	20	4.3	0	0	3	0.6	3	0.6	0	0	86	18.5
50-64	22	4.7	17	3.6	0	0	0	0	1	0.2	0	0	40	8.6
65-74	5	1.1	3	0.6	0	0	0	0	2	0.4	0	0	10	2.1
75+	1	0.2	1	0.2	0	0	0	0	0	0	0	0	2	0.4
Missing	8	1.7	9	1.9	3	0.6	1	0.2	1	0.2	1	0.2	23	4.9
Grand Total	**216**	**46.4**	**174**	**37.3**	**5**	**1.1**	**32**	**6.9**	**37**	**7.9**	**2**	**0.4**	**466**	**100.0**

Critical Review and Analysis of Cases

WHO-UMC causality assessment was performed for the 71 cases reported during the review period. There were 23 cases with WHO-UMC causality classified as "Unassessable" primarily due to missing event or vaccination dates where TTO could not be determined. There were 10 cases with WHO-UMC causality assessment classified as "Unlikely" due to an implausible, extended TTO of greater than two weeks (up to >1 year), as well as alternate etiologies (such as concomitant medications, history of urticaria, or other conditions predisposing to hypersensitivity reactions). There were 38 cases with a WHO-UMC causality assessment classified as "Possible" due to a plausible temporal relationship between the administration of elasomeran and the reported event

of mechanical urticaria and/or the lack of significant alternate etiology for the event. Of the 38 cases assessed as possibly related to elasomeran, six cases had a TTO of 0-6 days post-vaccination and 32 cases had a time to onset of 7-13 days post-vaccination.

The 71 cases were reviewed for medical history to characterize risk factors for the development of mechanical urticaria. The most frequently captured medical history PTs during this interval > 2 cases included "Seasonal allergy" (5 cases), "Drug hypersensitivity" (4 cases), and "Allergy to animal" (3 cases) suggesting that patients with a history of allergic or hypersensitivity conditions who are already predisposed to urticarial reactions may be more susceptible to developing mechanical urticaria.

Further review was performed to identify cases that included a medical history of PT "Urticaria chronic" or PT "Urticaria" for consideration of co-occurrence of both mechanical urticaria and CU. One case ([redacted]) was identified from the prior reporting period (none from this reporting period) that included urticaria as a historical condition (in addition to multiple allergies to metals, animals, and mites), however there was no evidence that this was CU.

Seven cases reporting events of CU as a co-occurrence with mechanical urticaria were identified in the review period. Six of the seven cases reported non-serious events of mechanical urticaria. One case reported a serious event of mechanical urticaria and is summarized below:

[redacted]: A health authority report concerning a 24-year-old female who experienced multiple events including mechanical urticaria and CU (reported as medically significant, but no evidence of hospitalization) following Dose 3 of elasomeran. The patient's medical history reported as negative for eczema, positive for multiple pets (presumably in household), prior right axillary "lymphoid tissue operation", and no reactions reported from two previous elasomeran doses. Within a month of receiving Dose 3, the patient started azithromycin for an unspecified indication and experienced rash pruritic, eczema, oropharyngeal pain, tonsillitis (timing of events and azithromycin not known). Two months after Dose 3, the patient experienced mechanical urticaria and 3 months after Dose 3 the patient experienced urticaria which was reported to progress to CU after one more month. Laboratory workup was unremarkable (including negative IgE to azithromycin) except for borderline antinuclear antibodies. At the time of the report, the event outcomes for mechanical urticaria were reported as "unknown" and for CU was reported as "ongoing".

MAH Comment: Despite the extended TTO, WHO-UMC causality is assessed as "Possible" considering the unremarkable diagnostic workup. Mechanical urticaria preceded CU and the

progression of the events is consistent with CU.

In three reports [**and** , WHO-UMC causality is considered "Possible" based on the temporal association between elasomeran and the events of mechanical urticaria and CU. However, important information necessary for adequate evaluation such as medical history, concomitant medications, evolution of the two events, and diagnostic workup was not provided. No conclusions could be drawn with regards to mechanical urticaria and the co-occurrence of CU.

: This regulatory case concerns a 37-year-old male patient with no medical history reported, who experienced the unexpected serious (medically significant) event of "Chronic spontaneous urticaria" and the non-serious event of "Mechanical urticaria" (Dermographism) 22 days after receiving Dose 2 of elasomeran. Diagnostic evaluation described human leukocyte antigen (HLA)-B27 assay as "positive" approximately 4 months after the most recent vaccination.

MAH Comment: Based on the TTO of 22 days and HLA-B27 positivity suggesting rheumatoid disease, WHO-UMC causality is considered "Unlikely". No conclusions can be drawn with regards to mechanical urticaria and the co-occurrence of CU.

Two reports [**and** were lacking important information necessary for adequate evaluation including event dates, medical history, concomitant medications, clinical course, and diagnostic workup. WHO-UMC causality is considered "Unassessable". No conclusions can be drawn with regards to mechanical urticaria and the co-occurrence of CU.

Subpopulation Analysis of Mechanical Urticaria Cases Among Children <17 Years of Age

During the reporting period, there was one non-serious case reported involving an adolescent patient. Case is a health authority report concerning a 17-year-old male who experienced the non-serious event of "Mechanical urticaria" 7 days after receiving Dose 2 of elasomeran. At the time of the report, the event outcome was reported as "not resolved". No other information was provided such as medical history, concomitant medications, clinical course, and diagnostic evaluation which are necessary for proper evaluation. According to the WHO causality assessment this case is considered "Possible" given the temporal association.

Mechanical Urticaria Cases Among Individuals Receiving Three or More Doses of

elasomeran

During the reporting period, there were 37 cases (5 serious, none with fatal outcome) that were reported in individuals receiving three or more doses of elasomeran. Of the 37 cases, seventeen (46%) were medically confirmed. There was no significant difference in regard to gender in this subpopulation with 17 cases (45.9%) cases reported in males compared to 19 cases (51.4%) reported in females and one case (2.7%) which did not report gender. Patient ages ranged from 23 years to 66 years with a mean age of 34.3 years and a median age of 32.0 years. The majority of events (35, 94.6%) occurred after Dose 3 with only 2 events reported after Dose 4 (these numbers should be interpreted with caution given the fewer number of patients receiving subsequent doses). When TTO was reported, the majority (70.3%) of events occurred in the post-vaccination window of days seven to thirteen with a median TTO of 10.0 days.

Mechanical Urticaria After Receiving Booster Dose with elasomeran/imelasomeran

During this reporting period, there were two non-serious reports (1 medically confirmed) of mechanical urticaria reported in individuals who received elasomeran/imelasomeran. Both cases are summarized below.

Case [redacted] concerned a 35-year-old pregnant patient (gravida 2, para 1), with relevant medical history of hypersensitivity and coeliac disease, who experienced the non-serious event of "Mechanical urticaria" (reported as dermatographia and full body skin itchiness) 13 days after Dose 4 of elasomeran/imelasomeran. Pregnancy outcome was still pending, although first trimester screenings were reported as normal. According to the WHO causality assessment this case is considered "Unlikely" given the patient's history of hypersensitivity and that hormonal changes during pregnancy can trigger urticaria.

Case [redacted] concerned a 47-year-old female who experienced the non-serious events of "Mechanical urticaria" (reported hives with redness and itching all over on the body, scalp, and face; spreads with scratching) and "Pruritus" 13 days after receiving Dose 4 of elasomeran/imelasomeran. No additional information was provided such as medical history, concomitant medications, clinical course, and diagnostic evaluation which are necessary for proper evaluation. According to the WHO causality assessment this case is considered "Possible" given the temporal association.

Mechanical Urticaria After Receiving Booster Dose with elasomeran/davesomeran

No cases of mechanical urticaria have been reported in individuals who received a booster dose with elasomeran/davesomeran.

16.3.6.5.1.4. Discussion

Cumulatively, there are a total of 466 cases of mechanical urticaria. Seventy-one of those cases were received during this reporting period. The cases describe events of mechanical urticaria that were mainly non-serious and often had little to no information reported regarding clinical course. No fatal cases of mechanical urticaria have been reported.

The occurrence of mechanical urticaria in reports during this PBRER interval mirrored the pattern observed prior to this interval; especially with regard to reports of urticaria in general. Mechanical urticaria occurred in a bimodal distribution during elasomeran post-vaccination window of days 0-6 and then again in the post-vaccination window of days 7-13, more often after Dose 3. The most common medical history reported in cases of mechanical urticaria described allergic or hypersensitivity conditions which would be expected to predispose patients to developing urticarial events. Furthermore, there was no evidence that suggests a co-occurrence of mechanical urticaria and CU in association with elasomeran administration. Overall, there was no appreciable change in the pattern of occurrence of mechanical urticaria noted in the reports received thus far.

Urticaria is recognized as a common dermatologic condition and inducible urticarias are considered subtypes of CU. Mechanical urticaria is the most common of the inducible urticarias and is present in 20 to 30 percent of adults with CU and also occurs in children, although there are fewer reports regarding this population [158]. Simple dermographism is thought to occur in approximately 2 to 5 percent of the general population.

Core labeling of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, as well as the SmPC, adequately describe urticaria observed to occur acutely following elasomeran vaccination including the delayed window of 7-13 days after vaccination, consistent with the findings in this review.

16.3.6.5.1.5 Conclusion

Based on the analysis of all the safety data received during the cumulative and reporting periods, ModernaTx, Inc. considers that the pattern of events of mechanical urticaria continues to present following the bimodal distribution previously described for urticaria events in general. The reports of mechanical urticaria are rare and no different than reports of urticaria, with no co-occurrence

identified with CU in association with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The current CCDS (v15.0) is considered to adequately reflect the understanding of urticaria with respect to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

ModernaTx, Inc. concludes that no further action is warranted at this time and will continue to monitor events of mechanical urticaria using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.6 Other Disorders

16.3.6.6.1 IgA Nephropathy

16.3.6.6.1.1 Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTx, Inc. for the Cumulative period for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Cumulatively, the data reviewed cover the period from 18 Dec 2020 to 17 Dec 2022.

16.3.6.6.1.2. Background Relevant to the Evaluation

IgA nephropathy is considered the most common type of primary glomerulonephritis and is diagnosed only by kidney biopsy, with a global incidence of 2.5/100,000 adults per year. This condition occurs more commonly in Asian populations, followed by Europeans, and less commonly in African populations. The most frequent sign or symptom of IgA nephropathy is blood in the urine (hematuria) followed by albuminuria; however, the frequent lack of signs or symptoms in the early stages of IgA nephropathy makes it difficult to determine how many people are affected. This glomerular disease results from deposits of immunoglobulin A (IgA) in the glomerulus and mesangium. IgA nephropathy can progress for years with no noticeable clinical symptoms or findings on routine tests. For example, a study in Japan found IgA deposition in 14.5% of donated kidneys from unrelated donors, and nearly 2% exhibited mesangio-proliferative changes with C3 deposits characteristic of IgA nephropathy. Also, IgA nephropathy accounts for up to 40% of native kidney biopsies from eastern Asia. In some cases, IgA nephropathy runs in families and scientific studies have recently found several genetic markers that may be associated with its development. In addition, development of IgA nephropathy may be related to respiratory or intestinal infections and the associated immune activity. Studies have found that patients with IgA nephropathy have serum IgA that contains less galactose than normal; such galactose-deficient

IgA may become immunogenic and lead to development of IgA and/or IgG antibodies against the galactose-deficient IgA, with the subsequent development of immune complexes. The only definitive diagnosis of IgA nephropathy is by renal biopsy with findings of IgA complexes deposited in the glomeruli and mesangium. IgA nephropathy is generally more common in men than women and can be diagnosed at all ages. Diagnosis is most common in the second and third decades of life, with approximately 80% of patients between the ages 16-35 years at time of diagnosis. The exact etiology and pathophysiology of IgA nephropathy are presently not known.

16.3.6.6.1.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

Clinical Trial Data

The topic of IgA nephropathy was cumulatively reviewed in the clinical trial datasets (no new data is available for this reporting period, hence no change in the available information from the previous PBRER#3), within the following studies of:

- P301 study (ages ≥18 years; DLP: 04 May 2021), There were approximately 30,000 participants randomized in 1:1 ratio to dose groups placebo (n = 15,000) and mRNA-1273 100 µg (n = 15,000) with vaccine schedule of 2 IM doses, 28 days apart.
- P203 study (ages 12-17 Years; DLP: 27 Jan 2022) There were approximately 3,000 participants randomized in 2:1 ratio with a vaccine schedule of 100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart.
- P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022). There were approximately 4500 participants in different age groups randomized in 3:1 ratio with a vaccine schedule of 25, 50, 100 µg mRNA-1273 (25 µg only for 6 months to < 2 years age group) or placebo (3:1) 2 IM doses, 28 days apart.

Review of these studies found zero cases.

List of PTs in MedDRA HLT of Glomerulonephritis and Nephrotic Syndrome:

Alagille syndrome, Alport's syndrome, Anti-LRP2 nephropathy, Anti-glomerular basement membrane disease, Benign familial haematuria, C1q nephropathy, C3 glomerulopathy, Chronic autoimmune glomerulonephritis, Congenital nephrotic syndrome, Denys-Drash syndrome, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Frasier syndrome, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis chronic, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion,

Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Goodpasture's syndrome, Granulomatosis with polyangiitis, HIV associated nephropathy, Henoch-Schonlein purpura nephritis, Hepatitis virus-associated nephropathy, IgA nephropathy, IgM nephropathy, Immunotactoid glomerulonephritis, Membranous-like glomerulopathy with masked IgG-kappa deposits, Mesangiolipidosis, Mesangioproliferative glomerulonephritis, Microscopic polyangiitis, Nephritic syndrome, Nephritis allergic, Nephrotic syndrome, Paraneoplastic glomerulonephritis, Paraneoplastic nephrotic syndrome, Post infection glomerulonephritis, Post streptococcal glomerulonephritis, Primary coenzyme Q10 deficiency and Pulmonary renal syndrome.

Review of the Pharmacovigilance Database

The MAH queried the GSDB, cumulative to 17 Dec 2022 for valid case reports of Glomerulonephritis and Nephrotic Syndrome received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the MedDRA HLT glomerulonephritis and nephrotic syndrome. All case reports identified from the above search (whether or not the PT IgA Nephropathy was coded) were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy.

16.3.6.6.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected

See Appendix 11.3.

Overview of Cases:

Cumulative data Review (cumulative to 17 Dec 2022)

Cumulatively as of the DLP (17 Dec 2022), a total of 237 cases (272 events) were retrieved using the broad search criteria specified above. These 237 cases (whether or not the PT IgA Nephropathy was coded) were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy. See the following (Appendix 11.17) for line listings and MAH review assessments of these 237 cases, with a focus on IgA nephropathy.

Medical review identified 68 cases involving IgA nephropathy; 43 cases were new onset (DeNovo) IgA nephropathy, and 25 cases were considered IgA nephropathy flares because they were reported to have exacerbation of IgA nephropathy that had been diagnosed prior to elasomeran

vaccination. The largest numbers of cases were reported from the United States (18; 33.3%), Japan (16; 23.5%), Germany (6; 8.8%), Switzerland (5; 7.4%) and Taiwan, Province of China (5; 7.4%) Table 16.101.

Table 16.101 Summary of Cases Reported, by Country, stratified by IgA DeNovo and IgA Flare

Region	IgA Nephropathy				Total # Of Cases	Total % Of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
United States	10	14.7	8	11.8	18	26.5
Japan	13	19.1	3	4.4	16	23.5
Germany	5	7.4	1	1.5	6	8.8
Switzerland	3	4.4	2	2.9	5	7.4
Taiwan	2	2.9	3	4.4	5	7.4
France	1	1.5	2	2.9	3	7.4
Spain	1	1.5	1	1.5	2	4.4
Norway	2	2.9	0	0	2	2.9
United Kingdom	0	0	2	2.9	2	2.9
Ireland	1	1.5	0	0	1	1.5
Italy	0	0	1	1.5	1	1.5
Sweden	1	1.5	0	0	1	1.5
Poland	0	1.5	1	1.5	1	1.5
Finland	1	1.5	0	0	1	1.5
Qatar	1	1.5	0	0	1	1.5
Korea, Republic Of	1	1.5	0	0	1	1.5
Denmark	0	0	1	1.5	1	1.5
Netherlands	1	1.5	0	0	1	1.5
Grand Total	**43**	**63.2**	**25**	**36.8**	**68**	**100.0**

There were no reports of fatalities in the medically confirmed IgA nephropathy cases. IgA nephropathy was reported more often in Females (38; 55.9%) compared to Males (30; 44.1%), which is different from general data showing that IgA nephropathy is more common in men than women. UpToDate states: "Patients with IgA nephropathy cases may present at any age, but there is a peak incidence in the second and third decades of life. There is approximately a 2:1 male-to-female predominance in North American and Western European populations in both adults and

children, although the sexes are equally affected among populations in East Asia." An Overview of 68 Cases is presented in Table 16.102.

Table 16.102 Summary of Cases Reported for IgA Nephropathy by Age and Gender

Age Group	Female		Male		Total # of Cases	Total % of Cases
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
12-17	2	2.9	1	1.5	3	4.4
18-29	8	11.8	7	10.3	15	22.1
30-39	8	11.8	5	7.4	13	19.1
40-49	9	13.2	7	10.3	16	23.5
50-64	6	8.8	6	8.8	12	17.6
65-74	3	4.4	4	5.9	7	10.3
Missing	2	2.9	0	0	2	2.9
Grand Total	**38**	**55.9**	**30**	**44.1**	**68**	**100.0**

Figure 16-14 and Figure 16-15 indicate the time from vaccination with elasomeran to onset of IgA nephropathy, where this information was available, and are based on medical review of the cases. Onset of IgA nephropathy occurs mostly in the two days following vaccination with more events after the second vaccination. This coincides with the known enhanced immune response seen with boosted vaccinations. This pattern is generally similar to that of all AEs reported following elasomeran immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. At this time, with the limited number of reports, this finding is an observation, as there is no clear biological explanation.

Figure 16-14. Reported IgA Nephropathy DeNovo Events by Dose & Time to Onset Cumulative thru 17 Dec 2022

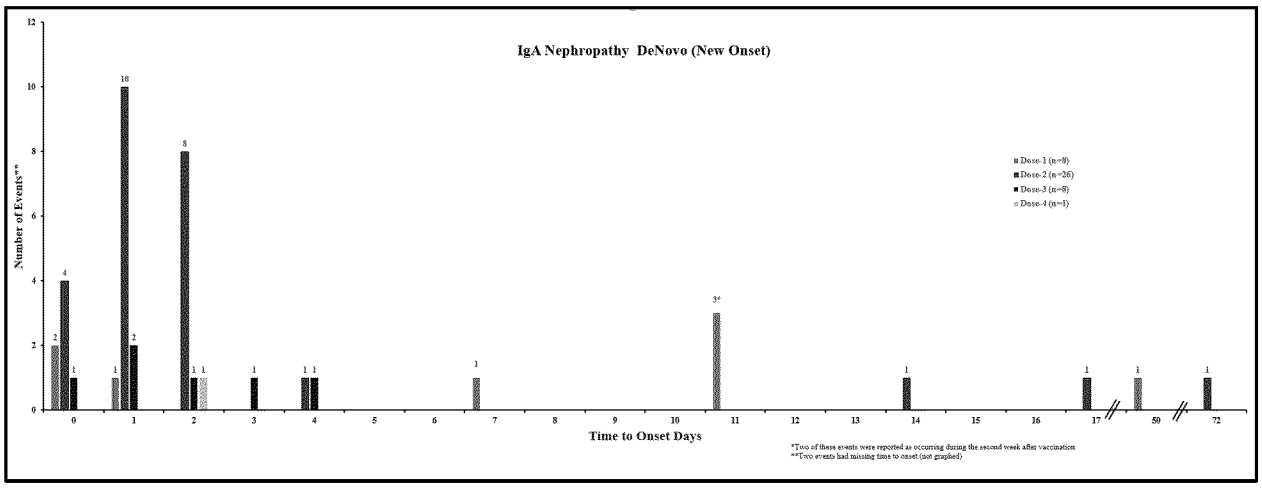
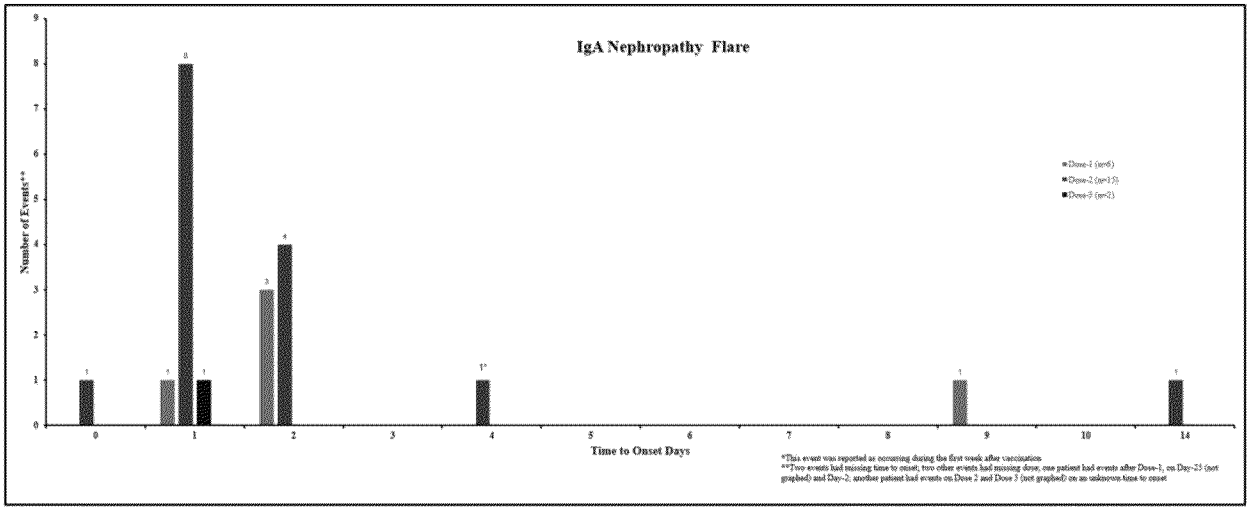


Figure 16-15 Reported IgA Nephropathy Flare Events by Dose & Time to Onset Cumulative thru 17 Dec 2022



The MAH has evaluated cumulatively all cases with IgA nephropathy, DeNovo and flare, temporally associated with elasomeran according to the WHO-UMC causality classification. Most of the cases (37; 54.4%) were considered possible due to temporal association and lack of adequate information for complete clinical evaluation. A summary of WHO causality assessments is presented below in Table 16.103.

Table 16.103 WHO-UMC Causality Classification for IgA Nephropathy Cases As of 17 Dec 2022

WHO Causality	IgA Nephropathy				Total # Of Cases	Total % Of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
Conditional	10	14.7	4	5.9	14	20.6
Possible	24	35.3	13	19.1	37	54.4
Probable	0	0	5	7.4	5	7.4
Unassessable	8	11.8	3	4.4	11	16.2
Unlikely	1	1.5	0	0	1	1.5
Grand Total	**43**	**63.2**	**25**	**36.8**	**68**	**100.0**

Review of counts of IgA nephropathy cases by initial receipt date and PBRER reporting period shows that in the current PBRER#4 reporting period there has been a decrease in number of cases reported (14 cases), compared to the prior two periods which both had 23 cases (Table 16.104). The cumulative reporting rate remains < 1 case per 10 million doses.

Table 16.104 Distribution of IgA Nephropathy Cases by PBRER Period and Reporting Rate

PBRER Period/# (Doses Administered)	IgA Nephropathy				Total Cases	Total % Cases	Cumulative Reporting rate per 10 million Doses
	DeNovo		Flare				
	# Cases	%	# Cases	%			
PBRER-1 (182,716,703)	6	8.8	2	2.9	8	11.8	0.44
PBRER-2 (466,804,529)	12	17.6	11	16.2	23	33.8	0.66
PBRER-3 (662,871,167)	16	23.5	7	10.3	23	33.8	0.81
PBRER-4 (903,896,822)*	9	13.2	5	7.4	14	20.6	0.75
Grand Total	**43**	**63.2**	**25**	**36.8**	**68**	**100.0**	-

*Doses administered include Bivalent elasomeran/imelasomeran and elasomeran/davesomeran

Reporting Period Data Review (19 Jun 2022 through 17 Dec 2022)

During the reporting period, a total of 52 cases (59 events) were identified using the broad search criteria specified above (using the HLT glomerulonephritis and nephrotic syndrome). These reports were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy; see Appendix 11.17 for line listings and MAH review assessments of these 52 cases.

Medical review identified 14 cases of IgA nephropathy; 5 cases were IgA flares, having already been diagnosed with IgA nephropathy prior to elasomeran, and 9 cases were newly diagnosed (DeNovo) IgA nephropathy. Most of the cases were reported from Japan (10; 71.4%), with four other countries reporting one case each Table 16.105).

Table 16.105 Summary of Cases Reported for Region stratified by IgA DeNovo and IgA Flare (19 Jun 2022 to 17 Dec 2022)

Region	IgA Nephropathy				Total # of Cases	Total % of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
Japan	7	50	3	21.4	10	71.4
Denmark	0	0	1	7.1	1	7.1
Ireland	1	7.1	0	0	1	7.1
Spain	0	0	1	7.1	1	7.1
Taiwan	1	7.1	0	0	1	7.1
Total Cases	**9**	**64.3**	**5**	**35.7**	**14**	**100**

There were no reports of fatal cases. IgA Nephropathy was reported in 9 females (64.3%) and 5 males (35.7%) In Asia, where background incidence of IgA nephropathy is highest, approximately equal proportions of men and women are affected. Patients with IgA nephropathy cases may present at any age, but there is a peak incidence in the second and third decades of life. There is approximately a 2:1 male-to-female predominance in North American and Western European populations in both adults and children (UpToDate). Demographic information on the 14 cases is presented in Table 16.106.

Table 16.106 Summary of Cases Reported for IgA Nephropathy by Age and Gender (19 Jun 2022 to 17 Dec 2022)

Age Group	Female		Male		Total # of Cases	Total % of Cases
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
18 -29	2	14.3	0	0.0	2	14.3
30 - 39	2	14.3	0	0.0	2	14.3
40 -49	2	14.3	3	21.4	5	35.7
50 -64	2	14.3	1	7.1	3	21.4
65 - 74	1	7.1	1	7.1	2	14.3
Grand Total	**9**	**64.3**	**5**	**35.7**	**14**	**100**

Figure 16-16 and Figure 16-17 indicate dose and time from vaccination with elasomeran to onset of IgA nephropathy, where this information was available, and are based on medical review of the cases. IgA nephropathy symptoms, whether from flare or DeNovo illness, were reported with onset in the two days following vaccination. This coincides with the known reactogenicity seen with vaccinations. This pattern is also generally similar to that of all AEs reported following elasomeran immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. At this time, with the limited number of reports, this TTO pattern remains an observation, not materially different from the pattern of previous reporting periods, and there is no clear biological explanation.

Figure 16-16. Reported IgA Nephropathy DeNovo Events by Dose & Time to Onset (19 Jun 2022 through 17 Dec 2022)

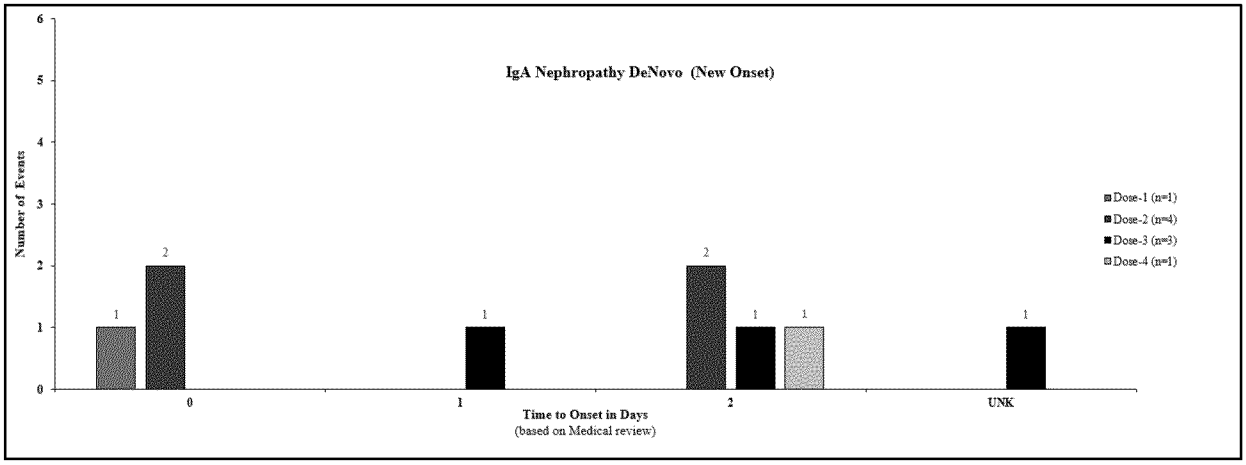
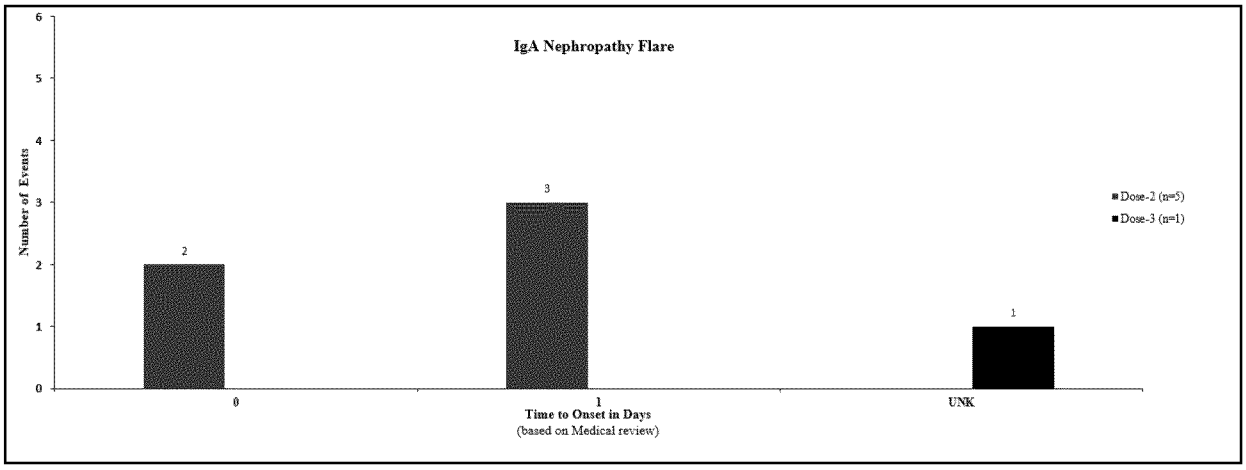


Figure 16-17. IgA Flare Events (*6 events in 5 cases*) by Dose and Time to Onset (19 Jun 2022 through 17 Dec 2022)



Brighton Collaboration/ CDC Working Case Definition/ WHO Causality Assessment

Neither the Brighton Collaboration nor CDC has established a case definition for IgA nephropathy. We have considered a case as IgA nephropathy if there was reported renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy.

WHO Causality Assessment. The MAH has evaluated cumulatively all cases with DeNovo or flare IgA nephropathy reported following elasomeran according to the WHO-UMC causality classification. Most of the cases (8; 57.1%) were considered possible due to temporal association and lack of adequate information for complete clinical evaluation, with the presence of confounding factors also in some cases. A summary of WHO causality assessments is presented in Table 16.107. Additional information on individual case assessments, with justification of the causality determinations, appears in the Appendix 11.17.

Table 16.107 WHO-UMC Causality Classification for IgA Nephropathy Cases (as of 19 Jun 2022 through 17 Dec 2022)

WHO Causality	IgA Nephropathy				Total # of Cases	Total % of Cases
	IgA DeNovo		IgA Flare			
	# Of Cases	% Of Cases	# Of Cases	% Of Cases		
Conditional	5	35.7	1	7.1	6	42.9
Possible	4	28.6	4	28.6	8	57.1
Grand Total	**9**	**64.3**	**5**	**35.7**	**14**	**100.0**

IgA Nephropathy in Persons with Age < 18 years

There were no reports of IgA in the pediatric population.

IgA Nephropathy After Receiving Booster Dose with elasomeran/imelasomeran

There were no reports of IgA nephropathy associated with elasomeran/imelasomeran.

IgA Nephropathy After Receiving Booster Dose with elasomeran/davesomeran

There were no reports of IgA nephropathy associated with elasomeran/davesomeran.

Literature Review:

The MAH performed a focused search of PubMed for elasomeran and IgA Nephropathy to retrieve relevant literature during this reporting period. The exact search criteria are specified in Appendix 12.1d. A total of 177 literature articles was retrieved. Medical/scientific review of these articles identified one article that provided new and significant safety findings. This article's key information is summarized below.

Title: Incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination is not increased [161].

Authors: Matthias Diebold, Eleonore Locher, Philipp Boide, Annette Enzler-Tschudy, Anna Faivre, Ingeborg Fischer, Birgit Helmchen, Helmut Hopfer, Min Jeong Kim, Solange Moll,Giliane Nanchen, Samuel Rotman, Charalampos Saganas, Harald Seeger and Andreas D. Kistler

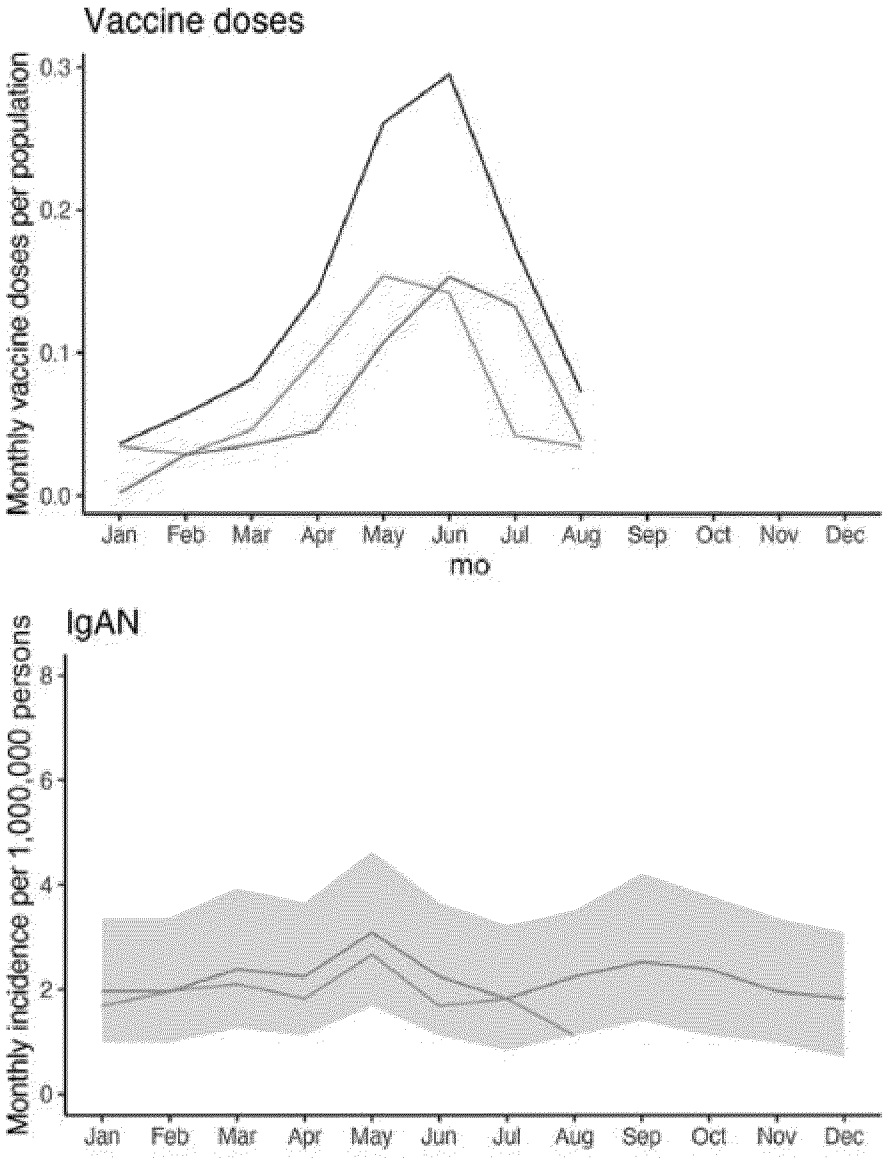
Citation: Kidney International 2022; 102:1409-1419. doi: 10.1016/j.kint.2022.08.021

Abstract: [161] studied the incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination in a nationwide retrospective cohort and case-cohort design study in Switzerland during the vaccination campaign in Jan 2021 to Aug 2021. Data from all Swiss pathology institutes processing native kidney biopsies were used to calculate incidence of IgA nephropathy and other nephropathies in the adult Swiss population. Using a Bayesian model based on the years 2015 to 2019 as the comparator, the observed incidence during the vaccination campaign was not significantly different from the expected incidence (incidence rate ratio 0.86, 95% credible interval 0.73–1.02) and did not cross the upper boundary of the 95% credible interval for any month. Among 111 patients 18 years and older with newly diagnosed glomerulonephritis between Jan 2021 and Aug 2021, 38.7% had received at least one vaccine dose before biopsy, compared to 39.5% of the general Swiss population matched for age and calendar time. The calculated risk ratio for the development of new onset biopsy-proven glomerulonephritis was not elevated at 0.97 (95%

confidence interval 0.66–1.42) in vaccinated vs. unvaccinated individuals. Patients with glomerulonephritis manifesting within four weeks after vaccination were similar clinically to those with illness temporally unrelated to vaccination. To summarize this article's main findings, mRNA vaccination against SARS-CoV-2 was not associated with new onset glomerulonephritis in these two complementary studies, and most temporal associations between SARS-CoV-2 vaccination and glomerulonephritis were likely coincidental and consistent with background events in the years prior to the pandemic.

With specific reference to IgA nephropathy, of the 111 new onset glomerulonephritis patients in the study the majority (58, 52.3%) were histologically diagnosed with IgA nephropathy. The figures below, from the article by Diebold et al, clearly and graphically demonstrate the lack of temporal association between the Swiss mRNA vaccination campaign and the incidence of IgA nephropathy in this nationwide study. In addition, in the case-cohort analysis, the risk ratio for development of biopsy-proven IgA nephropathy compared to matched comparator individuals was 1.14 (95% CI 0.67-1.97, p=0.73).

Figure 16-18 Expected and observed incidence of glomerulonephritis during the vaccination campaign



Reference: [161].

Figure 16-18 shows Expected and observed incidence of glomerulonephritis during the vaccination campaign. Shown is the number of first (orange), second (blue), and total (gray) doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines as a fraction of all patients aged

≥20 years (upper-left panel) and the observed incidence of glomerulonephritis in patients aged ≥18 years from Jan 2021 to Aug 2021 (red line) compared with the expected incidence based on the years 2015–2019 (blue line) with 95% credible intervals (green shading) for IgA nephropathy.

Company Comment: Taken together the findings of the article by Diebold et al provide rigorous population-based evidence against a causal association between mRNA vaccines and incidence of IgA nephropathy. The study included all renal biopsy centers in Switzerland, so that case ascertainment was complete, or nearly so. In addition, the study period was at the peak of mRNA vaccine administration; therefore, if an effect of vaccination on incident IgA nephropathy were to be observed, the dates of the study were optimal to detect such an effect; however, no effect was observed.

16.3.6.6.1.5. Discussion

IgA nephropathy is the most common form of primary glomerulopathy. The prevalence of IgA nephropathy is unknown because of the often-latent nature of the disease. It may remain silent for years without clinical signs or symptoms. IgA nephropathy has been found in families and recent data have demonstrated various genetic markers. Potential triggers include respiratory and gastrointestinal illnesses as well as other immune activation events. The exact etiology and pathophysiology of IgA nephropathy remain unknown.

There have been no high-quality studies finding a causal link between IgA nephropathy and elasomeran or the ModernaTx, Inc. bivalent vaccines. Moreover, the study by Diebold et al, summarized above, provided rigorous and reassuring findings from a nationwide study in Switzerland showing a lack of association between mRNA vaccines and DeNovo IgA nephropathy. Further, in the MAH's CTs noted above, there have been zero cases of IgA nephropathy. No pathophysiologic process has been shown to explain a causal association between elasomeran or the ModernaTx, Inc. bivalent vaccines and IgA nephropathy, and there is also no identified pathognomonic sign of such an association.

Cumulatively in the MAH's GSDB, there have been 68 reports of IgA nephropathy following elasomeran vaccination among an estimated 772.9 million vaccinees. This represents a reporting rate of < 1 case of IgA nephropathy per 10 million elasomeran vaccinees, constituting an extremely rare occurrence. For elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran 903,896,822 doses have been administered. For the elasomeran/imelasomeran an estimated total of 70,077,685 doses have been administered, with zero cases of IgA nephropathy reported. For the

elasomeran/davesomeran an estimated 60,910,179 doses have been administered, also with zero cases of IgA nephropathy reported.

Of the 68 reports of IgA nephropathy following elasomeran vaccination, 43 cases were DeNovo and 25 cases were flares. The number of vaccinees with IgA nephropathy is unknown. Persons with IgA nephropathy are already likely to seek medical attention when they have gross hematuria or other signs and symptoms of renal dysfunction. No data have indicated the value of active screening or additional education of IgA nephropathy patients' post-vaccination. Renal patients are at increased risk of serious illness and death due to COVID-19 disease; thus, vaccination is of great benefit to them.

16.3.6.6.1.6 Conclusion

Overall, similar to PBRER#3, based on the analysis of all available safety data as of 17 Dec 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the development of IgA nephropathy. No new or emerging safety issues of concern were identified in the current reporting period. The MAH will continue to carefully monitor IgA Nephropathy events using routine pharmacovigilance surveillance.

16.3.6.6.2 Hearing Loss

16.3.6.6.2.1 Source of the New Information

New information presented below includes analysis performed on new cases received by MAH from 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran as per request from a health authority. Cumulatively, the data reviewed covers the period from the 18 Dec 2020 to 17 Dec 2022.

16.3.6.6.2.2. Background Relevant to the Evaluation

A health authority requested to perform a cumulative review of all cases concerning elasomeran/imelasomeran and elasomeran/davesomeran associated with the HLT of "Hearing losses" from all sources, including any relevant articles from literature. Cumulatively, as of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685

doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran) had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

Sensorineural hearing loss refers to any cause of hearing loss due to pathology of the cochlea, auditory nerve or the central nervous system and is in contrast to conductive hearing loss which is related to obstruction of the ear canal or problems with the cochlear bones [162]. Sudden sensorineural hearing loss is defined as the development of hearing loss of at least 30 dB in three contiguous frequencies over a 72- hour period. The incidence in the United States is estimated to be 27 cases/100,000 population per year ranging from 11 per 100,000 in people less than 18 years of age to 77 per 100,000 in people over the age of 65 [163]. Etiologies include infections (bacterial and viral), metabolic causes including diabetes and hypothyroidism, hypertension, neoplastic disease, exposure to aminoglycosides and salicylates, vascular causes including cardiovascular bypass and cerebrovascular accident/stroke as well as congenital causes, but a majority of cases are idiopathic [164].

Sensorineural hearing loss has been reported in association with COVID 19 infection. A recent literature review detailed case reports and noted that most cases were associated with other symptoms including tinnitus and vertigo. About one half of the patients reported showed improvement with steroid therapy [165]. Mechanisms of action postulated include direct viral invasion of middle ear cells and vascular injury to the terminal vessels supplying blood to the middle ear [166] [167]. There have been numerous anecdotal case reports in the literature of sensorineural hearing loss after COVID 19 vaccination. These reports include cases associated with mRNA vaccines but also after viral vector vaccines produced by Janssen and Astra Zeneca. Although of interest clinically, these cases do not clearly establish a clear role for vaccination in causing hearing loss.

Three epidemiological studies have aimed to assess whether a relationship between COVID 19 vaccination and hearing loss could be established. Two studies found no association and the third found only a small effect, specifically for the BNT162b2 mRNA COVID-19 vaccine. These studies are summarized below.

The first study, a cross-sectional study and case series by [168] involved the analysis of 555 incident reports of probable sudden sensorineural hearing loss (SSNHL) in the Centers for Disease

Control and Prevention Vaccine Adverse Events Reporting System (VAERS) over the first 7 months of the US vaccination campaign (14 Dec 2020, through 16 Jul 2021) for COVID-19 primary series vaccination. In addition, data from a multi-institutional retrospective case series of 21 patients who developed SSNHL after COVID-19 vaccination were analyzed. The study included all adults experiencing SSNHL within 3 weeks of COVID-19 vaccination who submitted reports to VAERS and consecutive adult patients presenting to 2 tertiary care centers and 1 community practice in the US who were diagnosed with SSNHL within 3 weeks of COVID-19 vaccination. Mean patient age was 54 years [range, 15-93 years] with 305 women [55.0%] that met the definition off probable SSNHL (mean TTO, 6 days [range, 0-21 days]) over the period investigated, representing an annualized incidence estimate of 0.6 to 28.0 cases of SSNHL per 100 000 people per year. This rate compared to an estimated rate for the general population ranging from 11-77 cases per 100 000 people per year. The rate of incident reports of SSNHL was similar across all 3 vaccine manufacturers (0.16 cases per 100 000 doses for both Pfizer-BioNTech and ModernaTx, Inc. vaccines, and 0.22 cases per 100 000 doses for Janssen/Johnson & Johnson vaccine). The case series included 21 patients (mean age, 61 years [range, 23-92 years]; 13 women [61.9%]) with SSNHL, with a mean TTO of 6 days (range, 0-15 days). Patients were heterogeneous with respect to clinical and demographic characteristics. Pre-existing autoimmune disease was present in 6 patients (28.6%). Of the 14 patients with posttreatment audiometric data, 8 (57.1%) experienced improvement after receiving treatment. One patient experienced SSNHL 14 days after receiving each dose of the Pfizer-BioNTech vaccine. Inclusion criteria for probable SSNHL consisted of a temporal association with COVID-19 vaccination (defined as onset within 21 days after vaccination) and a high credibility of reporting. A report was deemed credible if it could demonstrate at least 1 of the following: (1) reference to an audiographic test result confirming hearing loss, (2) evaluation by an otolaryngologist, audiologist, or other physician resulting in a diagnosis of sudden hearing loss, or (3) evaluation by an otolaryngologist resulting in treatment with systemic steroid or intratympanic steroid medications, performance of magnetic resonance imaging, or any combination thereof. The authors concluded that the findings from an updated analysis of VAERS data and a case series of patients who experienced SSNHL after COVID-19 vaccination did not suggest that COVID-19 vaccination was associated with an increased incidence of hearing loss (compared with the expected incidence in the general population).

The second study by Nieminem *et al.*, [169], a register-based country-wide retrospective cohort study of 5.5 million Finnish residents was conducted from 01 Jan 2019, to 20 Apr 2022, and

included all individuals who were identified from the population information system who were alive or born during the study period except individuals who had SSNHL during 2015 to 2018 according to specialized care derived diagnosis codes for SSNHL (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] code H91.2) as a primary or secondary diagnosis. The primary risk period was 0 to 54 days following each COVID-19 vaccination. The secondary risk period was from 55 days following each COVID-19 vaccination until a subsequent COVID-19 vaccination. A secondary analysis included a risk time from 0 to 54 days following a positive polymerase chain reaction test result for SARS-CoV-2. The purpose of the study was to compare incidences of SSNHL following COVID-19 vaccination with the incidences before the COVID-19 epidemic in Finland. Before the COVID-19 epidemic in Finland,18.7/100 000 people received a diagnosis of SSNHL annually. According to the authors the study data suggested no increased risk for SSNHL following any COVID-19 vaccination. There was no association between SARS-CoV-2 infection and an increased incidence of SSNHL.

The third study, from Yanir *et al.*, [170] was a retrospective, population-based cohort study performed using data from the largest health-care organization in Israel from 20 Dec 2020 to 31 May 2021. Patients 16 years or older who received the first vaccine dose between 20 Dec 2020, and 30 Apr 2021, and the second vaccine dose between 10 Jan 2021, and 30 Apr 2021, were included in the study. The main outcome was sudden sensorineural hearing loss (SSNHL) based on International Classification of Diseases, Ninth Revision (ICD-9) codes in conjunction with concurrent prednisone dispensing. Observed cases of SSNHL, occurring within 21 days after each of the first and second vaccine doses, were compared with the expected cases based on the experience of the population in 2018 and 2019. Standardized incidence ratios (SIRs) and attributable risks were computed. The age- and sex-weighted SIRs were 1.35 (95% CI, 1.09-1.65) after the first vaccine dose and 1.23 (95% CI, 0.98-1.53) after the second vaccine dose. After the first vaccine dose, the estimated SIRs were more pronounced in female patients aged 16 to 44 years (SIR, 1.92; 95% CI, 0.98-3.43) and female patients 65 years or older (SIR, 1.68; 95% CI, 1.15-2.37). After the second vaccine dose, the highest estimated SIR was observed in male patients 16 to 44 years (SIR, 2.45; 95% CI, 1.36-4.07). The virtually linear increase in cumulative incidence (shown graphically), and the nearly equal magnitude of cumulative incidence following dose 1 and dose 2, of SSNHL over the 21 days following vaccination seem more consistent with background rather than vaccine-associated phenomena that often vary by dose and/or by TTO. According to the authors, this study suggests that the BNT162b2 mRNA COVID-19 vaccine might be associated with increased risk of SSNHL; however, the effect size is very small, and further

studies are needed to establish this possible association. The authors also noted that residual confounding was a major concern for their study.

Taken together, the three epidemiological studies addressing hearing loss, as discussed above, do not provide convincing evidence to show an association with vaccination; moreover, there is no biologically plausible explanation for such an association.

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and Hearing loss to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 558 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.6.2.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively to 17 Dec 2022 for valid case reports of hearing loss received from HCP, HA, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following HLT Hearing Losses.

Brighton Collaboration Classification

Cases identified in the review period were classified according to the Brighton criteria for hearing loss [171].

- Level 1 (Definitive case)
- Level 2 (Probable case)
- Level 3 (Possible case)
- Level 4 - Insufficient information available to confirm a possible, probable or definitive case of venous thrombosis or thromboembolism
- Level 5 - Sufficient information to determine that it is NOT a case of venous thrombosis or thromboembolism.

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case (of hearing loss). It is not used to ascertain causality.

In contrast, causality assessment (i.e., characterizing the likelihood that a case of hearing loss was attributable to vaccine exposure) was conducted utilizing the WHO-UMC standardized case causality assessment [17].

16.3.6.6.2.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed Vs Expected Analysis

See Appendix 11.3.

Clinical Trials Data

The topic of hearing loss was cumulatively reviewed in the clinical trial datasets, within the following studies of mRNA-1273-P301 study (ages ≥18 years; DLP: 04 May 2021), mRNA-1273-P203 study (ages 12-17 Years; DLP: 27 Jan 2022) and mRNA-1273-P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022), for any PT (listed below) included in the broad SMQ for "Hearing and Vestibular Disorders"(MedDRA version was 23.0 and 24.0).

mRNA-1273- P301 Study

The P301 (randomized, stratified, observer-blind, placebo-controlled study) included healthy adults ≥ 18 years of age, at appreciable risk of SARS-CoV-2 infection, with no known history of SARS-CoV-2 infection. There were approximately 30,000 participants randomized in 1:1 ratio to dose groups placebo (n = 15,000) and mRNA-1273 100 μg (n = 15,000) with vaccine schedule of 2 IM doses, 28 days apart.

In mRNA-1273-P301 the following PTs were reported:

- Hypoacusis: mRNA-1273 (1) vs Placebo (1)
- Deafness unilateral: mRNA-1273 (3) vs Placebo (3)
- Deafness neurosensory: mRNA-1273 (2) vs Placebo (0)

No imbalance was observed between the groups in the HLT of "Hearing losses"

mRNA-1273-P203 Study

The P203 (Phase 2/3, randomized, observer-blind, and placebo-controlled) included healthy adolescents in age group 12 to < 18 years. There were approximately 3,000 participants randomized in 2:1 ratio with a vaccine schedule of 100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart. There were no reports received under the SMQ for "Hearing and Vestibular Disorders".

mRNA-1273-P204 Study

The P204 (Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation, and randomized, observer-blind, placebo-controlled expansion) included healthy pediatrics between 6 months to < 12 years. There were approximately 750 to 4500 participants indifferent age groups randomized in 3:1 ratio with a vaccine schedule of 25, 50, 100 µg mRNA-1273 (25 µg only for 6 months to < 2 years age group) or placebo (3:1) 2 IM doses, 28 days apart. There were no reports received under the SMQ for "Hearing and Vestibular Disorders" for participants of P204.

Overview of Cases (Post-Authorization Data)

For more information about cases involving hearing loss refer to Appendix 11.18.

ModernaTx, Inc. conducts weekly, bi-weekly, and monthly signal detection activities that include analysis of relevant data in the GSDB and literature. As part of the signal detection activities, ModernaTx, Inc. conducted a cumulative review of the GSDB as of 18 Jul 2022 using the MedDRA HLT of "Hearing Losses" for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Information from that initial cumulative review is included below, in order to provide the full cumulative review of "Hearing loss" as requested by the agency.

Cumulative, from 18 Dec 2020 to 17 Dec 2022, ModernaTx, Inc. has received 2,327 case reports (2,589 events), under the HLT of "Hearing losses". Out of those 2,327 reports, 2,116 cases including 2,372 events, were evaluated in a previous cumulative review conducted by the MAH from 18 Dec 2020 to 18 Jul 2022. A summary of the evaluation conducted during that period is presented below, and in order to fulfil the regulatory request of performing a cumulative review of the HLT Hearing loss, an updated review was conducted covering the reporting period for this PBRER (19 Jun 2022 to 17 Dec 2022).

Hearing Loss (Cumulative review from 18 Dec 2020 to 18 July 2022)- elasomeran

Cumulative review of the GSDB from 18 Dec 2020 to 18 Jul 2022, yielded a total of 2,116 cases including 2,372 events. There were 1,201 medically confirmed cases (56.8%). Among the 2,372 events, 669 were reported as non-serious and 1,703 were reported as serious. Most of the cases

were reported in women (57.5%) with 40.3 % in men. The mean age was 51.8 years (SD 17.0) and the median age was 52.0 years (range: 0.3 to 101.0, noting that the cases in very young children were found to have age coding discrepancies which are being corrected). The highest proportion of cases occurred in the 50–64-year age group (27.9%) followed by the 40–49-year age group. (18.6%). Most of the cases were received from regulatory authorities (82.8%) and the remaining from spontaneous source (17.2%). The majority of these cases originated from the United States (55.8%), followed by EEA countries (31.6%) and other regions. Approximately 0.4% of the cases were from Canada.

When TTO was reported, most events occurred after Dose 1 (32.3%), with Dose 2 (30.7%), and Dose 3 (6.7%) with TTO not reported in 30.1% of the events. The time to onset of all doses was on average 12.4 days (SD 29.8) with a median of 2.0 days (0; 365). The outcomes of these 2,116 cases were reported as not recovered/not resolved (59.9%, which must be interpreted with caution as most reports do not have follow-up), recovered/resolved (14.6%), recovered/recovered with sequelae (1.9%), recovering/resolving (6.3%), unknown (17.2%).

The observed to expected analysis conducted as of 18 Jul 2022 included the MedDRA HLT of "Hearing losses" to identify the observed cases. The overall observed number of cases cumulatively as of 18 Jun 2022 with hearing loss was 2,116 (reporting rate of 5.6 per 100,000 person-years). The observed reporting rates were lower than all expected background incidence rates. The age and gender stratified analysis also did not change the interpretation of the results, however, the sensitivity analysis assuming 25% capture of observed cases showed increased rate ratio in 25–49-year age groups, overall and by gender. This increase was most notable in females 25-39 years old (RR= 1.93, 95% CI 1.73, 2.14). As hearing loss can be disruptive to the routine, it is unlikely that this condition is underreported. Therefore, the results of sensitivity analyzes should be interpreted with caution.

There were 3 cases with a reported a fatal outcome:

[redacted] (WWID: US-[redacted]): 73-year-old male patient with relevant medical history of Diabetes, who two days after the 1st dose of elasomeran was reported to experienced Hepatic failure, Renal failure, Dizziness, Vertigo and Deafness. Very limited information is provided in this report. The patient died nearly 8 months after the administration of the vaccine. Exact cause of death was not specified, and it remained unknown whether the autopsy was performed. This case is considered unassessable as no information was

provided to determine causality assessment for "deafness". The case is also heavily confounded by the associated comorbidities reported for this patient.

[redacted] (WWID: US-[redacted]): An 87-year-old, male patient with medical history of CAD, Obstructive sleep apnea syndrome, Hypothyroidism, COPD, Cardiomyopathy, Myocardial infarction, Rheumatoid arthritis Anemia, DM and hearing loss, who 5 days after the third dose of elasomeran experienced COVID-19, COVID-19 pneumonia, Acute respiratory failure, Respiratory arrest, Diarrhoea, Hypoacusis, Hypoglycaemia, Lactic acidosis, Mental status changes and SARS-CoV-2 test positive, which required hospitalization and ended fatally. The patient's medical history remains an important confounder. Autopsy results were not provided. COVID-19 infection and pneumonia along with patient's medical history likely caused the rest of the reported events. The patient had previous MH of hearing loss. According to the WHO causality assessment this case is considered unlikely related to the vaccine.

[redacted] (WWID: US-[redacted]): This is a case of a 96-year-old female patient with unknown medical history, who approximately seven months (216) after Dose 2 of elasomeran, experienced COVID-19 infection, Hypokalaemia, Depressed level of consciousness, Hypoxia, Asthenia, Feeling abnormal, Pleural effusion, and Urinary tract infection. It was reported: "Patient heard of hearing, does not answer nurses questions, opens eyes to sternum rub", which for a 96-year-old person could be consider part of medical history. No other information was provided on this or the clinical course of the other reported events. This is not considered a case of hearing loss.

Evaluation of disproportionality reporting in external databases provided the following conclusions:

- VAERS: None of the PTs of the HLT Hearing losses showed disproportionate reporting (EB05 > 2).
- EVDAS: Following PTs were disproportionately reported: Conductive deafness, deafness, deafness bilateral, deafness neurosensory, deafness permanent, deafness transitory, deafness unilateral and sudden hearing loss.

Disproportionality analysis conducted on the GSDB showed that none of the terms included in the HLT Hearing losses were disproportionate reported.

The conclusion of the review conducted from 18 Dec 2020 to 18 Jul 2022 was that based on review of available data, there is insufficient evidence to consider Hearing Loss as a safety concern.

Hearing Loss (Reporting Period- 19 June 2022 to 17 Dec 2022)- elasomeran

In order to fulfill the regulatory request of performing a cumulative review of the HLT Hearing loss, an updated review was conducted covering the reporting period for this PBRER (19 Jun 2022 to 17 Dec 2022).

During the reporting period of this PBRER there were 283 cases (293 events) of hearing loss identified, of which 210 (74.2 %) were serious and 83 (29.3%) cases were medically confirmed. There were no fatal event outcomes reported. Most cases were received from regulatory authorities (256; 90.5%).

The majority of cases were reported in females 164 (58.0%) compared to males 113 (39.9%) and 6 (2.1%) of the cases with missing gender information. The median age of patients 52.0 (min: 12/max: 93) years of age with a mean age of 50.9 (SD: 15.7). The age group with the highest proportion of events was the 50- to 64-year-old age group (95, 33.6%). (Table 16.108).

Table 16.108 Number and Percentage of Hearing Loss Events by Age and Gender (Reporting Period) - elasomeran

Age Group	Review Period					
	Female		Male		Unknown	
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases
(0-5 Months)	0	0	0	0	0	0
02-05Y	0	0	0	0	0	0
12-15Y	1	0.6	3	2.7	0	0
16-17Y	0	0	1	0.9	0	0
18-24Y	6	3.7	2	1.8	0	0
25-39Y	45	27.4	17	15.0	0	0
40-49Y	23	14.0	20	17.7	0	0
50-64Y	47	28.7	45	39.8	3	50.0
65-74Y	24	14.6	10	8.8	1	16.7
75Y+	7	4.3	11	9.7	0	0
Missing	11	6.7	4	3.5	2	33.3
Grand total	**164**	**100.0**	**113**	**100.0**	**6**	**100.0**

The majority of the hearing loss cases were reported in the EEA 216 (76.3 %), with the next highest number of cases reported in Australia 28 (9.9 %) (Table 16.109).

Table 16.109. Number and Percentage of Total Cases of Hearing Loss by Region (Reporting Period) - elasomeran

Region	Review Period	
	# Cases	% of Total Cases
Asia	5	1.8
Australia	28	9.9
Canada	4	1.4
European Economic Area	216	76.3
Latin America	1	0.4
Switzerland	6	2.1
United Kingdom	11	3.9
United States	12	4.2
Grand total	**283**	**100.0**

When evaluating events of hearing loss by time to onset (TTO), the highest number of events were reported after Dose 3 (43, 14.7%) followed by Dose 2 (40, 13.7 %), Dose 1 (19, 6.5%) and Dose 4 (8, 2.7%). There were 183 events (62.5%) that did not report information to determine TTO by dose (Table 16.110).

Table 16.110 Number and Percentage of Hearing loss Events by Dose Number and Time to Onset – (Reporting Period) - elasomeran

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% of Total Events
Dose 1	**Subtotal**	**19**	**6.5**
	0 days	2	0.7
	01-02	6	2.0
	03-04	1	0.3
	05-06	2	0.7
	07-13	0	0
	14-29	5	1.7
	30+	3	1.0
Dose 2	**Subtotal**	**40**	**13.7**
	0 days	4	1.4
	01-02	10	3.4

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% of Total Events
	03-04	2	0.7
	05-06	1	0.3
	07-13	5	1.7
	14-29	4	1.4
	30+	14	4.8
Dose 3	**Subtotal**	**43**	**14.7**
	0 days	6	2.0
	01-02	9	3.1
	03-04	1	0.3
	05-06	2	0.7
	07-13	6	2.0
	14-29	7	2.4
	30+	12	4.1
Dose 4	**Subtotal**	**8**	**2.7**
	0 days	1	0.3
	01-02	0	0
	03-04	1	0.3
	05-06	5	1.7
	07-13	1	0.3
Unknown	**Subtotal**	**183**	**62.5**
	0 days	5	1.7
	01-02	5	1.7
	03-04	5	1.7
	05-06	4	1.4
	07-13	8	2.7
	14-29	13	4.4
	30+	28	9.6
	Event onset prior to first dose reported	0	0
	Missing	115	39.2
Grand total		**293**	**100.0**

The most commonly reported top 3 MedDRA PT were Hypoacusis (111, 37.9%), deafness (74, 25.3%) and sudden hearing loss (47, 16.0%) (Table 16.111).

Table 16.111. Number and Percentage of Hearing Loss Events Reported by MedDRA Preferred Term (PT)– (Reporting Period) - elasomeran

PTs	Review Period	
	# Events	% of Total Events
Hypoacusis	111	37.9
Deafness	74	25.3
Sudden hearing loss	47	16.0
Deafness unilateral	39	13.3
Deafness neurosensory	12	4.1
Deafness bilateral	4	1.4
Deafness transitory	4	1.4
Neurosensory hypoacusis	1	0.3
Conductive deafness	1	0.3
Deafness permanent	0	0
Presbyacusis	0	0
Mixed deafness	0	0
Grand total	**293**	**100**.0

Medical review was conducted of the reported 283 cases in this reporting period to identify conditions or exposures associated with sensorineural hearing loss that could be confounders for a vaccine association. A total of 52 cases (18.4%) had one or more conditions associated with SSNHL (See Table 16.112). In addition, there were 5 cases where herpes zoster was reported after vaccination and the zoster infection was associated with hearing loss. ([redacted]).

Table 16.112. List of Potential Confounders- elasomeran

Potential Confounders
Infective: viral/bacterial (human immunodeficiency virus [90], cytomegalovirus [CMV], herpes simplex, mumps, rubella, syphilis)
Noise induced
Trauma (temporal bone fracture)
Ototoxic drugs
Autoimmune (systemic lupus erythematosis [SLE], granulomatosis with polyangiitis [formerly Wegener], Cogan syndrome, relapsing polychondritis, ulcerative colitis)
Tumor (vestibular schwannoma, leukaemia, myeloma)
Vascular (cerebrovascular disease, sickle cell disease)
Perilymphatic fistula

Potential Confounders
Barotrauma
Neurological (multiple sclerosis, cerebrovascular accident, migraine)
Other (diabetes mellitus, sarcoidosis)

Brighton Classification Review- elasomeran

The MAH conducted an evaluation of all the cases identified under the HLT "hearing losses" using the Brighton Collaboration case definition for acute sensorineural hearing loss. Sensorineural hearing loss (SNHL) is defined as a hearing loss of 30 dB or more in three sequential frequencies in the standard pure tone audiogram. A LEVEL 1 (Definite Case) was defined as a physical examination excluding conductive hearing loss and audiometry consistent with SNHL. A LEVEL 2 (Probable case) was defined a physical examination excluding conductive hearing loss and an Auditory Brainstem Response test consistent with SNHL or a Tuning fork exam consistent with SNHL. A LEVEL 3 (Possible case) was defined as a physical examination excluding conductive hearing loss and an Otoacoustic Emissions test consistent with hearing loss or a behavioral or neurodevelopmental testing questionnaire concerning hearing loss or remote screening using telehealth technology concerning hearing loss.

During the reporting period there was only one Level 1 case. The remaining cases were level 4 (Insufficient Information). Even where audiologic tests were mentioned values were not provided and, in most instances, where tests were reported the tests performed were not specified. Information on the Level 1 case is presented below:

[redacted] **(WWID:** [redacted]**):** This literature [172] case report concerns a 67-year-old female patient with no history of vertigo, dizziness, or tinnitus, or any previous hearing loss or ear discharge, who seven days after the patient had received the third dose of the elasomeran vaccine experienced sudden hearing loss of the left side. Relevant medical history included tested positive for coronavirus one year before the administration of the third dose, and allergies and reported the use of an antihistaminic during periods of allergies. Otoscopy was unremarkable on both ears, while Weber test was lateralized to the right ear and a Rinne test was positive on both sides. Pure tone audiometry was performed and showed profound right sensorineural hearing loss of at least 60 dB in every frequency. The patient did not have any other neurological deficits and the remaining investigations (otoscopy, chest X-ray, blood examination, MRI and Magnetic resonance angiography) were normal. The patient was treated with intratympanic dexamethasone injection and had almost full recovery from the event

at the time of this report.

WHO-UMC Causality: According to the WHO causality assessment this case is considered possible. The history of COVID-19 infection is an important risk factor and confounder in this case. Sensorineural hearing loss (SNHL), tinnitus, and/or vertigo have been described to occur during and following COVID-19 infection [165]. To date, different hypotheses have been proposed to explain the etiopathogenesis of neurological symptoms reported during the acute and post-acute phases of the infection. It is likely that many factors, or a combination of mechanisms, may be involved in the etiopathogenesis of different symptoms, including SNHL. These could consist of hypoxia, immune-mediated damage, coagulative disorders, and viral direct invasion/damage [173]. No additional information was presented in this report.

Hearing Loss in Children (<12 Years of Age) - elasomeran

There were no reports of hearing loss in children of < 12 years of age during the reporting period.

Hearing Loss in Adolescents (12-17 Years of Age) - elasomeran)

There were 5 cases (5 events) of hearing loss in adolescents 12 to 17 years of age during the reporting period. Of these, 3 cases (60%) were serious, all cases were medically confirmed cases. There are no cases with fatal outcome in the reporting period. A brief summary of these cases is presented below:

[redacted]): A 15-years-old male patient, with no medical history reported, who 24 days after the first dose of elasomeran vaccination developed SSNHL in the right ear. The hearing in the right ear had not recovered despite systemic steroids initially and then subsequently intra-tympanic steroid infiltrations was performed. The patient was treated with PREDNISOLONE. No additional information is available regarding clinical course and Concomitant medication.

Brighton Classification Level 4. Insufficient data to classify.

UMC-WHO Causality: This case is considered unassessable due to the lack of information necessary to establish a causality assessment.

[redacted]: A 14-year-old female patient with unknown medical history and who at an unknown TTO after an unknown vaccine dose experienced discomfort, hypoacusis and vision blurred. Important information is missing from this report including medical history, clinical

course, and any laboratory or diagnostic testing conducted. According to the Brighton Classification this case is considered Level 4. Insufficient information.

WHO-UMC Causality: Unassessable. TTO and dose are missing which are relevant in order to establish temporality to the vaccine.

[redacted]: A 16-year-old male patient with unknown medical history who after an unknown TTO after an unknown dose experienced blood pressure decreased, dyspnoea, heart rate increased, hypoacusis, vertigo and palpitations. No other information was provided including past medical history, concomitant medications or clinical course of the reported events.

Brighton Classification Level 4. Insufficient Information.

WHO-UMC Causality: Unassessable. TTO and dose are missing which are relevant in order to establish temporality to the vaccine.

[redacted] (WWID: [redacted]: A 15-year-old male patient, with no medical history provided, who at an unknown TTO after an unknown dose number experienced deafness, ear discomfort and tinnitus. No further information on lab data, clinical course, treatment details were received.

Brighton Classification Level 4. Insufficient Information

WHO-UMC Causality: Unassessable. The timing of the vaccination in relation to symptoms onset is unknown and no medical history, concomitant medications or treatments were provided.

[redacted] (WWID:[redacted]: 12-year-old male, with no medical history provided, who 2 days after the 2nd dose of elasomeran vaccine experienced tinnitus. Patient visited Ear Nose Throat department and after hearing testing, he was diagnosed with moderate hearing impairment in the right ear by the physician. The physician recommended taking steroids for a week and possibly using injections if hearing was not improved. No other information was provided.

Brighton Classification Level 4. Insufficient information.

WHO-UMC Causality: Unassessable. Important information is missing in this report including medical history, clinical course, any information on the laboratory and diagnostic testing conducted.

Hearing Loss in Patients After a Third Dose or Booster Dose of elasomeran)

During the reporting period, a total of 47 cases (51 events, with 40 [85.1%] serious)) of hearing loss related PTs were identified for elasomeran. The distribution of cases was higher in females (29; 61.7%) compared to males (18; 38.3%). The median age of patients 55.0 (min: 30/max: 80) years of age with a mean age of 53.7 (SD: 15.0) (Table 16.113). The majority of the hearing loss cases were reported in the EEA 40 (85.1%).

The event outcomes reported were as follows: 27 events (52.9 %) were not resolved, 5 (9.8%) events were resolving, 11 events (21.6%) resolved with sequelae, 5 events (9.8%) had recovered/resolved, and 3 events (5.9 %) did not report an outcome. There were no events with fatal outcome.

Most of the reports came from the EEA (40, 85.1%).

Table 16.113 Number and Percentage of Hearing Loss Events by Age and Gender (Reporting Period) – elasomeran 3 or more doses

Age Group	Review Period			
	Female		Male	
	# Cases	% of Total Cases	# Cases	% of Total Cases
18-24Y	0	0	0	0
25-39Y	11	37.9	3	16.7
40-49Y	1	3.4	5	27.8
50-64Y	9	31.0	5	27.8
65-74Y	6	20.7	2	11.1
75Y+	2	6.9	3	16.7
Missing	0	0	0	0
Grand total	**29**	**61.7**	**18**	**38.3**

The most commonly reported MedDRA PT were Deafness (16, 31.4%) Hypoacusis (15, 29.4%), Sudden hearing loss (11, 21.6%) and Deafness unilateral (6, 11.8%) (Table 16.114).

Table 16.114 Number and Percentage of Hearing Loss Events Reported by MedDRA Preferred Term (PT)– (Reporting Period) – elasomeran 3 or more doses

PT	Review Period	
	# Events	% of Total Events
Deafness	16	31.4

PT	Review Period	
	# Events	% of Total Events
Hypoacusis	15	29.4
Sudden hearing loss	11	21.6
Deafness unilateral	6	11.8
Deafness neurosensory	2	3.9
Deafness bilateral	0	0
Neurosensory hypoacusis	1	2.0
Grand total	**51**	**100.0**

When evaluating events of hearing loss by time to onset (TTO), the highest number of events were reported after Dose 3 (43, 84.3%) (Table 16.115).

Table 16.115 Number and Percentage of Hearing Loss Events by Dose Number and Time to Onset following a 3rd/Booster dose of elasomeran - Reporting Period

Dose Number	TTO	Review Period	
		# Events	% of Total Events
Dose 3	**Subtotal**	**43**	**84.3**
	0 days	6	11.8
	01-02	9	17.6
	03-04	1	2.0
	05-06	2	3.9
	07-13	6	11.8
	14-29	7	13.7
	30+	12	23.5
Dose 4	**Subtotal**	**8**	**15.7**
	0 days	1	2.0
	01-02	0	0
	03-04	1	2.0
	05-06	5	9.8
	07-13	1	2.0
Grand total		**51**	**100.0**

Hearing Loss After Receiving Booster Dose with elasomeran/imelasomeran (Reporting Period)

During the reporting period of this PBRER there were 11 cases (11 events) of hearing loss identified after receiving a dose of elasomeran/imelasomeran, of which, 2 cases were medically

confirmed, and no cases were reported with fatal outcomes. Most cases were received from regulatory authorities (10; 90.9 %).

No important differences were noted in the reported cases of hearing loss after elasomeran/imelasomeran, with 6 (54.5%) reports in females and 5 (45.5%) in males. The median age of patients experiencing hearing loss was 66.5 years (min:57/ max:75) years of age with a mean age of 66.3 years (SD: 9.1). The age group with the highest proportion of events was the 50- to 64-year-old age group (2, 18.2%) Table 16.116.

Table 16.116 Number and Percentage of Hearing Loss Events by Age and Gender (Reporting Period) - elasomeran/imelasomeran

Age Group	Review Period				# Cases	% Cases
	Female		Male			
	# Cases	% Cases	# Cases	% Cases		
50-64Y	1	9.1	1	9.1	2	18.2
65-74Y	0	0.0	1	9.1	1	9.1
75Y+	1	9.1	0	0.0	1	9.1
Missing	4	36.4	3	27.3	7	63.6
Grand total	**6**	**54.5**	**5**	**45.5**	**11**	**100.0**

The majority of the hearing loss cases after elasomeran/imelasomeran, were also reported in the EEA 6 (54.5%), with the next highest number of cases reported in the UK 4 (36.4 %).

When information was provided for events of hearing loss by dose number and time to onset (TTO), both events occurred within 7 days after dose 4. The other 9 events (81.8 %) did not provide information to determine TTO by dose (Table 16.117).

Table 16.117 Number and Percentage of Hearing loss Events by Dose Number and Time to Onset (Reporting Period) - elasomeran/imelasomeran

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% of Total Events
Dose 4	**Subtotal**	**2**	**18.2**
	01-02	1	9.1
	05-06	1	9.1
Unknown	**Subtotal**	**9**	**81.8**
	0 days	1	9.1
	Missing	8	72.7
Grand total		**11**	**100.0**

The most commonly reported MedDRA PT was Hypoacusis (4, 36.4%) followed by Deafness and Sudden hearing loss (3, 27.3%) (Table 16.118).

Table 16.118 Number and Percentage of Hearing Loss Events Reported by MedDRA Preferred Term (PT) (Reporting Period)-elasomeran/imelasomeran

PT	Review Period	
	# Events	% of Total Events
Hypoacusis	4	36.4
Deafness	3	27.30
Sudden hearing loss	3	27.30
Deafness unilateral	1	9.10
Grand total	**11**	**100.00**

Hearing Loss in Children (<12 Years of Age) - elasomeran/imelasomeran

There were no reports of hearing loss in children of < 12 years of age during the reporting period.

Hearing Loss in Adolescents (12-17 Years of Age) - elasomeran/imelasomeran)

There were no reports of hearing loss in children of 12-17 years of age during the reporting period.

Hearing Loss After Receiving Booster Dose with elasomeran/davesomeran

During the reporting period of this PBRER there were 5 cases (5 events) of hearing loss identified after administration of elasomeran/davesomeran, of which, 2 cases were medically confirmed. There were no fatal event outcomes reported. All of the reported cases were spontaneous reports.

Out of the 5 reported cases, there four in females and 1 report in a male, with most of reports in individuals >50 years of age. The median age of patients experiencing hearing loss events was 68.0 (min:48/ max:69) years of age (Table 16.119). All of the cases were reported in US.

Table 16.119 Number and Percentage of Hearing Loss Events by Age and Gender (Reporting Period)-elasomeran/davesomeran

Age Group	Female		Male		# Cases	% Cases
	# Cases	% Cases	# Cases	% Cases		
40-49Y	0	0	1	20.0	1	20.0
50-64Y	1	20.0	0	0	1	20.0
65-74Y	3	60.0	0	0	3	60.0
Grand total	**4**	**80.0**	**1**	**20.0**	**5**	**100.0**

When evaluating events of hearing loss by dose and TTO, when information was provided, there were no differences between events reported after Dose 3, Dose 4 and Dose 5 (1 each, 20.5%). Reported TTO was between the same day to more than 30 days after vaccination. (Table 16.120).

Table 16.120 Number and Percentage of Hearing loss Events by Dose Number and Time to Onset – (Reporting Period) - elasomeran/davesomeran

Dose Number	TTO (Days)	Review Period	
		# Events	% of Total Events
Dose 3	**Subtotal**	**1**	**20.0**
	30+	1	20.0
Dose 4	**Subtotal**	**1**	**20.0**
	07-13	1	20.0
Dose 5	**Subtotal**	**1**	**20.0**
	0 days	1	20.0
Unknown	**Subtotal**	**2**	**40.0**
	Missing	2	40.0
Grand total		**5**	**100.0**

The most commonly reported event by MedDRA PT was deafness (3, 60.0%) (Table 16.121).

Table 16.121 Number and Percentage of Hearing Loss Events Reported by all MedDRA Preferred Term (PT) (Reporting Period) - elasomeran/davesomeran

PT	Review Period	
	# Events	% of Total Events
Deafness	3	60.0
Deafness unilateral	1	20.0
Hypoacusis	1	20.0
Grand total	**5**	**100.0**

Hearing Loss in Children (<12 Years of Age)- elasomeran/davesomeran

There were no reports of hearing loss in children of < 12 years of age during the reporting period.

Hearing Loss in Adolescents (12-17 Years of Age)- elasomeran/davesomeran

There were no reports of hearing loss in adolescents 12 to 17 years of age during the reporting period.

Review of External Databases

VAERS and EVDAS were reviewed for Hearing loss related PTs (Conductive deafness, Deafness, Deafness bilateral, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness unilateral, Hypoacusis, Mixed deafness, Neurosensory hypoacusis, Presbyacusis and Sudden hearing loss).

EVDAS showed disproportionality of ROR for all PTs other than 'Deafness bilateral', 'Deafness transitory', 'Mixed deafness', 'Neurosensory hypoacusis' and 'Presbyacusis'. (Table 16.122)

- ***VAERS***: No Disproportionate Reporting of Hearing loss related Events Using EB05 >2 (elasomeran versus All vaccines in adults) in VAERS through 23 Dec 2022.
- ***EVDAS:*** Amongst the PTs of the HLT Hearing Losses, the PT of 'Deafness', 'Deafness neurosensory', 'Deafness permanent', 'Deafness unilateral', Hypoacusis' and 'Sudden hearing loss' showed disproportionality.

Table 16.122 EVDAS Disproportionality Analysis

PTs	ROR (-) All (31 Dec 2021- 31 Dec 2022)
Deafness	1.13
Deafness neurosensory	1.62
Deafness permanent	1.44
Deafness unilateral	3.73
Hypoacusis	1.01
Sudden hearing loss	3.01

16.3.6.6.2.5. Discussion

A cumulative review of the GSDB for reports under the HLT of "Hearing losses" received after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran was conducted, as per request received from a HA. The MAH identified 2,327 cases (2,589 events) for individuals between the ages of 5 to 101 years old. Only one case received during the reporting period of this PBRER, from a literature article had sufficient data to meet Brighton Collaboration case criteria (Level 1). The review of cases identified during the reporting period of this PBRER showed that most of the cases were heavily confounded by known risk factors associated with acute sensorineural hearing loss. There were five cases associated with herpes zoster reactivation.

In general, it is difficult to adequately analyze post-authorization data due to inherent limitations in spontaneous reporting. Evaluation of the data did not provide any new safety information that

would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomernan and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Based on the literature review of the mechanisms of action postulated including direct viral invasion of the middle ear and vascular injury to the terminal vessels of the middle ear and the three epidemiological studies that aimed to assess the relationship between COVID 19 vaccination and hearing loss do not provide convincing evidence to show an association with vaccination; moreover, a pathophysiologic process to explain such an association has not been shown. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Based on the cumulative review of available data as of 17 Dec 2022, the MAH considers there is insufficient evidence to consider Hearing Loss as a safety concern. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities. No changes to the product information are required at this time.

16.3.6.6.2.6 Conclusion

After review of all new safety data received during the reporting period and cumulatively, the MAH did not identify any safety concerns for cases reported under the HLT of "Hearing losses" and, thus, there is no change to the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable.

Based on the analysis of all safety data available as of 17 Dec 2022, the MAH considers reported cases of hearing loss to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The MAH will continue to monitor the reported events of hearing loss using routine surveillance activities. The benefit-risk evaluation remains positive.

16.3.6.6.3 Single Organ Cutaneous Vasculitis (SOCV)

16.3.6.6.3.1 Source of the New Information

ModernaTx, Inc. queried the CTs and its GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature cumulative from 18 Dec 2020 to 17 Dec 2022, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.6.3.2. Background Relevant to the Evaluation

ModernaTx, Inc. was requested by a regulatory authority to continue to provide an overview of SOCV using Brighton Collaboration categorization, and to provide a WHO Causality assessment for each event assessed as Brighton level 1-3.

SOCV refers to vasculitis in arteries or veins of any size in a single organ, the skin, and has no features of systemic involvement. Some patients initially diagnosed with SOCV may develop other disease manifestations, warranting re-evaluation for other systemic vasculitides. Therefore, the MAH adopted the Brighton Collaboration definition, which provides a means of categorizing cases according to level diagnostic certainty, and which refers to small vessel vasculitis of the skin where systemic involvement has been excluded.

SOCV typically presents with a single crop of lesions consisting of palpable purpura (hemorrhagic papules), erythematous papules, urticarial lesions, vesicles, and hemorrhagic vesicles 7–14 days after exposure to a triggering agent. SOCV favors dependent areas, as well as areas affected by trauma or compressed by tight-fitting clothing. The lesions are usually asymptomatic, or associated with burning, pain, or pruritus. Residual post-inflammatory hyperpigmentation may persist for months after the primary process resolves [174]. Skin biopsy is the gold standard method for the diagnosis of cutaneous vasculitis, also allowing differential diagnoses from vasculitis mimics, such as vaso-occlusive conditions and other diseases.

Disease-inducing or promoting factors for SOCV are either post-infectious or drug-induced, but more than half of cases are considered idiopathic. Although non-immunologic factors such as direct infection of endothelial cells can cause vasculitis, most lesions are mediated by immunopathogenic mechanisms. Small vessel vasculitis can also be associated with connective tissue diseases, and it may be a heralding sign of such diseases, particularly systemic lupus erythematosus (SLE).

16.3.6.6.3.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB using selected PTs from the MedDRA SMQ Vasculitis (Narrow scope) to include the following PTs: Administration site vasculitis, Cutaneous vasculitis, Hemorrhagic urticaria, Hemorrhagic vasculitis, Injection site vasculitis, Palpable purpura, Purpura, Purpura non-thrombocytopenic, Urticarial vasculitis, Vaccination site vasculitis, Vascular purpura, and Vasculitic rash.

To characterize the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration Single organ cutaneous vasculitis case definition (SOCV) [174]:

- Level 1 (certain)
- Level 2 (probable)
- Level 3 (possible)
- Level 4 (reported SOCV with insufficient evidence to meet the case definition)
- Level 5 (not a case of SOCV)

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case as SOCV. It is not used to ascertain causality.

Appendix 11.19 includes detailed summary of Cumulative cases that met Brighton's Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

Health Authority Request from PBRER#3:

Concerning Single Organ Cutaneous Vasculitis (SOCV), the MAH is requested to make an extra effort to provide the information missing to assess causality regarding the 2 cases deemed unassessable, and to update and re-evaluate all cases in the SOCV case listings in the next PSUR. The DLP of PSUR no 4 should be applied, and the MAH is requested to add clear argumentation where the MAH does not agree with the reporter or the description in the case narrative. Also, the MAH is requested to comment on the apparent discrepancy between the total number of literature reports on SOCV (n=47), the number of cases previously listed in PSUR (n=30) and the number of listed cases in the new appendices 1 and 2 (n=12) Appendix 11.22.

MAH Response:

Cases that are assessed as unassessable are as follows and following are the updated MAH comments:

[redacted]):

PSUR #3 MAH Comment: Literature report of a 14-year-old female patient who received elasomeran and on an unknown date, experienced cutaneous vasculitis with biopsy findings of infiltration of lymphocytes into the subcutaneous vessel wall with fibrinoid necrosis. No medical history or concomitant medications were provided. Laboratory evaluation including White blood

cells, Rh factor, ESR, C3/C4, ANCA, ANA was normal except for slightly elevated CRP. In light of the missing information that would be beneficial in further characterizing causality, WHO-UMC causality is classified as unassessable.

Updated MAH Evaluation: ModernaTx, Inc. reviewed the full literature case report in detail. The authors describe a 14-year-old female without any previous medical history, who experienced cutaneous arteritis, also known as cutaneous polyarteritis nodosa (PAN), following Dose 2 elasomeran given four weeks after Dose 1. The patient had fever and fatigue the day after Dose 2, which resolved spontaneously the same day. Clinical features of cutaneous vasculitis were identified a week later with no obvious manifestations suggestive of extracutaneous involvement. A skin biopsy revealed infiltration of lymphocytes into the subcutaneous vessel wall with fibrinoid necrosis, compatible with the pathological diagnosis of medium-sized vessel vasculitis. The skin biopsy findings of vasculitis of medium-sized vessels are consistent with the authors' diagnosis of cutaneous PAN, however because PAN is characterized by specific clinical and histological features due to the involvement of medium-size vessels, it is envisioned to be defined separately from SOCV which involves small vessel vasculitis. Based on this exclusionary finding, this case is classified as Brighton Collaboration level 5 and is not a case of SOCV.

[redacted]:

PSUR #3 MAH Comment: Case report presented at a scientific meeting of a 49-year-old male patient who experienced erythema and purpura 9 days after receiving dose 1 of an unspecified mRNA vaccine with (presumably from biopsy) "perivascular lymphocytes, neutrophils, nuclear dust, and bleeding images were noted in the tissue at the purpura". No further information such as medical history, concomitant medications and clinical course was provided. In light of the missing information that would be beneficial in further characterizing causality, WHO-UMC causality is classified as unassessable.

Updated MAH Evaluation: The marketing partner originally transmitting the case to ModernaTx, Inc. indicated that follow-up will be performed and ModernaTx, Inc. amends WHO-UMC causality to conditional. While there are clinical features of SOCV, any level of diagnostic certainty cannot be established because the provided information does not exclude involvement of other organs, nor does it specify that the results are from a skin biopsy. Based on the provided information, this case is classified as Brighton Collaboration level 4 (reported SOCV with insufficient evidence to meet the case definition).

Upon receipt of any follow-up information such as the proprietary mRNA vaccine and date administered, event date (or information to determine TTO), biopsy source etc, a follow-up report will be submitted according to applicable reporting requirements.

Health Authority also stated that apparent discrepancy between the total number of literature reports on SOCV (n=47), the number of cases previously listed in PSUR (n=30) and the number of listed cases in the new appendices 1 and 2 (n=12) Appendix 11.19.

Response: The review of the published literature in PubMED retrieved 47 articles which are not necessarily valid case reports, as some of these 47 articles lacked one or more for the four basic elements required (identifiable patient, suspect drug, AE, reporter [if not author]) to create a valid ICSR. Furthermore, articles may contain general information, provide reviews, meta-analyzes or other scientific communications, and are returned in the search results due to the search strategy and keywords. It may also be that a literature article is shared by a regulatory agency as an individual case report which is captured in the safety database as a regulatory case rather than literature case. The apparent discrepancy noted by the health authority is reconciled by considering that PSUR lists the subset of cases that are classified as Brighton Collaboration Levels 1 to 3 for diagnostic certainty for SOCV from the larger set articles retrieved from the literature search. The new Appendices 1 and 2 (n=12) list the Literature Non-Study cases as requested by the health authority. Appendix 11.19.

16.3.6.6.3.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected Analysis

See Appendix 11.3.

Literature Review:

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and SOCV Events to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 47 literature articles were retrieved using these search criteria for the review period *(note that PBRER#3 and PBRER#4 each had 47 literature articles were retrieved which were different in each report).* The literature search results were medically/scientifically reviewed. Most of these

47 articles are case reports presenting data on adverse cutaneous reactions or other conditions such as immune-mediated thrombotic thrombocytopenic purpura or thrombocytopenia. Review of these retrieved literature articles describe the occurrence of SOCV with COVID-19 vaccination but none of these provided compelling evidence of a causal association from mRNA vaccines. Overall, a detailed review of the search results found no articles with new and significant safety information.

Overview of Cases

For more details on SOCV cases please refer to Appendix 11.19.

GSDB

Cumulative review (SOCV, Cumulative to 17 Dec 2022)

Cumulatively, a total of 367 cases (and 380 events) were identified for vasculitis of which 197 cases were serious and 1 case had a fatal outcome secondary to systemic complications. There were 267 (72.8%) cases that were medically confirmed. Regulatory authority reports accounted for 82.8% of received reports (304 reports), followed by spontaneous case reports (45;12.3%) and literature reports (18; 4.9%). The largest number of cases originated from the USA (126; 34.3%) followed by France (60; 16.3%) and Germany (26; 7.1%).

There were disproportionately higher cases reported for females (244;66.5%) than for males (113;30.8%). 2.7% of cases had no information on gender. The age group with the highest number of cases was the 50-64 years group (117 cases: 31.9%) (Table 16.123). The median age of reported cases was 57.0 years, ranging from 14.0 years to 94.0 years.

During the reporting period, a total of 41 cases (and 42 events) were identified for vasculitis of which 27 cases were serious and none had a fatal outcome. There were 30 (73.2%) cases that were medically confirmed. Regulatory authority reports accounted for 85.4% of received reports (35 reports), followed by literature reports (6; 14.6%). The largest number of cases originated from France (13; 31.7%) followed by Germany (4; 9.8%) and Japan (4; 9.8%). Overall, the distribution for the reporting period is generally in line with that observed cumulatively.

Table 16.123 Case Distribution by Age Group, Cumulative as of 17 Dec 2022

Age Group All (11)	Prior to Review Period		Review Period		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15Y	1	0.3	0	0	1	0.3

Age Group All (11)	Prior to Review Period		Review Period		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
16-17Y	1	0.3	1	2.4	2	0.5
18-24Y	4	1.2	3	7.3	7	1.9
25-39Y	53	16.3	7	17.1	60	16.3
40-49Y	45	13.8	5	12.2	50	13.6
50-64Y	107	32.8	10	24.4	117	31.9
65-74Y	59	18.1	8	19.5	67	18.3
75Y+	43	13.2	7	17.1	50	13.6
Missing	13	4.0	0	0	13	3.5
Grand total	**326**	**100.0**	**41**	**100.0**	**367**	**100.0**

Of the 380 events, 189 were serious and 191 were non-serious. Purpura was the most frequently reported event (242, 63.7%) with the majority of those reports being non-serious, followed by cutaneous vasculitis (87; 22.9%) events (Table 16.124). During the reporting period, Purpura (21; 50.0%) was most frequently reputed PT, similar to the cumulative reports. Overall, this pattern for the reporting period is generally in line with that observed cumulatively.

Table 16.124 Event Distribution by PT, Cumulative as of 17 Dec 2022

PT	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
	# Events	% of Total Events	# Events	% of Total Events		
Purpura	221	65.4	21	50.0	242	63.7
Cutaneous vasculitis	72	21.3	15	35.7	87	22.9
Urticarial vasculitis	16	4.7	3	7.1	19	5.0
Vasculitic rash	14	4.1	1	2.4	15	3.9
Vascular purpura	5	1.5	2	4.8	7	1.8
Palpable purpura	3	0.9	0	0	3	0.8
Vaccination site vasculitis	3	0.9	0	0	3	0.8
Haemorrhagic vasculitis	2	0.6	0	0	2	0.5

PT	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
	# Events	% of Total Events	# Events	% of Total Events		
Injection site vasculitis	2	0.6	0	0	2	0.5
Grand total	**338**	**100.0**	**42**	**100.0**	**380**	**100.0**

Cumulative event distribution by dose number and time to onset (TTO) are described in Table 16.125. Most of the events were reported after Dose 1 (120; 31.6%), with a TTO within <4 days (55; 14.5%). Dose number and TTO were not reported for 175 events (46.1%). SOCV typically presents 7-14 days after exposure, so the relatively disproportionate number of events reported on post dose days 0-6 is likely driven by cutaneous injection reactions and other events such as purpura.

During the reporting period, event distribution by dose number and time to onset (TTO) are described in Table 16.125. Most of the events were reported after Dose 3 (8; 19.0%). Majority 25 events (59.5%). SOCV typically presents 7-14 days and similar pattern of TTO was observed in cumulative ad reporting period data.

Table 16.125 Event Distribution by Dose and TTO, Cumulative as of 17 Dec 2022

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
		# Events	% of Total Events	# Events	% of Total Events		
Dose 1	**Subtotal**	**115**	**34.0**	**5**	**11.9**	**120**	**31.6**
	0 days	16	4.7	0	0	16	4.2
	01-02	28	8.3	1	2.4	29	7.6
	03-04	10	3.0	0	0	10	2.6
	05-06	7	2.1	0	0	7	1.8
	07-13	33	9.8	3	7.1	36	9.5
	14-29	17	5.0	1	2.4	18	4.7
	30+	4	1.2	0	0	4	1.1
Dose 2	**Subtotal**	**57**	**16.9**	**1**	**2.4**	**58**	**15.3**
	0 days	7	2.1	0	0	7	1.8
	01-02	20	5.9	0	0	20	5.3
	03-04	7	2.1	0	0	7	1.8

Dose Number	TTO All Doses (Days)	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
		# Events	% of Total Events	# Events	% of Total Events		
	05-06	3	0.9	0	0	3	0.8
	07-13	11	3.3	0	0	11	2.9
	14-29	4	1.2	0	0	4	1.1
	30+	5	1.5	1	2.4	6	1.6
Dose 3	**Subtotal**	**16**	**4.7**	**8**	**19.0**	**24**	**6.3**
	0 days	1	0.3	0	0	1	0.3
	01-02	3	0.9	1	2.4	4	1.1
	03-04	3	0.9	0	0	3	0.8
	05-06	1	0.3	2	4.8	3	0.8
	07-13	5	1.5	1	2.4	6	1.6
	14-29	2	0.6	2	4.8	4	1.1
	30+	1	0.3	2	4.8	3	0.8
Dose 4	**Subtotal**	**0**	**0**	**1**	**2.4**	**1**	**0.3**
	14-29	0	0	1	2.4	1	0.3
Dose 5	**Subtotal**	**0**	**0**	**2**	**4.8**	**2**	**0.5**
	03-04	0	0	2	4.8	2	0.5
Unknown	**Subtotal**	**150**	**44.4**	**25**	**59.5**	**175**	**46.1**
	0 days	10	3.0	0	0	10	2.6
	01-02	19	5.6	1	2.4	20	5.3
	03-04	8	2.4	3	7.1	11	2.9
	05-06	3	0.9	0	0	3	0.8
	07-13	13	3.8	0	0	13	3.4
	14-29	7	2.1	2	4.8	9	2.4
	30+	8	2.4	2	4.8	10	2.6
	Event onset prior to first dose reported	2	0.6	0	0	2	0.5
	Missing	80	23.7	17	40.5	97	25.5
Grand total		**338**	**100.0**	**42**	**100.0**	**380**	**100.0**

Cumulatively, a total of 133 events (35.0%) were considered not recovered and 167 (43.9%) events were considered recovered or recovering (Table 16.126). Cumulatively, there has been 1 case with a fatal outcome ([redacted]). Summary of this fatal case is described below, and no fatal

cases were reported for the review period.

Table 16.126 Event Distribution by Outcome, Cumulative as of 17 Dec 2022

Event Outcome	Prior to Review Period		Review Period		Grand total # of Events	Grand total % of Events
	# Events	% Of Events	# Events	% Of Events		
Fatal	1	0.3	0	0	1	0.3
Not Recovered/Not Resolved	123	36.4	10	23.8	133	35.0
Recovered/Resolved	77	22.8	11	26.2	88	23.2
Recovered/Resolved with Sequelae	1	0.3	3	7.1	4	1.1
Recovering/Resolving	63	18.6	12	28.6	75	19.7
Unknown	73	21.6	6	14.3	79	20.8
Grand total	**338**	**100.0**	**42**	**100.0**	**380**	**100.0**

Description of the Fatal Cases (Cumulatively as of 17 Dec 2022):

Cumulatively as of 17 Dec 2022, there was one fatal case which was presented in the previous PBRER. During this reporting period (19 Jun 2022 to 17 Dec 2022) there are no fatal reports.

Case Assessment using the Brighton Collaboration Case Definition and WHO-UMC Causality Assessment

Cumulatively, there have been a total of 367 cases (380 events) involving SOCV. All cases were medically reviewed and classified according to the criteria as specified in the SOCV case definition by the Brighton Collaboration [174] and 29 cases were identified as Levels 1 to 3. Note: two (2) cases which were previously assessed as Level-1 and Level-2 were re-assessed and considered as Level-4 and Level-5, hence cumulative counts in Brighton Collaboration Level 1 to 3 were decreased from PBRER#3 to PBRER#4.

For the reporting period, 41 cases including 42 events were received. Of these 41 cases, one was classified as Brighton Collaboration level 1 for SOCV and WHO-UMC causality was assessed as possible due to a plausible temporal relationship.

Cumulatively, 3 cases (4 events) met Brighton Collaboration Level 1 diagnostic certainty, 6 cases (8 events) met the criteria for Level 2, and 20 cases (20 events) for Level 3. All remaining cases either had insufficient evidence to meet the case definition or were determined not to be cases of SOCV. The 29 cases (32 events) that met case definition Levels 1 to 3 are presented in Appendix

11.19. These 29 cases that met Brighton Collaboration case definition for SOCV had a median age of 48 years, with a range from 28 years to 77 years. with. Eight patients were male and 21 were female.

Of the 29 cases meeting Brighton Collaboration level 1-3 for the case definition of SOCV, 28 were assessed as WHO-UMC possible for causality based primarily on temporal association between vaccination and TTO of events; however, a causal relationship cannot be excluded due to the lack of supporting information, including medical history, concomitant medications, clinical course, laboratory information, etc. There was 1 report that was considered unlikely related to vaccine exposure due to prolonged TTO.

Of the 32 events in the 29 cases that were classified as Level 1 to 3, 14 events (13 cases) occurred after Dose 1. Events mostly occurred during the period 7-13 days after vaccination which is when SOCV usually develops, although events are noted to occur earlier, and this may represent some variation in presentation. Table 16.127 presents TTO by Event and Dose for the 32 events in the 29 cases.

Table 16.127 Time to Onset by Event and Dose:

TTO Group in Days	Dose 1	Dose 2	Dose 3	Unknown	Grand Total
<7 Days	3	3		4	10
≥ 7 days and <14	8	1		2	11
≥ 14 days and <30	3		1	1	5
≥ 30 Days			1		1
Missing				5	5
Grand Total	**14**	**4**	**2**	**12**	**32**

In many of cases reported as SOCV, the information provided was inconsistent with the condition, generally due to multiple systemic events involving other organ systems occurring concurrently, or the provided information being insufficient for adequate assessment. In the vast majority of cases, biopsies were not performed, or results were not provided.

Subpopulation Analyzes

SOCV in Children (<12 Years of Age)

Cumulatively, no reports were received in children <12 years of age.

SOCV in Adolescents (12-17 Years of Age)

Cumulatively, three cases of SOCV were received in adolescents 12-17 years of age with one case ([redacted]) presented below which was received during this interval.

[redacted]): This literature-non-study case, concerns a 16-year-old male patient, with no medical history reported, who received heterologous dose 3 elasomeran vaccination (after Pfizer BNT162B2 primary series) and 3 days later experienced maculo-papular rash with purpuric aspect located on the lower limbs and forearms. Skin biopsy revealed superficial and deep dermal small vessels with lymphocytic perivascular infiltrate, wall aggression and endothelial cell swelling, in absence of thrombosis or fibrinoid necrosis. Patient was diagnosed as cutaneous lymphocytic vasculitis. SARS-CoV-2 test was negative. No further information on risk factors, treatment of the event was available in the report. Outcome of the event was not known at the time of report.

MAH Comment: This is a literature report of a 16-year-old male with no CM, MH provided who experienced cutaneous vasculitis 72 hours after elasomeran and earlier vaccine interchange with Comirnaty x 2. Skin biopsy showed lymphocytic perivascular infiltrate, wall aggression and endothelial cell swelling, in absence of thrombosis or fibrinoid necrosis. This report is classified as Brighton Collaboration level 2 (lacking necrosis) and WHO-UMC causality considered as possible considering plausible TTO with vaccine interchange as confounder.

SOCV in Patients After Bivalent Dose of elasomeran

SOCV After Receiving Booster Dose with elasomeran/imelasomeran)

Cumulatively through 17 Dec 2022, two (2) cases (2 events) of SOCV were reported in recipients of elasomeran/imelasomeran. One case was medically confirmed and there was no case with a fatal outcome. Both cases were reported during this reporting period and classified as Brighton Collaboration level 5. Details of these reports are as follows:

[redacted] This regulatory authority case concerns a 22-year-old male patient, who had COVID-19 infection 3 weeks prior to vaccination, received Influenza vaccine the same day as dose 4 elasomeran/imelasomeran vaccine; and one day post-vaccination, experienced the unexpected and non-serious event of purpura. No details of previous doses were provided. A week prior vaccination, a negative SARS-CoV-2 test was performed. Influenza vaccination remains as a confounder.

[redacted]: This regulatory authority case concerns an unknown adult female patient, with no relevant medical history reported, who experienced the unexpected, serious) event of cutaneous vasculitis after a dose (reported as "Dose 3 or more") of Spikevax bivalent vaccine was administered. No further details on onset date of the event, clinical course, diagnostic tests and treatment were reported. At the time of the latest report, the event was resolving.

SOCV After Receiving Booster Dose with elasomeran/davesomeran)

No reports elasomeran/davesomeran were reported as of 17 Dec 2022.

Review of Other Databases

Clinical Trial Data Review:

There are no new data available from the CTs database during this reporting period.

Subpopulation Clinical Trial Data Analyzes

Children ages 6 Months to 11 Years (mRNA-1273-P204 study): As of the last cut-off 21 Feb 2022, there are no cases for the topic of SOCV

Adolescents ages 12-17 Years (mRNA-1273-P203 Study): As of the last cut-off 27 Jan 2022, there are no cases for the topic of SOCV.

16.3.6.6.3.5. Discussion

SOCV refers to vasculitis in arteries or veins of any size in a single organ, the skin, and has no features of systemic involvement. Disease-inducing or promoting factors for SOCV are either post-infectious or drug-induced, but more than half of cases are considered idiopathic. SOCV typically presents with a single crop of lesions consisting of palpable purpura (hemorrhagic papules), erythematous papules, urticarial lesions, vesicles, and hemorrhagic vesicles 7–14 days after exposure to a triggering agent. Skin biopsy is the gold standard method for the diagnosis of cutaneous vasculitis, also allowing differential diagnoses from vasculitis mimics, such as vaso-occlusive conditions and other diseases.

Through 17 Dec 2022, 662,871,167 doses of elasomeran were administered and during the same period, 367 cases SOCV were reported after elasomeran administration, yielding a very low reporting rate of 0.49 reports per million doses. The overall observed reporting rate was 0.86 cases per 100,000 person-years vs an expected rate of 6.03 cases per 100,000 person-years, which is significantly lower than expected. In addition, a substantial proportion of reports lack important

information such as clinical presentation, TTO, concomitant medications/comorbidities and other pertinent details necessary to perform a proper evaluation. Very importantly, most reports lack documented results of skin biopsy necessary to establish a diagnosis of SOCV.

Based on the analysis of all the safety data available as of 17 Dec 2022, the MAH assessed those cases considered under the AESI of SOCV are temporally associated with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran. However, the information provided is inadequate and uncompelling to establish a causal association between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and SOCV.

16.3.6.6.3.6 Conclusion

After careful review of all new safety data received cumulatively and during the reporting period, the MAH does not consider there is evidence for a causal association between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and SOCV. The benefit-risk profile for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran remains favorable and ModernaTx, Inc. will continue to monitor events of SOCV using routine surveillance.

16.3.6.7 Other Clinical Topics

16.3.6.7.1 Medication Errors

16.3.6.7.1.1 Source of the New Information

New information includes valid case reports of medication errors involving elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran received from HCPs, HAs, consumers and literature, for the reporting period of 19 Jun 2022 through 17 Dec 2022, worldwide.

16.3.6.7.1.2. Background Relevant to the Evaluation

A medication error is an unintended failure in the drug treatment (or in this case, vaccine use) process that leads to, or has the potential to lead to, harm to the patient. European Union (EU) legislation requires information on medication errors to be collected and reported through national pharmacovigilance systems.

16.3.6.7.1.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The ModernaTx, Inc. GSDB was searched using the SMQ *Medication errors*, with a broad scope. The results were reviewed to exclude cases describing scenarios of off-label use and intentional product use issues. The MedDRA Concept Description for medication errors includes any

preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health-care professional, patient or consumer. Such events may be related to professional practice, health-care products, procedures and systems, including prescribing, order communication, product labeling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use. Intentional use issues are excluded from this analysis, where identifiable, because these were not considered true medication errors.

16.3.6.7.1.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on medication error cases please refer to Appendix 11.20.

Overview of Cases

During this reporting period, there were 4,931 cases with 7,383 medication error events, and 4,373 of the cases (88.7%) were medically confirmed. There were 1,644 cases (33.3%) reported in males and 1,963 cases (39.8%) reported in females; gender information was not provided in 1,324 cases (26.9%). The majority of cases were received directly by the MAH as spontaneous reports from the public (4,038; 81.9%). Most cases reporting medication errors were received from the United States (2,912; 59.1%), with the regions reporting the next highest volumes being much smaller at 490 (9.9%) from Latin America and 437 from Australia (8.9%).

Of the events with a known dose number, the greatest portion of events occurred after the 2nd dose (799; 10.8%). 4,749 events (64.3%) were associated with an unknown dose number. (Table 16.128).

Table 16.128 Number and Percentage of Medication Error Events by Dose Number - Review Period 19 Jun 2022 to 17 Dec 2022

Dose Number	# Events	% Total Events
Dose 1	450	6.1
Dose 2	799	10.9
Dose 3	545	7.4
Dose 4	779	10.6
Dose 5	60	0.8
Dose 6	1	0
Dose 7	0	0
Unknown	4,749	64.3

Dose Number	# Events	% Total Events
Grand total	**7,383**	**100**

In this reporting period, the MedDRA PTs of Expired product administered (2,393; 32.4%), and Product storage error (1,494; 20.2%) are among the most frequently reported medication errors (Table 16.129). The events included in this analysis that were coded to product administered to patient of inappropriate age (215; 2.9%) or inappropriate schedule of product administration (745; 10.1%) may or may not represent true medication errors as there was not enough information in the report to determine whether these instances were intentionally administered outside of labeled product use guidance. Overall, there were fewer medication error events from this review period and the last review period.

Table 16.129 Number and Percentage of the Top 10 Medication Error Events by PT - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Expired product administered	2,393	32.4
Product storage error	1,494	20.2
Inappropriate schedule of product administration	745	10.1
Medication error	521	7.1
Wrong product administered	351	4.8
Product temperature excursion issue	303	4.1
Poor quality product administered	278	3.8
Vaccination error	278	3.8
Product administered to patient of inappropriate age	215	2.9
Incorrect dose administered	176	2.4

During the reporting period, there were 1361 cases (4,665 events) of medication error reported with an associated AE. The most frequent AE reported were COVID 19 (289; 6.2%), Pyrexia (180; 3.9%) (Table 16.130).

Table 16.130 Number and Percentage of Adverse Events Reported in Medication Error Cases with Associated Adverse Events by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
COVID-19	289	6.2
Pyrexia	180	3.9
Fatigue	150	3.2
Headache	119	2.6

PT	# Events	% Total Events
Pain in extremity	109	2.3

Subpopulation Analyzes

Medication Errors in Adolescents (12 to 17 years old) – Reporting period 19 Jun 2022 to 17 Dec 2022

During this reporting period, there were 223 cases (317 events) reporting medication errors in adolescents 12 to 17-years-old. There were 93 cases (41.7%) reported in males and 97 cases (43.5%) reported in females; gender information was not provided in 33 cases (14.8%). The majority of cases were received from regulatory authorities (129; 57.8%) with majority of the cases received from the Australia (79; 35.4%)

Of the events with a known dose number, the greatest proportion of the events occurred after the 3rd dose (34; 10.7%). 230 events (72.6%) were associated with an unknown dose number (Table 16.131).

Table 16.131 Number and Percentage of Medication Error Events Reported in Adolescents by Dose Number - Review Period 19 Jun 2022 to 17 Dec 2022

Dose Number	# Events	% Total Events
Dose 1	12	3.8
Dose 2	26	8.2
Dose 3	34	10.7
Dose 4	15	4.7
Unknown	230	72.6
Grand total	**317**	**100**

The most frequent medication error event reported was Product administered to patient of inappropriate age (109; 34.4%). (Table 16.132).

Table 16.132 Number and Percentage of Medication Error Events Reported in Adolescents by PT (≥2% of Events)- Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Product administered to patient of inappropriate age	109	34.4
Vaccination error	72	22.7
Medication error	50	15.8
Wrong product administered	27	8.5
Expired product administered	16	5.0

PT	# Events	% Total Events
Inappropriate schedule of product administration	12	3.8
Product storage error	11	3.5

During the reporting period, there were 34 cases (80 events) of medication error reported with an associated AE in adolescents. The most frequent AE reported were Myalgia (11; 13.8%), and Pyrexia (9; 11.3%). (Table 16.133).

Table 16.133 Number and Percentage of Adverse Events Reported in Medication Error Cases with Associated Adverse Events in Adolescents by PT (n>2) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Myalgia	11	13.8
Pyrexia	9	11.3
Headache	8	10.0
Fatigue	5	6.3
Pain in extremity	4	5.0
Nausea	3	3.8
Chest pain	3	3.8
Malaise	3	3.8
Dyspnoea	3	3.8

Medication Errors in Children (6-11 years old) – Reporting period 19 Jun 2022 to 17 Dec 2022

During this reporting period, there were 164 cases (207 events) reporting medication errors in children <12-years-old. There were 69 cases (42.1%) reported in males and 78 cases (47.6%) reported in females; gender information was not provided in 17 cases (10.4%). Cases were equally reported through spontaneous reports (82; 50%), and regulatory authority reports (82; 50%), most cases were received from the United States (78; 47.6%).

Of the events with a known dose number, the greatest proportion of the events occurred after the 1st dose (47; 22.7%). 96 events (46.4%) were associated with an unknown dose number (Table 16.134).

Table 16.134 Number and Percentage of Medication Error Events Reported in Children by Dose Number - Review Period 19 Jun 2022 to 17 Dec 2022

Dose Number	# Events	% Total Events
Dose 1	47	22.7

Dose Number	# Events	% Total Events
Dose 2	36	17.4
Dose 3	20	9.7
Dose 4	8	3.9
Unknown	96	46.4
Grand total	**207**	**100**

The most frequent medication error event reported was unspecified Medication error events (61; 29.5%) (Table 16.135).

Table 16.135 Number and Percentage of Medication Error Events Reported in Children by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Medication error	61	29.5
Product administered to patient of inappropriate age	25	12.1
Wrong product administered	24	11.6
Expired product administered	20	9.7
Vaccination error	17	8.2
Incorrect dose administered	14	6.8
Product storage error	8	3.9
Product temperature excursion issue	8	3.9
Poor quality product administered	7	3.4
Inappropriate schedule of product administration	5	2.4

During the reporting period, there were 20 cases (37 events) of medication error reported with an associated AE in children 6-11years old. The most frequent AEs reported was Myalgia (5; 13.5%) (Table 16.136).

Table 16.136 Number and Percentage of Adverse Events Reported in Medication Error Cases with Associated Adverse Events in Children by PT (n>2) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Myalgia	5	13.5
Pyrexia	4	10.8
Injection site reaction	4	10.8

Medication Errors in Children (2-5 years old) – Reporting period 19 Jun 2022 to 17 Dec 2022

During this reporting period, there were 337 cases (619 events) reporting medication errors in children 2-5 years old. There were 138 cases (40.9%) reported in males and 160 cases (47.5%) reported in females; gender information was not provided in 39 cases (11.6%). The majority of cases were received from regulatory authorities (283; 84%), and majority of the cases were from the United States (235; 69.7%).

Of the events with a known dose number, the greatest proportion of the events occurred after the 2nd dose (127; 20.5%). 364 events (58.8%) were associated with an unknown dose number. (Table 16.137).

Table 16.137 Number and Percentage of Medication Error Events Reported in Children (2-5-years old) by Dose Number - Review Period 19 Jun 2022 to 17 Dec 2022

Dose Number	# Events	% Total Events
Dose 1	117	18.9
Dose 2	127	20.5
Dose 3	11	1.8
Unknown	364	58.8
Grand total	**619**	**100**

The most frequent medication error event reported were Expired product administered (160; 25.8%), and Product storage error (157; 25.4%). (Table 16.138).

Table 16.138 Number and Percentage of Medication Error Events Reported in Children (2-5years old) by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Expired product administered	160	25.8
Product storage error	157	25.4
Product temperature excursion issue	66	10.7
Poor quality product administered	63	10.2
Medication error	52	8.4
Inappropriate schedule of product administration	41	6.6
Product administered to patient of inappropriate age	28	4.5

During the reporting period, there were 20 cases (36 events) of medication error reported with an associated AE in children 2-5 years old. The most frequent AEs reported was Pyrexia (7; 19.4%) (Table 16.139).

Table 16.139 Number and Percentage of Adverse Events Reported in Medication Error Cases with Associated Adverse Events in Children (2-5years old) by PT (n>2) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Pyrexia	7	19.4
Fatigue	5	13.9
Pain	3	8.3
Somnolence	3	8.3

Medication Errors in Children (6-23months old) – Reporting period 19 Jun 2022 to 17 Dec 2022

During this reporting period, there were 117 cases (211 events) reporting medication errors in children 6-23 months old. There were 54 cases (46.2%) reported in males and 52 cases (44.4%) reported in females; gender information was not provided in 11 cases (9.4%). The majority of cases were spontaneous reports (110; 94%) with majority of the cases from the United States (103; 88%). Of the events with a known dose number, the greatest proportion of the events occurred after the 1st dose (48; 22.7%). 124 events (58.8%) were associated with an unknown dose number (Table 16.140).

Table 16.140 Number and Percentage of Medication Error Events Reported in Children (6-23 months old) by Dose Number - Review Period 19 Jun 2022 to 17 Dec 2022

Dose Number	# Events	% Total Events
Dose 1	48	22.7
Dose 2	38	18
Dose 4	1	0.5
Unknown	124	58.8
Grand total	**211**	**100**

The most frequent medication error event reported were Expired product administered (74; 35.1%), and Product storage error (66; 31.3%) (Table 16.141).

Table 16.141. Number and Percentage of Medication Error Events Reported in Children (6-23 months old) by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Expired product administered	74	35.1
Product storage error	66	31.3

PT	# Events	% Total Events
Poor quality product administered	16	7.6
Product temperature excursion issue	15	7.1
Inappropriate schedule of product administration	14	6.6

During the reporting period, there were 11 cases (23 events) of medication error reported with an associated AE in children 6-23months old. There were 3 cases (27.3%) in males, and 8 cases (72.7%) in females, and the most frequent AEs reported was Pyrexia (6; 26.1%).

Medication Errors in Children (0-5 months old) – Reporting period 19 Jun 2022 to 17 Dec 2022

During this reporting period, there were 8 cases (12 events) reporting medication errors in children 0-5 months old. There was 1 case (12.5%) reported in males and 6 cases (75%) reported in females; gender information was not provided in 1 case (12.5%). Half of the cases were received from regulatory authorities (4; 50%), and the other half were spontaneous reports (4; 50%); with half of the cases from the United States (4; 50%)

Of the medication error events with a known dose number, the greatest portion of the events occurred after Dose 1 (6, 50%); there were no events associated with dose 2 and doses 3, and 1 event (8.3%) was associated with dose 5. There were 5 events (41.7%) associated with an unknown dose number.

The most frequent medication error event reported were Product administered to patient of inappropriate age (3; 25%), and Medication Error (3;25%).

During the reporting period, there was 1 case (1 event) of medication error reported with an associated AE in children 0-5 months old. The case was reported in a 4-month-old female, and the AE reported was Pyrexia (1; 100%).

During this reporting period, both bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran were authorized in some countries and continue to be authorized worldwide.

Medication Errors Involving elasomeran/imelasomeran

During this reporting period, the MAH became aware of reports of medication errors related to product confusion between elasomeran booster and elasomeran/davesomeran booster (mainly in the United States) and accidental underdosing of the elasomeran/imelasomeran and elasomeran/davesomeran boosters in the rest of the world. Instances of accidental underdosing

typically were due to administration of a 0.25 mL dose (equivalent to 25 µg) instead of 0.5 mL (50 µg) per product label for the bivalent boosters. The volumes drawn for bivalent boosters were confused with the volume to be drawn for the elasomeran booster used earlier in 2022 (0.25 mL, equivalent to 50 µg).

Based on the findings of the safety assessment evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a potential risk and was classified as Priority 1 (Urgent (emerging) Safety Issues: Issues which have a significant impact on the product's benefit-risk profile, and which require the most rapid communication and implementation) and that risk minimization measures needed to be implemented in agreement with the respective HAs in the countries where the bivalent vaccines have been authorized. Therefore, safety letters from the MAH have been disseminated worldwide regarding the issue.

Therefore, communication letters have been disseminated worldwide regarding the issue.

During this reporting period, and cumulatively, there were 622 cases (1,106 events) reporting medication errors in elasomeran/imelasomeran. There were 79 cases (12.7%) reported in males and 129 cases (20.7%) reported in females; gender information was not provided in 414 cases (66.6%). The majority of cases were reported through spontaneous reports (589; 94.7%), and most cases were received from the UK (249; 40%).

The most frequent medication error event reported was unspecified Product storage error (267; 24.1%) (Table 16.142).

Table 16.142. Number and Percentage of Medication Error Events Reported in elasomeran/imelasomeran by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Product storage error	267	24.1
Expired product administered	227	20.5
Accidental underdose	172	15.6
Product temperature excursion issue	146	13.2
Product dispensing error	100	9.0
Wrong product administered	30	2.7

During the reporting period, there were 49 cases (165 events) of medication error reported with an associated AE in elasomeran/imelasomeran. There were 15 cases (30.6%) in males, 32 cases in

females (65.3%); 2 cases (4.1%) were missing gender information. The most frequent AEs reported was Headache (10; 6.1%). (Table 16.143).

Table 16.143. Number and Percentage of AEs Reported in Medication Error Cases with Associated AEs in elasomeran/imelasomeran by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Headache	10	6.1
Malaise	7	4.2
COVID-19	6	3.6
Pyrexia	6	3.6
Immunisation reaction	5	3.0
Pain in extremity	5	3.0
Dyspnoea	4	2.4
Fatigue	4	2.4
Feeling abnormal	4	2.4

Medication Errors Involving elasomeran/davesomeran

During this reporting period, and cumulatively, there were 1,583 cases (2,505 events) reporting medication errors in elasomeran/davesomeran. There were 439 cases (27.7%) reported in males and 523 cases (33%) reported in females; gender information was not provided in 621 cases (39.2%). All cases were reported through spontaneous reports (1,583; 100%), and most cases were received from the United States (1,375; 86.9%).

The most frequent medication error events reported were Product temperature excursion issue (597; 23.8%), and Poor-quality product administered (512; 20.4%) (Table 16.144).

Table 16.144. Number and Percentage of Medication Error Events Reported in elasomeran/davesomeran by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Product temperature excursion issue	597	23.8
Poor quality product administered	512	20.4
Accidental underdose	369	14.7
Expired product administered	286	11.4
Product storage error	286	11.4
Wrong product administered	128	5.1

PT	# Events	% Total Events
Underdose	69	2.8

During the reporting period, there were 60 cases (193 events) of medication error reported with an associated AE in elasomeran/davesomeran. There were 12 cases (20%) in males, 44 cases in females (73.3%), and 4 cases (6.7%) had missing gender information. The most frequent AEs reported was Pain in extremity (12; 6.2%). (Table 16.145).

Table 16.145. Number and Percentage of AEs Reported in Medication Error Cases with Associated AEs in elasomeran/davesomeran by PT (≥2% of Events) - Review Period 19 Jun 2022 to 17 Dec 2022

PT	# Events	% Total Events
Pain in extremity	12	6.2
Vaccination site pain	11	5.7
Pyrexia	9	4.7
Feeling abnormal	7	3.6
Vaccination site erythema	7	3.6
Chills	6	3.1
Vaccination site swelling	6	3.1
Arthralgia	5	2.6
Fatigue	5	2.6
Headache	5	2.6
Myalgia	5	2.6
Nausea	4	2.1

16.3.6.7.1.5. Discussion

Review of the data does not suggest any identifiable patterns or trends in the reports of medication errors received by the MAH, including those reports concerning patients who received doses of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccine beyond the primary series or any interchange of other COVID-19 vaccine products. For more details about interaction with other vaccines/heterologous vaccines, please refer to Section 16.3.6.7.4. During this reporting period, the MAH became aware of reports of medication errors related to product confusion between elasomeran booster and elasomeran/davesomeran and accidental underdosing of the elasomeran/imelasomeran and elasomeran/davesomeran boosters. The MAH considered that this was a potential risk and classified as Priority 1 Safety Issues. Therefore, safety letters from the MAH have been disseminated worldwide regarding the issue. However, there seemed no

difference for bivalent boosters and original booster for the nature of reported medication errors and importantly associated AEs in general. AEs associated with reported medication errors were usually known to the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran safety profile, and no events were associated with significant harm to the patient due to the medication error. There were no significant changes in the frequencies and types of medication error events in general from this review period and the last review period.

16.3.6.7.1.6 Conclusion

After careful review of all new safety data received during the review period and cumulatively for medications errors, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. Medication errors reported to ModernaTx, Inc. will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.2 Overdose

16.3.6.7.2.1 Source of the New Information

ModernaTx, Inc. queried the GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.2.2. Background Relevant to the Evaluation

Assessing harm due to administration of an extra dose of a vaccine is not well understood. Among all the VAERs reports received from 2007-2018, more than three-fourths of the reports of an excess dose of vaccine did not describe an AE. Among reports where an AE was reported, most of the common events included expected conditions such as pyrexia, injection site erythema, pain, and headache. Although most of the reports were of other vaccines (e.g., trivalent inactivated influenza, varicella, hepatitis A, and measles, mumps, rubella, varicella, the percentage of the AEs among these vaccine reports were comparable to all reports submitted to VAERS during the same period [175]. A case report of excess administration (or overdose) in a woman in Italy, who accidentally received six doses of the Pfizer-BioNTech COVID-19 vaccine all at once, without experiencing any serious side-effects has been published [176]. Although these data have been mainly anecdotal, overdose appears to be rare with limited harm/effects.

16.3.6.7.2.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively through 17 Dec 2022, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The search criteria applied for identification of Overdose cases included the following terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.

All cases identified from the GSDB search were classified using the European Medicines Agency's Good Pharmacovigilance Practices (GVP) definition of Overdose (//efaidnbmnnnibpcajpcglclefindmkaj/https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf. Accessed: 17 Jul 2022 10:53AM). This guideline defines overdose as "Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information". Once classified, case reports reporting overdose; or administration of more than 2 doses; or more than the indicated volume of elasomeran were medically reviewed.

Previously, 2 doses of elasomeran were recommended and an "overdose" was considered a dose(s) above the EUA-approved recommended 2 doses. Many countries/regions now approve elasomeran use for a 3rd primary series dose, and a 1st and 2nd booster dose [177] [178]. In many jurisdictions a 3rd dose primary series and a 1st and 2nd booster dose may be administered to immune compromised persons or as a booster dose to other (immune competent) persons. In this report, the definition of "overdose" takes these approvals into consideration and assesses reported "overdose" accordingly.

For serious cases classified as meeting the definition of Overdose, the Company causality assessment was provided utilizing the WHO-UMC standardized case causality assessment.

The data for this PBRER/PSUR No. 4 was examined critically to determine any new and significant Overdose patterns that may indicate new trends, risks, or signals of elasomeran not previously known or identified in the last reporting interval and in the context of cumulative information on risks and benefits. Also, any inter-relatedness of Overdose and Off-Label Use was evaluated. Overall, medical review of Overdose data for the reporting interval of this PBRER relative to the cumulative information also focused on identifying and summarizing new overdose safety information that may impact benefit-risk balance.

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and Overdose to retrieve relevant literature during this reporting interval. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 176 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran.

16.3.6.7.2.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on overdose cases please refer to Appendix 11.21.

Overview of Overdose Cases

Cumulative Review

Cumulatively, 923 overdose cases (3,102 events; 242 serious events) have been reported of which 77 cases were serious, 8 with a fatal outcome, and 645 cases were medically confirmed. Most of the cases were from the United States (418; 45.3%) followed by Asia (373; 40.4%). More cases were reported in females (38.6%) than males (25.0%) with gender not reported in 36.4% of the cumulative cases.

Cumulatively, among the top 10 most frequently reported MedDRA PT, "Accidental overdose" (467; 15.1%) ranked the highest followed by "Overdose" (451 events; 14.5%), and "No AE" (308 events; 9.9%), respectively. The most frequently reported clinical events reported in the overdose cases were "Pyrexia" (129 events; 4.2%) followed by "Headache (87 events; 2.8%) and "Chills" (75 events; 2.4%). Overall, the most frequently reported clinical events reported were consistent with the elasomeran reactogenicity profile.

Other than events which are specific to the overdose cases, the events most frequently reported in the overdose cases were comparable or lower in reporting frequency to events reported in the general reporting population.

Reporting Interval

During the reporting interval, 110 Overdose cases (346 events; 8 serious events) were reported. Of these, 6 cases were serious, and 92 cases were medically confirmed. No cases reported a fatal outcome.

The most frequently reported Overdose term was "Accidental overdose" (57; 16.9%), followed by "Overdose" (51; 14.7%). "No AE" (41; 11.8%), "Inappropriate schedule of product administration" (11; 3.2%), "Product administered to patient of inappropriate age" (6; 1.7%) and "Incorrect dose administered" (4; 1.2%) in the reporting interval. The most frequently reported clinical events reported in Overdose cases were "Pyrexia" (20; 5.8%), followed by "Headache" (15; 4.3%), "Malaise" (11; 3.2%), "Chills" (10; 2.9%) and "Fatigue" (4; 1.2%).

Overall, with the exception of product administration errors, the clinical events reported in the overdose cases were generally consistent with the known reactogenicity profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran (Table 16.146).

Table 16.146 The Top 10 Most Frequently Report PTs with Overdose and General Population (Reporting Interval)

Reporting interval-Overdose[1]			Reporting interval-General Population[2]		
PT	**# Events**	**% Of Total Events**	**PT**	**# Events**	**% Of Total Events**
Accidental overdose	57	16.9%	Headache	20,326	6.2%
Overdose	51	14.7%	Fatigue	19,244	5.9%
No adverse event	41	11.8%	Pyrexia	18,726	5.7%
Pyrexia	20	5.8%	Myalgia	13,373	4.1%
Headache	15	4.3%	Chills	11,127	3.4%
Expired product administered	14	4.0%	Malaise	10,449	3.2%
Inappropriate schedule of product administration	11	3.2%	Injection site pain	10,156	3.1%
Malaise	11	3.2%	Arthralgia	8,647	2.6%
Chills	10	2.9%	Nausea	8,346	2.5%
Product storage error	9	2.6%	Dizziness	8,036	2.5%

[1] Percentages are calculated based on the cumulative number of events in cases (346) of Overdose with other associated events. Overview of Reporting Interval cases and demographics data for Overdose cases are presented above.
[2] Percentages are calculated based on the total number of reporting interval events (327,956) in cases reported for the general population.

During the reporting interval, the median age of patients was 54.5 years (min: 0.4 and max: 96.0) with events occurring in 39 males (35.5%), 61 females (55.5%), and 10 (9.1%) individuals missing gender values. Females in the 50-64 age group represent the highest population of cases (17;

27.9%) followed by males in the 50-64 and 75+ age groups (7; 19.9 % each). The distribution of case count by gender and age group is shown in Table 16.147 below.

Table 16.147 Number and Percentage of Reported Overdose Cases by Gender and Age (Reporting Interval)

Age Group	Female		Male		Unknown		# Of Total Cases	% Of Total Cases
	# Cases	% Of Total Cases	# Cases	% Of Total Cases	# Cases	% Of Total Cases		
(0-5 Mths)	1	1.6%	0	0	0	0	1	1.6%
(6Mths - <2Y)	2	3.3%	1	2.6%	0	0	3	5.8%
02-05Y	1	1.6%	2	5.1%	3	30.0%	6	36.8%
06-11Y	1	1.6%	2	5.1%	0	0	3	6.8%
12-15Y	1	1.6%	1	2.6%	0	0	2	4.2%
16-17Y	0	0	0	0	0	0	0	0.0%
18-24Y	5	8.2%	2	5.1%	0	0	7	13.3%
25-39Y	5	8.2%	4	10.3%	0	0	9	18.5%
40-49Y	8	13.1%	5	12.8%	0	0	13	25.9%
50-64Y	17	27.9%	7	17.9%	0	0	24	45.8%
65-74Y	7	11.5%	5	12.8%	2	20.0%	14	44.3%
75Y+	7	11.5%	7	17.9%	2	20.0%	16	49.4%
Missing	6	9.8%	3	7.7%	3	30.0%	12	47.5%
Grand Total	**61**	**100.0%**	**39**	**100.0%**	**10**	**100.0%**	**110**	**NA**

Mths – months, Y- years

A similar pattern was observed during the reporting interval compared to prior to the reporting interval with the highest number of Overdose-associated events reported following Dose 3: reporting interval (66, 19.1%). This can possibly be attributed to increased exposure to Dose 3 following recent regulatory approvals in various countries (Table 16.148). Regardless of the dose, the TTO was less than 3 days with the median TTO of events during the reporting interval of 0.0 days (min.: 0 days; max.: 363 days).

Table 16.148 Events: Latency by Dose number (Reporting Interval)

Dose Number	TTO All Doses (Days)	# Of Total Events	% Of Total Events
Dose 1	**Subtotal**	**14**	**4.0%**

Dose Number	TTO All Doses (Days)	# Of Total Events	% Of Total Events
	0 days	13	3.8%
	01-02	1	0.3%
	03-04	0	0
	05-06	0	0
	07-13	0	0
	14-29	0	0
	30+	0	0
Dose 2	**Subtotal**	**10**	**2.9%**
	0 days	10	2.9%
	01-02	0	0
	03-04	0	0
	05-06	0	0
	07-13	0	0
	14-29	0	0
	30+	0	0
Dose 3	**Subtotal**	**66**	**19.1%**
	0 days	55	15.9%
	01-02	0	0
	03-04	0	0
	05-06	0	0
	07-13	1	0.3%
	14-29	0	0
	30+	10	2.9%
Dose 4	**Subtotal**	**53**	**15.3%**
	0 days	40	11.6%
	01-02	4	1.2%
	05-06	1	0.3%
	07-13	6	1.7%
	30+	2	0.6%
Dose 5	**Subtotal**	**1**	**0.3%**
	0 days	55	15.9%
Dose 7	**Subtotal**	**0**	**0**
	0 days	0	0
	30+	0	0
Unknown	**Subtotal**	**1**	**0.3%**

Dose Number	TTO All Doses (Days)	# Of Total Events	% Of Total Events
	0 days	0	0
	01-02	10	2.9%
	03-04	53	15.3%
	05-06	40	11.6%
	14-29	4	1.2%
	30+	1	0.3%
	Event onset prior to first dose reported	6	1.7%
	Missing	2	0.6%
Grand Total		**346**	**100.0%**

Children aged 0 months to 5 months

As of 17 Dec 2022, 1 Overdose case (2 non-serious events) have been reported. The non-serious events of "Accidental overdose" and "Wrong product administered" (1 event, 50% each) occurred in a 5-month-old female, located in the UK, and was not medically confirmed. This case is most likely an age coding error as the patient was reported to have received a fifth dose of vaccine instead of an influenza immunization one week after receiving the fourth dose of vaccine.

Children aged 6 to 23 months

As of 17 Dec 2022, 4 Overdose cases (13 non-serious events) have been reported in the United States and were medically confirmed. The most frequently reported Overdose terms were "Accidental overdose" (4 events; 30.8%) followed by "Incorrect dose administered", "No adverse event" and "Product administered to patient of inappropriate age" (1 event, 7.7% each). The 4 non-serious events of "Accidental overdose" occurred in a 15-month-old male, two females (18-month and 19-month) and a 15-month-old child whose gender was not reported. The median age for this age group was 1.4 years; (min.1.3; max. 1.6).

Two children reported symptoms associated with the diagnosis of overdose. One child experienced Pain in extremity, Pyrexia, Somnolence and "Tachycardia". The symptoms were managed with antipyretics and ondansetron ([redacted]). Another patient experienced otitis media, and Upper respiratory tract infection confounded by the parents having a respiratory illness ([redacted]).

Children aged 2-5 Years

As of 17 Dec 2022, 7 Overdose cases (17 non-serious events) have been reported in the United States and were medically confirmed. The most frequently reported Overdose term was

"Accidental overdose" (7 events; 41.2%) and occurred in 3 males (ages 2, 3 and 4 years), 1 female (age 3 years) and 3 children, one aged 2, one aged 3 and one aged 5 years, whose gender was not reported. Additional non-serious Overdose terms included "No adverse event" (5 events, 29.4%), "Inappropriate schedule of product administration" and "Wrong product administered" (1 event each, 5.9%). Two other non-serious events reported included "Expired product administered" and "Product storage error" The median age for this age group was 3.0 years (min:2.0; max: 5.0).

The AE of pyrexia was reported in a 4-year-old male after receiving the booster for patients 12 and older as his second primary dose ([redacted]).

Children aged 6-11 Years

As of 17 Dec 2022, 3 Overdose cases (12 non-serious events) have been reported in the United States and were medically confirmed. The most frequently reported Overdose terms were "Incorrect dose administered", "No adverse event" and "Overdose" (2 events; 16.7% each) and occurred in 2 males (ages 7 and 8 years) followed by "Accidental overdose" and "Product administered to patient of inappropriate age" (1 event, 8.3% each) which occurred in 1 female (age 10 years). The median age for this age group was 8.0 years (min: 7.0; max: 10.0).

A 10-year-old female had the AEs of "Feeling abnormal", "Illness", "Neck pain" and "Respiration abnormal" after receiving a 2.5 ml dose of vaccine as a booster after a primary series of Pfizer vaccine. All events were considered non serious ([redacted]).

Data for children ages 6-11 years are still nascent and limited to support critical evaluation.

Adolescents ages 12-17 Years

During the reporting interval, 2 overdose cases (4 events; 0 serious events) have been reported. Two of the cases were medically confirmed. The median age of the adolescent was 14.5 years (min: 14.0 and max: 15.0) with events occurring in equally in males and females (1;50% each). The female was 14 years of age, and the male was 15. Both reported "Accidental overdose" and "Product administration to patient of inappropriate age", as both individuals received the 2.5 ml full vial of the ModernaTx, Inc. vaccine as their 4th dose. No clinical symptoms were reported for either patient.

Overall, the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran Adolescent Overdose data remain limited, and there was no new significant information that deviated from the known cumulative safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Original and Booster Serious Cases (Reporting interval)

During the reporting interval there were 6 serious Overdose cases (5 females and 1 male) which included 8 serious events (1 each, 12.5%): "Pericarditis" (Recovered/Resolved), "Ventricular extrasystoles" (Unknown), "Anaphylactic shock" (Unknown), "Cardiac flutter" (Not Recovered/Not Resolved), "Colitis microscopic" (Not Recovered/Not Resolved), "Deafness neurosensory" (Unknown), "Diarrhoea haemorrhagic" (Recovered/Resolved), and "Leukaemia monocytic" (Not Recovered/Not Resolved).

The serious events occurred in 3 females (50-64 Y; 60%), 1 female (65-74 Y; 20%), 1 female (age not reported; 20%) and 1 male (18-24 Y;100%). Prior to the reporting interval, more serious events were reported in the 25-39 Y age group for males (30.8%) and females (30.4%).

The serious events were reported as Dose 3 (1; 12.5%), Dose 7 (1; 12.5%) and the Dose was Unknown for 6 (75%) of the serious events. Prior to the reporting interval, more serious events were reported after Dose 2 (34%) and 29.4% reported an Unknown Dose. Due to the small number of serious events reported during the reporting interval, and the high number of events reporting an Unknown Dose, no conclusions can be made from this limited information.

Following medical review, 4 of the 6 serious cases were considered to be of interest and are described below.

[redacted] **(WW Identifier** [redacted] This spontaneous case reported by the patient concerning a 57-year-old female patient, with a medical history of Giant Cell Myocarditis and Irritable bowel syndrome, who experienced Pericarditis colitis microscopic and Ventricular extrasystoles the month after receiving a third dose of elasomeran, which was considered an overdose since there is no evidence suggesting patient was immunocompromised. After vaccination she experienced premature ventricle contractions, her heart hurt upon exertion, and she was extremely fatigued. Her cardiologist prescribed an external heart monitor to make a diagnosis. Since she got worse, an echocardiogram and subsequent cardiac MRI were performed, and diagnosis of pericarditis was made. She received ibuprofen as treatment and states that symptoms resolved after 3 months. She also experienced diarrhea that was severe and debilitating and was diagnosed with microscopic colitis. Budesonide was prescribed. The event was resolving but she reports a second occurrence at the time of the report.

WHO-UMC Causality: Unlikely. The medical history of Giant Cell Myocarditis could be a confounder for the event pericarditis. The medical history of irritable bowel syndrome could be a

confounder for the event colitis microscopic. The temporal relationship to the vaccine administration is also attenuated.

[redacted] **(WW Identifier** [redacted]**):** This spontaneous case concerns a 64-year-old female patient, with a history of hypothyroidism managed with levothyroxine, who experienced Diarrhoea haemorrhagic (Bloody diarrhea), which occurred unknown days after a booster dose of elasomeran vaccine administration (given as the third dose). The patient reported that she got "a full dose" as a booster and was thus considered an overdose report. The outcome was reported as resolved. It was reported that immediately after receiving the dose of ModernaTx, Inc. vaccine, the patient felt unwell - nausea and dizziness, for which she took ibuprofen at home. Over the next few days, the patient reported no appetite, no energy, had nausea, vomiting, had very sore arm, bloody diarrhea and confusion. While the diarrheic and nausea dissipated over the next couple of weeks (especially with anti-diarrheal meds) the sense of feeling unwell (confused, lethargic, headache and no appetite) remained for several weeks.

WHO-UMC Causality: Possible based on temporal association. Levothyroxine can be associated with some of these symptoms including diarrhea. We have no information concerning monitoring of her hypothyroidism.

[redacted] **(WW Identifier** [redacted]**:** This spontaneous case concerns a 20-year-old male patient who experienced Cardiac flutter, Palpitations and Chest pain. Concurrent medical conditions included Drug allergy [redacted], Latex allergy, Dust allergy, Allergy to animal dander (Animal fur and hair), Asthma (Taking Albuterol inhaler, nebulizing machine - only when with attacks.), bipolar disorder (On Lithium carbonate) and attention deficit hyperactivity disorder (ADHD) (Low dose Adderall for ADHD for 3.5 years).

The event Chest pain occurred on the same day and the events Cardiac flutter and Palpitations occurred approximately 4 days after the third dose of elasomeran vaccine. After the vaccination patient felt very sick, like he had flu and chest pains. On the 4th day he had chest pain/discomfort and palpitations while exercising. He also stated that his asthma medications were not giving him full relief as before. Upon consulting primary physician an ECG was done, and the results were "not alarming", but he was advised to see a cardiologist for echocardiogram. Additionally Accidental overdose is also reported as the patient received a full dose instead of a half a dose for

the first booster. No further details on clinical course, other lab test results and treatment received were reported. The outcome of the events was reported as not resolved.

WHO-UMC Causality: Possible based on temporal association. The findings are confounded by concurrent asthma and the medications for the management of asthma and ADHD. His underlying psychiatric conditions could also play a role in the symptoms reported.

[redacted] **(WW Identifier** [redacted]**):** This spontaneous case was reported by a patient and describes the occurrence of Deafness neurosensory (Sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side) in a 66-year-old female patient who received elasomeran (Moderna COVID-19 Vaccine) for COVID-19 prophylaxis. Concurrent medical conditions included Sulfonamide allergy, Dust allergy and Autoimmune disorder NOS (No change - Flares Occasionally) since [redacted]1993. Concomitant medications included Budesonide, formoterol fumarate (Symbicort) for Asthma, Vitamin C [ascorbic acid] for Supplementation therapy, Vitamin D [Vitamin D NOS] and magnesium citrate for an unknown indication. On 18 Aug 2021 at [redacted], received 0.5 ml of elasomeran (Moderna COVID-19 Vaccine) as a third dose. This dose was twice the recommended dose and was considered an overdose. On 10 Oct 2021, the patient experienced Tinnitus (started hearing ringing/buzzing in ear / the ringing is there all the time/ ringing in the ears all the time is an annoyance). On 28 Oct 2021, the patient experienced Deafness neurosensory (Sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side) (seriousness criterion medically significant) and Rhinitis (Chronic rhinitis). On an unknown date, the patient experienced Headache (Headache). The patient was treated with prednisone on 03 Nov 2021 at a dose of 10 mg; azelastine on 19 Oct 2018 at a dose of 0.1 % (137 ug) and triamcinolone acetonide on 28 Oct 2021 at an unspecified dose and frequency. At the time of the report, Deafness neurosensory (Sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side), Rhinitis (Chronic rhinitis) and Headache (Headache) outcome was unknown and Tinnitus (started hearing ringing/buzzing in ear/the ringing is there all the time/ ringing in the ears all the time is an annoyance) had not resolved.

WHO-UMC Causality: Unassessable because important medical history is lacking; for example, the specific autoimmune disorder of the patient is not specified. Moreover, the TTO of nearly two months is quite long.

Overdose Involving Use of elasomeran/imelasomeran

During the reporting interval, there was 1 non-serious case which contained 2 events. The medically confirmed case included the non-serious events of "Accidental overdose" and "No adverse event" and was reported from a 67-year-old female for elasomeran/imelasomeran. It was reported that the patient received 0.25 ml dose instead of 0.5 ml, however the event was coded to "Accidental overdose". The outcome of the events was unknown.

The event coding of this case is being reviewed by the MAH and will be corrected as appropriate.

Overdose Involving Use of elasomeran/davesomeran

During the reporting interval, 15 overdose cases (50 events; 0 serious events) were reported. Twelve of the cases were medically confirmed. Three events resolved, 2 were not resolved and the outcome of the remaining 45 events was unknown. "Accidental Overdose" (12; 24%) was the most frequently report overdose event, followed by "No adverse event" (11; 22%) and "Overdose" (2; 4%). The most frequently reported clinical events included "Feeling abnormal" and "Pyrexia" (2; 4% each). The other 21 events were each reported once (2% each). Most of the cases (46.7%) were reported in the 6–11-year age group (2 females, 2 males, 13.3% each and 3 unknown gender, 20%) followed by the 50-64 year age group (2 females, 13.3%).

16.3.6.7.2.5. Discussion

Cumulatively, 923 overdose cases (3,102 events; 242 serious events) have been reported of which 77 cases were serious, 8 with a fatal outcome, and 645 cases were medically confirmed.

During the reporting interval, 110 Overdose cases (346 events; 8 serious events) were reported. Of these, 6 cases were serious, and 92 cases were medically confirmed. No cases reported a fatal outcome. Four of the 6 serious cases reported in the reporting interval were considered of interest. However, all 4 cases contained confounding factors and were clinically dissimilar. Temporal association was the primary association that made elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran considered possibly related to these events. Due to the small number of cases in the pediatric population, no trends were identified.

16.3.6.7.2.6 Conclusion

Cumulatively and based on the analysis of all the safety data received during the reporting interval of this PBRER, ModernaTx, Inc. considers that Overdose cases reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, did not raise any safety concerns, and the information provided does not support or is inadequate

to provide evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and reported Overdose and Overdose-associated events. The cumulative and reporting interval data do not represent a new safety issue of concern. ModernaTx, Inc. will continue to monitor events for Overdose and Overdose-associated events using routine surveillance.

Overall, based on the analysis of all the Overdose safety data in this reporting interval, there is no change in the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. No significant information was identified that impacts elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran benefit-risk balance. Therefore, the benefit-risk evaluation of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains positive.

16.3.6.7.3 Off-label use

16.3.6.7.3.1 Source of the New Information

Off-label Use data presented below includes valid case reports of medication errors involving elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran received from HCPs, HAs, consumers and literature, for the reporting period of 19 Jun 2022 through 17 Dec 2022.

16.3.6.7.3.2. Background Relevant to the Evaluation

ModernaTx, Inc. performs routinely monitors cases of Off-label use of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in patient populations, dosage or dosage form for which it is not currently authorized.

Off-label use is defined as, "Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization. Examples include the intentional use of a product in situations other than the ones described in the authorized product information, such as a different indication in terms of medical condition, a different group of patients (e.g., a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorization in the country where the product is used." (EMA GVP Annex 1 – Definitions [Rev 4]).

16.3.6.7.3.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, from 19 Jun through 17 Dec 2022, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran,

elasomeran/imelasomeran and elasomeran/davesomeran. The search criteria applied for identification of Off-label use cases included the following terms: Off-label use, Off-label use of device, Intentional dose omission, Intentional product misuse, Intentional product misuse to child, Intentional product use issue.

All cases identified from the GSDB search were classified using the European Medicines Agency's Good Pharmacovigilance Practices definition of Off-label use [179]. This guideline defines Off-label use as "Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization". Examples provided to clarify the definition are "the intentional use of a product in situations other than the ones described in the authorized product information, such as a different indication in terms of medical condition, a different group of patients (e.g., a different age group), a different route or method of administration or a different posology". Once classified, cases reporting Off-label use and Off-label use terms like: "Interchange of vaccine products", "Intentional product use issue", "Intentional dose omission", and "Inappropriate schedule of product administration" were medically reviewed.

If warranted, a Company causality assessment (utilizing WHO-UMC standardized case causality assessment) was provided for serious cases classified as meeting the definition of Off-label use.

During this reporting period, data was examined critically to determine any new and significant Off-label use patterns that may indicate new trends, risks or signals of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran not previously known or identified in the last reporting interval and in the context of information on risks and benefits. Overall, medical review of Off-label use data for this PBRER reporting interval relative was also focused on identifying and summarizing new Off-label use safety information (if any) that may impact benefit-risk balance.

16.3.6.7.3.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

During this reporting period, there were 60 cases (63 events; 32 serious cases) and 37 of the cases were medically confirmed. There were no fatal cases. Most of the cases were from Germany (16; 26.7%), and Canada (13; 21.7%). The most frequently reported PT was Off-label use (58; 92.1%), followed by Intentional product use issue (4; 6.3%), and Intentional dose omission (1; 1.6%).

There were 25 cases (41.7%) reported in males, 28 cases (46.7%) in females; gender information was not provided in 7 cases (11.7%). The median age was 44.0 years (min: 0.5 and Max: 81). The distribution of case count by gender and age group is shown in Table 16.149.

Table 16.149 Number and Percentage of Reported Off-Label Use Cases by Gender and Age – Reporting Period (19 Jun to 17 Dec 2022)

Age Group	Female		Male		Unknown		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
(0-5 Months)	0	0.0	0	0.0	0	0.0	0	0
(6Mths - <2Y)	1	1.7	1	1.7	0	0.0	2	3.3
02-05Y	0	0.0	0	0.0	0	0.0	0	0
06-11Y	0	0.0	1	1.7	0	0.0	1	1.7
12-15Y	0	0.0	0	0.0	1	1.7	1	1.7
16-17Y	0	0.0	0	0.0	1	1.7	1	1.7
18-24Y	1	1.7	1	1.7	0	0.0	2	3.3
25-39Y	5	8.3	6	10.0	1	1.7	12	20.0
40-49Y	5	8.3	0	0.0	0	0.0	5	8.3
50-64Y	6	10.0	6	10.0	0	0.0	12	20.0
65-74Y	3	5.0	3	5.0	0	0.0	6	10.0
75Y+	2	3.3	1	1.7	0	0.0	3	5.0
Missing	5	8.3	6	10.0	4	6.7	15	25.0
Grand total	**28**	**46.7**	**25**	**41.7**	**7**	**11.7**	**60**	**100**

During this reporting period, 6 events (9.5%) were reported following Dose 2, 3 events (4.8%) were reported after Dose 3, and 2 events (3.2%) were reported after Dose 1 and 4. There were 50 events (79.4%) that had unknown dose numbers.

Subpopulation Analyzes

Off-Label Use in Children (0-5months old)- Reporting period 19 Jun 2022 to 17 Dec 2022 elasomeran

During this reporting period, there were no cases received by the MAH of "off-label use" events in children 0-5 months old.

Off-Label Use in Children (6-23months old)- Reporting period 19 Jun 2022 to 17 Dec 2022 elasomeran

During this reporting period, there were 2 medically confirmed non-serious cases (2 events) reporting off-label use in children 6-23 months old. One case was reported in a 6-month-old male in the United States whose dose number and event outcome are unknown. The other case was in a 20-month-old female in Canada whose event outcome is unknown after the 1st dose. Both cases reported the PT term of off-label use (2; 100%) (Appendix 11.22).

Off-Label Use in Children (2-5 years old)- Reporting period 19 Jun 2022 to 17 Dec 2022 elasomeran

During this reporting period, there were no cases received by the MAH of "Off-label Use" events in children 2-5 years old.

Off-Label Use in Children (6-11 years old)- Reporting period 19 Jun 2022 to 17 Dec 2022 elasomeran

During this reporting period, there was one medically confirmed non-serious case (1 event) in children 2-5 years old. This case was reported in a 6-year-old male in the Unites States after the 1st dose, and the outcome of the event was reported as "unknown". The PT term of Off-label use was reported (1; 100%) %) (Appendix 11.22).

Off-Label Use in Adolescents ages 12-17 Years (Reporting period 19 Jun 2022 to 17 Dec 2022) elasomeran

During this reporting period, there were 2 medically confirmed non-serious cases (2 events) in adolescents 12 to 17 years old. Both cases were from Japan with missing gender information, unknown event outcome and dose number. One case was reported in a 15-year-old, and the other case was reported in a 17-year-old. Both cases reported the PT term of off-label use (2; 100% (Appendix 11.22).

Off-Label Use Reported in Individuals who Received ≥ 3 Doses (Reporting period 19 Jun 2022 to 17 Dec 2022)-elasomeran

During this reporting period, there were 5 cases (5 events; 4 serious cases) and 4 medically confirmed cases were reported. There were no fatal cases. There were 2 cases each (40%) from Germany and Australia, and 1 case (20%) from the UK. All cases reported the PT term of off-label use.

There were 1 case (20%) reported in males, and 4 cases (80%) in females. The mean age was 60.4 years, with the median age of 63 years (min: 43 and Max: 75) The distribution of case count by gender and age group is shown in (Table 16.150) (Appendix 11.22).

Table 16.150. Number and Percentage of Reported Off-Label Use Cases by Gender and Age – ≥ 3 Doses (Reporting period 19 Jun 2022 to 17 Dec 2022) elasomeran

Age Group	Female		Male		# Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
06-11Y	0	0	0	0	0	0
25-39Y	0	0	0	0	0	0
40-49Y	1	20	0	0	1	20
50-64Y	1	20	1	20	2	40
65-74Y	1	20	0	0	1	20
75Y+	1	20	0	0	1	20
Missing	0	0	0	0	0	0
Grand total	**4**	**80**	**1**	**20**	**5**	**100.0**

Serious Cases (Reporting period 19 Jun 2022 to 17 Dec 2022) (elasomeran)

During this reporting period, there were 32 cases. However, only 26 cases (137 events) reported serious events of Off-label use. The majority of the cases were considered Off-label use because a subsequent vaccine dose was different from the primary series (interchange of vaccines) and drug ineffectiveness. When known, the highest frequency of events was seen after dose 2 (13; 9.5%) (Appendix 11.22).

Fatal outcomes reports (Reporting period 19 Jun 2022 to 17 Dec 2022) (elasomeran)

During this reporting period, there were no fatal cases received by the MAH in "Off-label Use". During this reporting period, both bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran) were authorized in some countries and continue to be authorized worldwide.

Off-Label Use of elasomeran/imelasomeran

During this review period, there were 2 cases (2 events). One case was reported for a 40-year-old female in Germany, whose dose number and event outcome were unknown. The other case was for an 88-year-old female in the UK, whose event outcome and dose number are unknown. Both cases reported the PT term of off-label use (2; 100%) (Appendix 11.22).

Off-Label Use of elasomeran/davesomeran

During this reporting period, there was 1 medically confirmed non-serious case (1 event) in the United States with missing gender information and unknown event outcome (Appendix 11.22).

16.3.6.7.3.5. Discussion

During the reporting period, the total number of off-label use cases was significantly lower than last review period (60 vs 212) as well as the number of medically confirmed cases (37 vs 114). The reported serious cases were also lower compared with the last review period (32 vs 64). Same as the last review period, "off-label use" was the most frequent reported term. Only isolated non serious case of off-label use were received from both bivalent booster during the review period. No fatal cases were reported during this review period. The reported AEs representing harm reported and cases of Off-label use were in line with expectation for reactogenicity following elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. There was no pattern of Off-label use observed that changes the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.3.6 Conclusion

Based on the analysis of all the safety data received during this reporting period of this PBRER, ModernaTx, Inc. considers that Off-label use cases, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, did not raise any new safety concerns, and the information provided does not support or is inadequate to provide evidence of causality between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran exposure and reported Off-label use/ Off-label associated events. The reporting period data do not present a new safety issue of concern. ModernaTx, Inc. will continue to monitor Off-label use cases and associated events using routine surveillance.

Overall, based on all the information presented in this analysis, ModernaTx, Inc. considers that there is no change to the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The benefit-risk evaluation of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains positive.

16.3.6.7.4 Interactions with Other Vaccines

16.3.6.7.4.1 Source of the New Information

The Company (herein referred to as ModernaTx, Inc.) GSDB was queried for valid, clinical, and spontaneous case reports received from HCP, HA, consumers, and literature, from 19 Jun 2022 through 17 Dec 2022, reported for elasomeran (including boosters and recent bivalent approvals) for cases of vaccine coadministration with all other vaccines (not including COVID 19 products).

16.3.6.7.4.2. Background Relevant to the Evaluation

The safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when co-administered with non-COVID-19 vaccines is being monitored, including their use with the new Spikevax bivalent vaccines.

Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show increased AEs. Therefore, WHO considers that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

As COVID-19 vaccines become available to children who are also being vaccinated against childhood infectious diseases, the safety and efficacy of coadministration is being evaluated with routine surveillance activities.

As of the DLP of this PBRER (17 Dec 2022), the review of post-approval/EUA data has not identified any patterns or specific safety concerns in individuals receiving concomitant vaccines with elasomeran.

Literature Review for Interactions with Other Vaccines Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and interactions with other vaccines (non-COVID-19) to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d. A total of 16 literature articles were retrieved using these search criteria.

There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.4.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

Vaccine Interchange/Interaction events were retrieved from the Company safety database using the following MedDRA v25.1 preferred terms (PTs) and the following search strategy: 1) WHODRUG codes corresponding to ATC 3rd Level. J07: VACCINES (excluding 152686 WHODRUG (COVID-19)) for Co-Suspect and Concomitant medications. 2) Manual review was performed to identify events occurring within a 28-day window of the administration of elasomeran and a non-COVID vaccine.

Additional search and data analyzes were done using Statistical Analysis System (SAS) statistical tool.

16.3.6.7.4.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Vaccine-Vaccine Interactions:

Overview of Cases of elasomeran with Other Non-COVID-19 Vaccines

Cumulatively, there were 590 cases (2,712 events) reported after elasomeran was administered with other non-COVID-19 vaccines (within 28 days of elasomeran). One-hundred and eighty-five (185, 31.4%) cases were serious of which 5 had a fatal outcome. More cases (359 cases; 60.8%) were reported in females than in males (219 cases; 37.1%) with gender missing in 12 cases (2.0%). The median age of reported cases was 56.0 years, with a range from infancy (6 months) to 92 years. The highest number of cases of interactions were reported in the age group > 65 years old (29.7%). The cases were most frequently reported in the EEA (39.2%) followed by the UK (25.4%) and the United States (24.4%).

During the reporting period, there were 148 cases (648 events) reported after elasomeran was administered with other non-COVID-19 vaccines (within 28 days of elasomeran). Thirty-nine of these cases (39, 26.4%) were serious of which 1 case had a fatal outcome. More cases were reported in females (83; 56.1%), than males (63 cases; 42.6%), and the gender was not reported in 2 cases (1.4%). The median age of reported cases was 51.5 years, with a range from infancy (6 months) to 92 years. The highest cases of interactions were reported in the age group 65-74 years old. See Table 16.151.

Table 16.151 Distribution by Age of cases of elasomeran with non-COVID-19 Vaccines (Reporting Period and Cumulative)

Age Group	Review Period		Cumulative # of Cases	Cumulative % of Total Cases
	# Cases	% of Total Cases		
(6Mths - <2Y)	4	2.7	4	0.7
02-05Y	2	1.4	2	0.3
06-11Y	2	1.4	3	0.5
12-15Y	0	0	1	0.2
16-17Y	1	0.7	1	0.2
18-24Y	5	3.4	21	3.6
25-39Y	29	19.6	92	15.6
40-49Y	19	12.8	79	13.4
50-64Y	27	18.2	159	26.9
65-74Y	36	24.3	128	21.7
75Y+	9	6.1	47	8.0
Missing	14	9.5	53	9.0
Grand total	**148**	**100.0**	**590**	**100.0**

Mths: months; Y: year
Most of the case reports were from the United States (30.4%), Japan (23.6%), and United Kingdom (14.9%).

The most frequently reported PTs were generally consistent with expected reactogenicity with elasomeran and are presented in Table 16.152.

Table 16.152 Most frequently reported PTs after elasomeran administration with Non-COVID-19 Vaccines >=2% (Reporting Period)

PT	# Events	% of Total Events
Headache	48	7.4
Injection site pain	46	7.1
Fatigue	44	6.8
COVID-19	34	5.2
Myalgia	26	4.0
Malaise	22	3.4
Pyrexia	18	2.8
Arthralgia	16	2.5
Chills	16	2.5
Vaccination failure	16	2.5

PT	# Events	% of Total Events
Dizziness	13	2.0
Injection site swelling	13	2.0

The vaccine that was co-administered with elasomeran most commonly was the influenza vaccine (22.2%). Other non-COVID vaccines included those for Japanese encephalitis, tetanus, pneumococcus, meningococcus, and the Diphtheria, Tetanus, acellular Pertussis, Polio and Haemophilus influenzae type b vaccine. The most frequently administered medication was levothyroxine (3.7%). Table 16.153 below presents concomitant medications >1%.

Table 16.153 Most frequently reported Medications after elasomeran coadministration with non-COVID-19 Vaccines >=1% (Cumulative)

Concomitant Medication	# of Cases	% (denominator = 590)
LEVOTHYROXINE	22	3.73
ATORVASTATIN	15	2.54
PARACETAMOL	12	2.03
RAMIPRIL	10	1.69
FOLIC ACID	9	1.53
OMEPRAZOLE	9	1.53
AMLODIPINE	8	1.36
GABAPENTIN	8	1.36
SERTRALINE	7	1.19
VITAMIN D3	7	1.19
COLECALCIFEROL	6	1.02

When dose number was known, the greatest number of events (73;11.3%) was reported to occur after dose 3 of elasomeran coadministration with a non-COVID-19 vaccine. Latency could not be determined for 485 events (74.8%) because dose or event dates were not reported.

When known, the most frequently reported outcome reported during this period was Recovered/ Recovering (322, 49.7%), followed by Not Recovered/Not Resolved (113, 17.4%), Recovering/Resolving (100, 15.4%) and Recovered/Resolved with Sequelae (4, 0.6%). There were 4 fatal events (0.6%) reported.

Serious cases of non-COVID-19 vaccines with elasomeran administration

In this reporting period, there were 39 serious cases, 1 with a fatal outcome, reporting elasomeran and other non-COVID-19 vaccines, of which 6 cases were with influenza alone, and one case with influenza and another vaccine (meningococcal vaccine). Five cases were of different non influenza vaccines (including Japanese encephalitis, Yellow fever, Rabies, Polio, Cholera, Hep A, Hep B, and Typhoid BCG). The most frequently reported serious events included COVID-19 (7, 8.6%), Headache (4, 4.9%), Postmenopausal haemorrhage (3, 3.7%), Cataract, Cerebrovascular accident, Glaucoma, Nasopharyngitis, Pneumonia and Small intestine carcinoma (2, 2.5% each). The remaining 55 serious events were reported once (1.2% each). Details from the 39 serious cases are provided in Appendix 11.23. The case with a fatal outcome is presented below.

No new safety concerns were identified following a review of these cases.

Fatal Case of Primary Vaccine Series

[redacted] **(WW Identifier GB-MHRA-**[redacted]**:** This regulatory authority case concerns a 92-year-old female patient from the UK with relevant medical history of cerebrovascular accident, atrial fibrillation, dementia and coronary arterial stent insertion. Concomitant use of clopidogrel was noted. The patient was vaccinated with elasomeran (unknown dose number) and Quadrivalent Influenza Vaccine (non-company product) on the same day. It was reported that staff was unable to rouse patient the following day. The patient was admitted to hospital and a new right sided stroke was confirmed by CT scan. Other events reported were heart rate irregular, hemiparesis and somnolence. The patient passed away 19 days later. The cause of death was stroke; it is unknown if an autopsy was performed.

WHO Causality: Alternative etiology is suspected in this patient of advanced age with the relevant medical history of cerebrovascular accident, atrial fibrillation, hypertension and a coronary arterial stent insertion, these constitute significant risk factors and that provide a more likely explanation for the reported events leading to the fatal outcome, the causality is assessed as unlikely.

Subpopulation Analyzes

Non-COVID-19 vaccine coadministration with elasomeran in Children (6 -23 Month of Age):

There were 4 reports (3 female; 1 male) from the USA of non-COVID-19 vaccine coadministration with elasomeran in < 2-year-old age group during this reporting period. All reports were non-serious and associated with product administration errors (expired product administration). Only one of the cases was associated with AEs. This report was in a 6-year-old female patient with no

known acute illness at the time of vaccination or up to one month leading to vaccination. The day after receiving the first dose of elasomeran and the third dose of each of the following vaccines, Pediarix, HIB, Rotateq, Pneumococcal, and Influenza, she experienced pyrexia, which is a clinical ADR for this age group according to the CCDS, and an URI, which is common in little children. ([redacted] **WW Identifier:** [redacted])

Non-COVID-19 vaccine coadministration with elasomeran in Children (2-5 Years of Age).

There were 2 reports (USA [female, 3 years]and Asia [male, 4 years]) of non-COVID-19 vaccine coadministration with elasomeran in 2–5-year age group during this reporting period. Both reports were non-serious and involved product administration errors (underdose and inappropriate age). Both cases were associated with AEs. One case in a 4-year-old-male had vaccination site reactions of rash and papule (co-suspect with influenza vaccine), The other case in a 3-year-old female included AEs of fatigue, gait disturbance, pain in extremity, and somnolence. Co-suspects included Diphtheria and tetanus toxoids and acellular pertussis, mumps, measles and rubella vaccines, and varicella zoster vaccine.

Non-COVID-19 vaccine coadministration with elasomeran in Children (6-11 Years of Age).

There were 2 reports from the USA of non-COVID-19 vaccine coadministration with elasomeran in the 6–11-year age group during this reporting period. Both reports associated with product administration errors (wrong product administered) and neither had an AE reported.

Non-COVID-19 vaccine coadministration with elasomeran in Adolescents (12-17 Years of Age)

There was 1 case reported from Japan of non-COVID-19 vaccine coadministration with elasomeran in adolescents 12-17 years of during this reporting period which described a product administration error (inappropriate age) without AEs.

Non-COVID-19 vaccine reported in cases of Third Dose or Booster Dose of elasomeran

In this reporting period, there were 42 cases (95 events) reporting interactions associated with coadministration of non-COVID-19 vaccines with 3rd dose of elasomeran. Of the 42 cases, 9 cases (21.4%) reported at least 1 non-COVID-19 vaccine as a co-suspect medication including: Influenza (7), Entyvio, Humira, Pneumococcal (polyvalent) and Varicella Zoster (1 each).

Eleven (11) of the 42 cases (26.2%) were serious and none were fatal. Dose 3 had the highest frequency of events (76.8%) followed by dose 4 (20.0%) and dose 5 (3.2%) within the first 3 days of vaccination. The most frequently reported events were consistent with reactogenicity and were

similar across the reported doses. The majority of reports of product administration errors did not involve AEs, when AEs were reported, these typically described reactogenicity and did not otherwise demonstrate any safety concerns.

Non-COVID-19 Vaccine Coadministration with elasomeran/imelasomeran

There were 56 case reports (9 serious) of non-COVID-19 vaccine coadministration with elasomeran/imelasomeran booster during this reporting period. One report had a fatal outcome. More cases were reported in females (40; 71.4%), than males (15 cases; 26.8%) with gender not reported in 1 case (1.8%). The median age was 67.5 years (min:23.0/max: 92.0) and mean 66.4 (SD:15.2). The highest percentage of cases were reported in the elderly >65 (23.2%). With the exception of Injection site pain, Injection site swelling, and Injection site erythema, the most frequently reported events (>2%) were consistent with reactogenicity and included: Malaise (25, 8.4%), Fatigue (22, 7.4 %), Headache (20, 6.8%), Myalgia (19, 6.4%), Chills (18, 6.1%), Pyrexia (16, 5.4%), Arthralgia and Nausea (14, 4.7% each) and Dizziness (7, 2.4%).

Influenzae vaccines were the most frequently co-administered non-COVID vaccine with elasomeran/imelasomeran and were reported in 51 of the 56 cases. There were 16 cases with pneumococcal vaccine and 1 case with typhoid vaccine co-administered with elasomeran/imelasomeran. The majority of cases were non-serious and contained insufficient information for a detailed causality assessment. Case [redacted] concerned an 89-year-old female with relevant medical history of hypertension and breast cancer, who experienced acute kidney injury and myocardial infarction one day after dose 5 mRNA-1273.214 co-administered within 28 days of the influenza vaccine. The patient had two doses of Vaxzevria and two doses of Comirnaty previously. The patient presented to ED non-specifically unwell with a late presentation of an inferior myocardial infarction (inferior ST Elevated Myocardial Infarction [STEMI]) and acute kidney injury and died in less than 24 hours. No further clinical details were provided. Reported cause of death was inferior myocardial infarction. It is unknown if an autopsy was performed. (**WW Identifier: GB-MHRA-**[redacted].

The causality is assessed as unlikely given the patients advanced age and the relevant medical history of hypertension and breast cancer could be the predisposing risk factors and provide a more likely explanation for the events.

Non-COVID-19 Vaccine Coadministration with elasomeran/davesomeran

There were 49 case reports (149 events) of non-COVID-19 vaccine coadministration with elasomeran/davesomeran booster during this reporting period. Six of the cases were serious, of which none were fatal. -An influenza vaccine was reported in all of the cases, either as a co-suspect (26) or concomitant medication (23). Cases were almost equally distributed among genders (females: 22 cases; 44.9% and males: 23 cases; 46.9%) and the gender was not reported in 4 cases (8.2%). The median age of reported cases was 69.0 years (min:3.0/max: 85.0) and mean 62.7 (SD:19.3). The highest cases were reported in the elderly >65+ (57.1%). Majority of events were non-serious (87.8%). The most frequently reported events, except for No AE (5.4%) and Expired Product Administration (2.7%), were consistent with reactogenicity events and included Pyrexia (6.0%), Pain in extremity (4.7%), Fatigue (4.0%), COVID-19 and Vaccination site pain (3.4% each), Headache and Malaise (2.7% each), Chills, Erythema, Feeling abnormal and Nausea (2.0% each). All other events were reported in <1.5% of the cases. For the exception of COVID-19 and vaccine failure, AEs were similar to reactogenicity reactions, therefore no meaningful differences were seen with elasomeran alone compared to elasomeran with other vaccines.

Overall, the safety profile has not changed despite increase in use across age groups becoming eligible as well as more doses administered.

16.3.6.7.4.5. Discussion

Overall, cumulatively, AEs reported for individuals receiving non-COVID-19 vaccines concomitantly with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran were generally comparable to those seen in the general population after vaccination with non-COVID-19 vaccines and were related to reactogenicity events commonly seeing after vaccination with elasomeran elasomeran/imelasomeran and elasomeran/davesomeran. A review of the data received cumulative and during the reporting period of this PBRER, showed that events reported in individuals receiving concurrent vaccines with elasomeran continue to primarily occur in individuals >50 years of age, with a higher number of reports involving females, as it is seeing in the general population, with a TTO of less than 7 days. Reports in the pediatric population comprised mainly product administration errors. The highest reported events were seen with coadministration with the influenzae vaccine.

Cumulative review of the safety information has not identified any patterns/trends or specific safety concerns in individuals receiving concurrent vaccines with elasomeran elasomeran/imelasomeran and elasomeran/davesomeran. Serious events and fatal reports are

heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported AEs in those individuals receiving concurrent vaccines with elasomeran is comparable to the general population.

As of the DLP of this PBRER (17 Dec 2022), the review of post-approval/EUA data has not identified any patterns or specific safety concerns in individuals receiving concomitant vaccines with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. No interactions between elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and other non-COVID-19 vaccines have been observed.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered.

After careful review of all new safety data received during the reporting period for the safety topic of Interaction with other vaccines, the benefit-risk profile for elasomeran remains favorable.

The MAH has monitored interactions with other vaccines in each MSSRs as well as in PSURs since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data on individuals receiving concurrent vaccines with elasomeran reported in the GSDB indicates that the general pattern of commonly reported AEs is consistent with expected reactogenicity events and are comparable to events observed in the general population receiving other widely used vaccines.
- Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show an increase in reporting of AEs. Health authorities consider that coadministration

of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

- Use of elasomeran with other vaccines, including childhood immunization vaccines is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Rationale for removal:

- Extended use of the elasomeran vaccines in conjunction with other vaccines has provided extensive safety information for "Interactions with other vaccines" no longer be considered missing information.
- Concomitant use of other vaccines with elasomeran is included in the Summary of Products Characteristics: High dose quadrivalent influenza vaccine can be concomitantly administered with elasomeran.
- The MAH continues to evaluate "Interaction with other vaccines" in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies.
- Concomitant use of the vaccine with the influenza vaccine is already included in the product's labeling, and the use of with other vaccine is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to Interaction with other vaccines' as long-term safety is being kept as missing information.

Based on all the information provided the MAH is requesting to discontinue presenting analysis of events for "Interactions with other vaccines" in each PSUR, and rather only include new information in the applicable section that would present a change to the safety profile of the vaccine. The MAH is also proposing the removal of "Interactions with other vaccines" as Missing Information from the Spikevax EU-RMP, and to continue monitoring "Interactions with other vaccines" through routine surveillance.

16.3.6.7.4.6 Conclusion

After careful review of all new safety data received during the reporting period and cumulatively for interactions of non-COVID-19 vaccines co-administered with elasomeran,

elasomeran/imelasomeran and elasomeran/davesomeran, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The MAH continues to evaluate "Interaction with other vaccines" in reports of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran via routine pharmacovigilance activities as well as through post-authorization safety studies.

16.3.6.7.5 Lack of Efficacy/ Vaccine Failure

16.3.6.7.5.1 Source of the New Information

ModernaTx, Inc. queried the GSDB for the reporting period for valid, spontaneous case reports of lack of efficacy/vaccination failure received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.5.2. Background Relevant to the Evaluation

Lack of efficacy/vaccine failure is defined as COVID-19 infection occurring 14 days or more after the second dose of elasomeran. In order to better characterize the effect of the booster dose on vaccine failure, ModernaTx, Inc. has further broken down its definition of lack of efficacy into primary series vaccine failure (breakthrough infection 14 days or more after 2nd dose of primary vaccination) and booster dose vaccine failure (breakthrough infection 14 days or more after booster dose of vaccine. Recently emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron sublineages, including the BA.2-derived BA.2.75.2 and the BA.5-derived BQ.1.1 and XBB.1, have accumulated additional spike mutations that may affect vaccine effectiveness [180]. In a CDC Morbidity and Mortality Weekly Report study, relative benefits of a bivalent booster compared with monovalent vaccine doses alone increased with time since receipt of last monovalent dose [181]. The article discusses more rapid waning of efficacy overtime since receipt of monovalent during the Omicron-predominant period Omicron BA.4/BA.5 lineages.

Results from this study show that bivalent boosters provide protection against symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages; and restore protection observed to wane after monovalent vaccine receipt, as demonstrated by increased rVE with longer time, since the most recent monovalent dose. BA.5 bivalent booster elicited a high neutralizing titer against elasomeran/davesomeran measured at 14–32 days after boost; however, the BA.5 bivalent booster did not produce robust neutralization against the newly emerged BA.2.75.2, BQ.1.1 or XBB.1.

ModernaTx, Inc. continues to monitor breakthrough infections and lack of efficacy/vaccine failure cases, and the impact of booster doses. Based on the MAH data supporting their authorizations, the bivalent COVID-19 vaccines are expected to provide increased protection against the currently circulating omicron variant.

16.3.6.7.5.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

ModernaTx, Inc. queried the GSDB for the reporting period for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The database was searched using the criteria IPR-VED (>=14), which includes COVID-19 Preferred Terms and Lack of Efficacy Preferred Terms (PTs) occurring 14 days or more after the second dose of vaccination.

Vaccine failure cases occurring 14 days or more after the 2nd elasomeran dose or less than 14 days after the 3rd elasomeran dose were defined as "primary vaccine failure," as they were attributable to the primary vaccine series. Vaccine failures occurring 14 days or more after the 3rd dose or subsequent were defined as "secondary vaccine failure" and attributed to the booster dose

In an attempt to characterize the variants reported in relation to vaccine failure, a search of the narrative field for keywords of alpha, beta variant, delta, gamma, Omicron was also performed.

Additional Literature Search

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and lack of efficacy/vaccine efficacy to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (e.g., All Fields, MeSH Terms, Text Word, Date-Publication, etc.) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 83 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.5.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

Cumulatively, there were 12,370 cases of vaccine failure (primary [11,165] and booster [1,205]) reporting 21,455 events of which 15,891 were serious events (8,863 serious cases, 71.6%). Of the 12,370 cases, 11,255 cases (91.0%) were medically confirmed, and 449 cases (3.6%) had a fatal outcome.

During this reporting period, there were 1,857 cases of vaccine failure (primary and secondary series/booster) reporting 2,992 events of which 2,167 were serious events (1,190 serious cases, 64.1%). Of the 1,857 cases, 1,523 cases (82.0%) were medically confirmed, and 4 cases (0.2%) had a fatal outcome. In the primary vaccine series and booster series combined, most of the cases were from Austria (845; 45.5%), followed Japan (307; 16.5%), Spain (121; 6.5%), Australia (119; 6.4%), Sweden (117; 6.3%), Italy (91; 4.9%) and the United States (44; 2.4%). Cases from all other countries were responsible for <2% of the cases reported in the reporting period per country. Gender distribution of these 1,857 cases was 1,056 (56.9%) males, 776 females (41.8%) and 25 missing gender (1.3%). In primary vaccine series, the mean age was 42.3 years (SD:13.3), with most cases (34.2%) being reported in the 25–39-year age group, followed by the 40 – 49-year age group (29.7%). Only 7 cases (0.6%) of the 1,258 primary vaccine series and none of the 599 secondary vaccine series cases were in children under ≤ 17 years and 64 (5.1%) of the primary vaccine series and 170 (28.3%) of the secondary series cases were in the elderly (≥65 years). Of the 1,857 cases of vaccine failure in this reporting period, 1,258 (67.7%) of the cases were attributable to the primary vaccine series while 599 (32.3%) were attributable to the secondary series/booster vaccine.

Primary Vaccine Series: Lack of Efficacy/Vaccine Failure (Reporting Period)

During the reporting period, there were 2,197 events reported in 1,258 cases of which 917 cases (72.8%) were serious, 3 cases (0.2%) were fatal, and 1,192 cases (98.4%) were medically confirmed.

Gender distribution was 61.2% male, 38.3% female and 0.5% missing gender with mean age of 42.3 (SD:13.3).

Regardless of dose, the median TTO of events during the reporting period for cases of vaccine failure after the primary vaccine series was 155.0 days (min 14; max 584). Outcome was Unknown

in 83.2% of the events, Recovered in 15.2%, and Not Recovered in 0.6%, Recovering in 0.5%, Recovered with Sequelae in 0.2% and fatal in 0.2% of the events for the reporting period.

The case distribution by age group for the reporting period is provided below in Table 16.154.

Table 16.154 Primary Vaccine Series: Lack of Efficacy/Vaccine Failure Case Distribution by Age Group

Age Group	Reporting Period	
	# Cases	% of Total Cases
6 Mths - < 2 Y	1	0.1
12-15Y	3	0.2
16-17Y	3	0.2
18-24Y	98	7.8
25-39Y	430	34.2
40-49Y	373	29.7
50-64Y	274	21.8
65-74Y	36	2.9
75+	28	2.2
Missing	12	1.0
Grand total	**1,258**	**100.0**

Mths – months; Y – years

Primary Vaccine Series: Lack of Efficacy/Vaccine Failure - Subpopulation Analyzes

Children ages 0-5 Months

There were no cases of primary vaccine series vaccine failure reported in children ages 0-5 months during the reporting period.

Children ages 6-23 Months

As of 17 Dec 2022, 1 serious case of primary vaccine series vaccine failure reporting 2 events, "COVID-19" and "Vaccination failure" was reported in a 1-year-old male patient. No medical history or concomitant medications were reported. The events of "COVID-19" and "Vaccination failure" occurred approximately 4 months and 16 days after the second dose of the elasomeran vaccine. There is inappropriate schedule of vaccine administration as the interval between the first dose and second dose was 42 days, which was not in accordance with labeled vaccination schedules No further information on the clinical course, investigations and treatment received was

available in the report. The outcome of the events was reported as unknown. ([redacted]).

No other cases were reported for this age group during the reporting period.

Children ages 2-5 Years

There were no cases of primary vaccine series vaccine failure reported in children ages 2-5 years during the reporting period.

Children ages 6-11 Years

There were no cases of primary vaccine series vaccine failure reported in children ages 6-11 years during the reporting period.

Adolescents ages 12-17 Years

As of 17 Dec 2022, 6 serious cases of primary vaccine series vaccine failure reporting 11 serious events "COVID-19" (6; 54.5%) and "Vaccination failure" (5;45.5%) were reported in females ages 12-15 (3) and 16-17 (3) years. The 6 cases received during the reporting period were medically confirmed.

All six cases were reported by regulatory authorities. One case originated from Finland and five originated from Austria. None one the cases reported medical history, concomitant medications or the outcome of the events. The 11 events occurred 30+ days after the second dose of the elasomeran.

Primary Vaccine Series: Lack of Efficacy/Vaccine Failure - Serious Cases

There were 917 serious cases (1,866 events) of primary vaccine series vaccine failure reported in this reporting period, of which 886 cases were medically confirmed. There were 3 cases with a fatal outcome representing 0.2% of all vaccine failure cases (1,258 cases) in this reporting period. The 25-39 age group was the most frequently represented age group in serious cases of primary vaccine failure (31.1% of serious cases) followed by the 40-49 age group (29.7%) (Table 16.155).

Table 16.155 Primary Vaccine Series: Lack of Efficacy/Vaccine Failure Distribution of Serious Cases by Age Group

Age Group	Reporting Period	
	# Cases	% of Total Serious Cases
6 Mths - < 2 Y	1	0.1
12-15	3	0.3

Age Group	Reporting Period	
	# Cases	% of Total Serious Cases
16-17	3	0.3
18-24Y	71	7.7
25-39Y	285	31.1
40-49	272	29.7
50-64	221	24.1
65-74	30	3.3
75+	24	2.6
Missing	7	0.8
Grand total	**917**	**100.0**

Mths – months; Y – years

Of the 1,866 events reported in the serious cases of primary vaccine failure during the reporting period, the most frequently reported PTs were "COVID-19" (902; 48.3%) and "Vaccination failure" (854; 45.8%). The remaining 110 events were reported in < 1.0% of the serious cases of primary vaccine failure during the reporting period.

Regardless of dose, the median TTO of events during the reporting period for serious cases of vaccine failure after the primary vaccine series was 148.5 days (min 0: max 572) in this reporting period. The outcome was not reported in 93.9% of the serious primary vaccine failure events and reported as Recovered, Not Recovered, Recovering, Recovering with Sequalae, and Fatal in 3.4%, 1.3%. 0.6%, 0.3% and 0.3% respectively.

Primary Vaccine Series: Lack of Efficacy/Vaccine Failure - Fatal Cases

There were 3 fatal cases of primary vaccine series vaccine failure in this reporting period. All 3 cases occurred in patients ≥ 65 years-old (2 males, 1 female) and are summarized below.

[redacted]: This regulatory authority case from France concerns a 73-year-old male patient with relevant medical history of Ischaemic heart disease, Arterial hypertension, Chronic obstructive broncho pneumopathy, Chronic alcoholism, Tabaquism, Stroke, Implantable defibrillator, Cerebrovascular accident and Coronary arterial stent insertion. Patient on concomitant polypharmacy. The events of "COVID-19" and "Vaccination failure" occurred approximately 5.5 months after the second dose of elasomeran. Of note the patient received the second dose 43 days after first. The reported cause of death was SARS-CoV-2 infection and

Vaccination failure. It is unknown if an autopsy was performed. The elderly patient's medical history likely contributed to the fatal outcome.

[redacted]: This regulatory authority case from Philippines concerns a 74-year-old male patient with no reported medical history or concomitant medications. The events of "COVID-19" and "Vaccination failure" occurred approximately 9 months after receiving a dose of elasomeran vaccine, reported as second COVID-19 vaccine. The clinical course leading to the patient's demise was not reported. The reported cause of death was community acquired pneumonia and COVID-19. It is unknown if an autopsy was performed.

[redacted]: This regulatory authority case from France concerns an 85-year-old female patient with relevant medical history of Type 2 DM, Hypothyroidism, Chronic Renal Failure, Atrial Fibrillation status post-Cardiac pacemaker insertion, Breast carcinoma and Fracture of the sacral fin secondary to fall, and past drug history of administration of Comirnaty (Pfizer/BioNTech COVID-19 mRNA vaccine) as the first dose in the COVID-19 vaccination series. Patient on polypharmacy. The events of "COVID-19" and "Vaccination failure" occurred approximately 5 months after the second dose of elasomeran. The patient had emergency hospitalization due to breathing difficulties in the context of SARS-CoV-2 infection. While hospitalized the patient had marked neurological and then hemodynamic deterioration before expiring 18 days after the onset of the event "COVID-19". It is unknown if an autopsy was performed. The reported cause of death was Cardiorespiratory arrest. The patient's relevant medical history and advanced age likely contributed to the fatal outcome.

Secondary Vaccine Series (Third or Booster Dose): Lack of Efficacy/Vaccine Failure (Reporting Period)

During this reporting period there were 599 cases of vaccine failure reporting 795 events of which 592 were serious events (276 serious cases). Of the 599 cases, 331 cases (55.3%) were medically confirmed, and 2 cases (0.2%) had a fatal outcome. In this reporting period, all events of vaccine failure (795 events) occurred 14 days or more after receiving a booster dose of elasomeran: Dose 3 (89.9%), Dose 4 (9.6%) and Dose 5 (0.5%). Most of the cases were from the EEA (204; 34.1%), followed Asia (127; 21.2%), UK (119; 19.9%), United States (118; 19.7%), Switzerland (14; 2.3%), and Australia and Canada (8; 1.3% each). Cases from all other countries were responsible for 0.2% of the cases reported during the reporting period. Gender distribution of these 599 cases was 286 (47.7%) males, 294 females (49.1%) and 19 missing gender (3.2%). The mean age was 53.7 years (SD: 16.0), with most cases (29.4%) reported in the 50–64-year age group, followed by

the 40 – 49- and 25-39-year age groups (18.7% each). Time to onset is presented below in Table 16.156.

Table 16.156 Secondary Vaccine Series: Lack of Efficacy/Vaccine Failure Event Counts by Dose Number and TTO

Dose Number	TTO All Doses (Days)	Reporting Period	
		# Events	% of Total Events
Dose 3	**Subtotal**	**715**	89.9
	14-29	151	19.0
	30+	564	70.9
Dose 4	**Subtotal**	**76**	9.6
	14-29	11	1.4
	30+	65	8.2
Dose 5	**Subtotal**	**4**	0.5
	14-29	0	0
	30+	4	0.5
Grand total		**795**	**100%**

Secondary Vaccine Series (Third or Booster Dose): Lack of Efficacy/Vaccine Failure - Serious Cases

Of the 276 serious cases, 592 events were serious. The mean age was 54.9 years (SD: 15.7), with most cases reported in the 50–64-year group (85; 30.8%) (Table 16.157). The outcome was not reported in 64.2% of the serious secondary vaccine series vaccine failure events and reported as Recovered, Recovering, Not Recovered, Recovering with Sequalae, and Fatal in 13.8%, 10.7%. 9.1%, 2.0% and 0.2% respectively.

Table 16.157 Secondary Vaccine Series: Lack of Efficacy/Vaccine Failure Distribution of Serious Cases by Age Group

Age Group	# Cases	% of Total Cases
18-24Y	3	1.1%
25-39Y	55	20.1%
40-49Y	40	14.6%
50-64Y	85	30.8%
65-74Y	46	16.7%
75Y+	32	11.6%
Missing	15	5.5%
Grand total	**276**	**100.0%**

Regardless of dose, the median TTO of events during the reporting period for serious cases of vaccine failure after the secondary series (booster dose) was 57.0 days (min 14: max 1096).

When outcome was known (Unknown in 64.2%), it was most frequently reported as Recovered (13.8%) followed by Recovering (10.7%) in the reporting period. There were 2 fatal cases which are discussed below

Secondary Vaccine Series (Third or Booster Dose): Lack of Efficacy/Vaccine Failure - Subpopulation Analyzes

Children ages 0-5 Months

There were no cases of secondary vaccine series vaccine failure reported in children ages 0-5 months during the reporting period.

Children ages 6-23 Months

There were no cases of secondary vaccine series vaccine failure reported in children ages 6-23 months during the reporting period.

Children ages 2-5 Years

There were no cases of secondary vaccine series vaccine failure reported in children ages 2-5 years during the reporting period.

Children ages 6-11 Years

There were no cases of secondary vaccine series vaccine failure reported in children ages 6-11 years during the reporting period.

Adolescents ages 12-17 Years

There were no cases of secondary vaccine series vaccine failure reported in adolescents ages 12-17 years during the reporting period.

Secondary Vaccine Series (Third or Booster Dose): Lack of Efficacy/Vaccine Failure - Fatal Cases

Both cases occurred in the elderly males with significant comorbidities.

[redacted]: This is a regulatory case from Germany concerning a 77-year-old male patient with relevant medical history of arterial hypertension, renal atrophy, spinal osteoarthritis who experienced the events of Acute respiratory failure, Cerebrovascular accident, COVID-19,

Hypernatraemia, Pneumonia, Pulmonary embolism, Right ventricular failure, Staphylococcal sepsis and Thrombophlebitis 22 days after the fourth dose of elasomeran vaccine. The patient died 34 days after the fourth dose of elasomeran vaccine. No concomitant medications or treatment details for the events were reported. The reported cause of death was SARS-CoV-2 infection, Nosocomial pneumonia, and Arterial hypertension. An autopsy was not performed.

Causality: The case was assessed as possibly related however it is confounded by the elderly patient's significant medical history and other progressive concurrent medical conditions which were complicated in the context of a COVID-19 infection and provide a more plausible alternative explanation for the fatal outcome in this case.

[redacted]: This is a regulatory case from Japan concerning a 66-year-old male patient with a relevant medical history of hypertension, diabetes, and alcoholic cirrhosis who experienced Acute interstitial pneumonitis, Aspiration, Cough, COVID-19 pneumonia, Dyspnoea, Hypoxia, Multiple organ dysfunction syndrome, and Productive cough approximately 1 month after the fourth dose of elasomeran. The patient had previously been vaccinated with Comirnaty (doses 1, 2 and 3) on unspecified dates. The patient died two weeks after the initial onset of symptoms. The cause of death was reported as hypoxaemia and multiple organ failure dysfunction syndrome.

Causality: The case was assessed as possibly related however the patients underlying medical conditions of diabetes and hypertension represent significant risk factors in the context of developing a COVID-19 infection and the consequent complications potentially leading to a fatal outcome.

Comorbid Conditions in all cases of vaccine failure (Primary + booster)

During this reporting period, there were 1,857 cases of lack of efficacy/vaccine failure (primary [1,258] and booster [599]) reporting 2,992 events of which 2,167 were serious events (1,190 serious cases, 64.1%).

Other Confounders

The most frequently reported medical history in cases reporting lack of efficacy/vaccine failure was hypertension in 10% of cases. Many of the conditions listed are known to increase severity of COVID-19 disease as well as being independent risk factors for death Table 16.158.

Table 16.158 Most Frequently Reported Medical History in Cases Reporting Lack of Efficacy/Vaccine Failure (Cumulatively)

Medical History	Cases (N)	Cases (%)
Obesity	320	2.58
Chronic obstructive pulmonary disease	326	2.63
Asthma	335	2.7
Gastrooesophageal reflux disease	336	2.71
Type 2 diabetes mellitus	366	2.95
Diabetes mellitus	444	3.58
Hyperlipidaemia	448	3.62
Drug hypersensitivity	1,132	9.14
Hypertension	1,239	10
Non-Documented Cases	8,963	72.36
Total Unique Cases	**12,386**	**100**

The most frequently reported concomitant medications cumulatively in cases reporting lack of efficacy/vaccine failure were indicative of comorbidities that increase the risk for severe COVID-19 disease or of thromboembolic events (Table 16.159).

Table 16.159 Most Frequently Reported Concomitant Medication in Cases reporting Lack of Efficacy/Vaccine Failure (Cumulatively)

Concomitant Medication	Cases (N)	Cases (%)
Losartan	86	0.69
Acetaminophen	88	0.71
Metformin	98	0.79
Omeprazole	100	0.81
Aspirin [Acetylsalicylic Acid]	114	0.92
Amlodipine	124	1
Levothyroxine	131	1.06
Lisinopril	131	1.06
Atorvastatin	172	1.39
Non-Documented Cases	10,776	87
Total Unique Cases	**12,386**	**100**

Lack of Efficacy/Vaccine Failure in Patients After Administration of elasomeran/imelasomeran

Given increasing circulating variants and recent bivalent approvals, reports during this interval are

predominantly attributable to the Omicron and newer subvariants such as XBB. During the reporting period, there have been 6 cases of vaccine failure (9 events), of which 3 cases were considered serious and none had fatal outcomes. Case distribution by region included 2 from UK and one each from Sweden, Australia, Switzerland and Germany. Three cases reported with females (50.0%), two males (33.3%) and one missing (16.7%) with the median age was 68.0 (min:34.0/ max:82.0).

Lack of Efficacy/ Vaccine Failure in Patients After Administration of elasomeran/davesomeran.

During the reporting period, there were 10 cases of vaccine failure (10 events), of which all were non-serious. Four cases reported with females (40.0%), 5 males (50.0%) and one missing (10.0%) with the median age was 70.0 (min:34.0/ max:84.0). All cases were from the United States with most cases occurring (70.0%) were in the elderly 65 years and older.

16.3.6.7.5.5. Discussion

Research suggests the protection offered by COVID-19 vaccines might wane over time, prompting consideration of booster vaccinations. Vaccine failure reports represent 2.3% of all cases in this reporting period (80,461 cases). Likely due to recent approvals, relatively fewer cases have been reported for elasomeran/imelasomeran and elasomeran/davesomeran.

In this PBRER period, the reported gender distribution was approximately 56.9% males and 41.8% females with the median age reported was 42.3. There were 7 cases (0.6%) in the primary vaccine series and none of the secondary vaccine series cases were in children under ≤ 17 years; and 64 (5.1%) of the primary vaccine series and 170(28.4%) of the secondary series cases were in the elderly (≥65 years). 64.1% of cases of vaccine failure were serious.

The median TTO for cases of vaccine failure after the primary vaccine series was 155 days and that for the secondary series cases was 88 days.

In this PBRER period, the primary vaccine series and booster series combined, most of the cases were from Austria (45.5%), followed Japan (16.5%), Spain (6.5%), Australia (6.4%), Sweden (6.3%), Italy (4.9%) and the United States (2.4%). Cases from all other countries were responsible for <2% of the cases reported in the reporting period per country.

Additionally, all of the .214 cases and 70% of the .222 cases were in the elderly age group for bivalents. No specific safety patterns or concerns for these differences could be established. The elderly, the frail and those with immunosuppressive conditions are more prone to vaccine failure

due to multifactorial reasons including host immune response and preponderance of comorbid conditions. Immunosenescence is known to be associated with decreased immune response and is more common in the elderly. Though older age is also a known risk factor for severe COVID disease, it is also an independent risk factor for death from comorbid conditions or natural causes. Fatalities attributed to vaccine failure may therefore be an overrepresentation, especially in the elderly.

The institution of 3rd dose boosters has become more widespread in different countries, with percentage of vaccine failure cases reported after dose 3 representing 89.9% of all vaccine failure cases in this reporting period. Current data is still limited from spontaneous reporting with 715 case reports in the reporting period >= 14 days after 3rd dose (booster vaccine failure).

In all 4 fatal cases reported during this reporting period, the patients reported significant comorbidities that either may have interfered with the mounting of an adequate immune response to vaccine or in other ways contributed to fatality. No new safety patterns or concerns were identified following a review of these data.

No published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran were identified during the reporting period of this PBRER.

Although there may be occasional breakthrough cases, based on reports received it is reassuring that many such cases are rare and generally mild (not commonly resulting in hospitalization).

16.3.6.7.5.6 Conclusion

After careful review of all new safety data received during the reporting period and cumulatively for vaccine failure, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The safety topic of vaccine failure will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.6 Subpopulation Analysis: Elderly 65 years and above

16.3.6.7.6.1 Source of the New Information

Information presented below includes analysis performed on worldwide reports received by ModernaTx, Inc. cumulatively (18 Dec 2020–17 Dec 2022) and for the PBRER#4 reporting period (19 Jun 2022 to 17 Dec 2022) for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.6.2. Background Relevant to the Evaluation

The impact of COVID-19 on older populations is well documented. The elderly is highly vulnerable to severe COVID-19 infection. This subpopulation is at most risk due to comorbidities and age-related complex conditions. During this reporting period, based on concerns of waning immunity, viral mutation and different VOCs (Delta, subvariants of Omicron [BQ.1.1, BQ.1, BA,5, XBB), characterized by unclear transmissibility and possible immune escape, some countries authorized bivalent, variant containing vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) The biological rationale for the bivalent booster doses of both Moderna COVID-19 mRNA vaccines is increased immune response directed against SARS-CoV-2, including the Omicron variants, in those who have completed a primary series and previous booster.

The impact of immunosenescence (the decline of immunity with age) on the safety of COVID-19 vaccines in the elderly is not well documented. Lack of consistency has been observed in both quantitative and qualitative aspects of immune system responses in the elderly which impact the safety and efficacy of vaccines in this subpopulation [182]. Advancing age has been associated with a reduction in naive T-cells which are needed to respond to a vaccine. Due to a significant decrease in CD8 T-cells in older age, the ratio of CD4:CD8 cells becomes much higher. [183] also reported that aging causes a loss of T-cell receptor diversity in both CD8 and CD4 cells and a general reduction in T-cell survival. Qualitative changes include the production of short-lived effector T-cells over memory cells, resulting in "an impaired response of T follicular helper cells to vaccination." [184] reported consistent B-cell numbers with age but observed the production of fewer functional antibodies due to a reduced expression of select proteins in old age. Based on the above variability in immune response in the elderly, Soiza et al hypothesized that the risk of serious AEs mediated by overactivation of the immune system may be lower [182] and the benefits outweigh the risks.

16.3.6.7.6.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB for the reporting period 19 Jun 2022 through 17 Dec 2022 for valid case reports received from healthcare professionals (HCP), health authorities (HA), consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The search strategy and criteria included using a "Age group >=65years.

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and [Elderly] to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 73 literature articles were retrieved using these search criteria. There was no other published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in the elderly population. The Liz et al article reinforced the positive safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in the elderly.

Liz et al conducted a systematic review and meta-analysis of 32 randomized clinical trials that investigated the efficacy, immunogenicity, and safety of COVID-19 vaccines in older people aged ≥ 55 years and their influencing factors. The authors found that COVID-19 vaccines showed acceptable efficacy, immunogenicity, and safety in older people, especially providing a high protection rate against severe disease. They reported that the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccine was the most efficacious for advanced age groups.

16.3.6.7.6.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on cases involving the Elderly subpopulation please refer to Appendix 11.25.

Overview of Cases

Cumulatively, a total of 133,331 cases (476,590 events and 76,819 cases were medically confirmed) were reported in the elderly aged 65 years and older, of which 33,236 (24.9%) cases were assessed as serious, and 4,423 cases (3.3%) reported fatal outcome Cases were disproportionately reported in females compared to males (65.6% vs 32.7%, respectively), and were most frequently reported from the United States (63.2 %) followed by France (5.4%) and the Netherlands (4.9 %). Case reports in the elderly represent 20.2% of all cases (658,759 cases) cumulatively.

During this reporting period, a total of 10,686 cases (34,471 events), 4652 (43.5%) medically confirmed cases) were reported in the elderly 65 years and older, of which 2,993 (28.0%) were

assessed as serious, and 191 cases (1.8%) with fatal outcome. Where gender information was provided, cases were disproportionately reported in females compared to males (59.6% vs 34.5%, respectively) and were most frequently reported from the United States (19.4%) followed by the UK (13.8%) and Germany (13.1%). Case reports in the elderly represent 13.3% of all cases (80,461 cases) in this reporting period. The reporting interval cases in the elderly were mostly reactogenicity and consistent with those in the cumulative period except for a drop in the percentage of cases reporting a fatal outcome, from 3.3% in prior period to 1.8% (191 cases) in the review period. There was no cluster/trend of note.

During this reporting period, the top three SOC in which events in the elderly were reported were general disorders and administration site conditions (34.7%), nervous system disorders (12.3%), and musculoskeletal and connective tissue disorders (12.0%.); the top three High Level Terms (HLT) were asthenic conditions (8.2%), vaccination site reactions (5.3%), and headaches Not elsewhere Classified (NEC) (4.3%). The ten most frequently reported MedDRA preferred term (PT)s among the elderly are presented below in Table 16.160.

Table 16.160 Top 10 MedDRA PT Elderly Age ≥ 65 Years by Frequency elasomeran (Review Period)

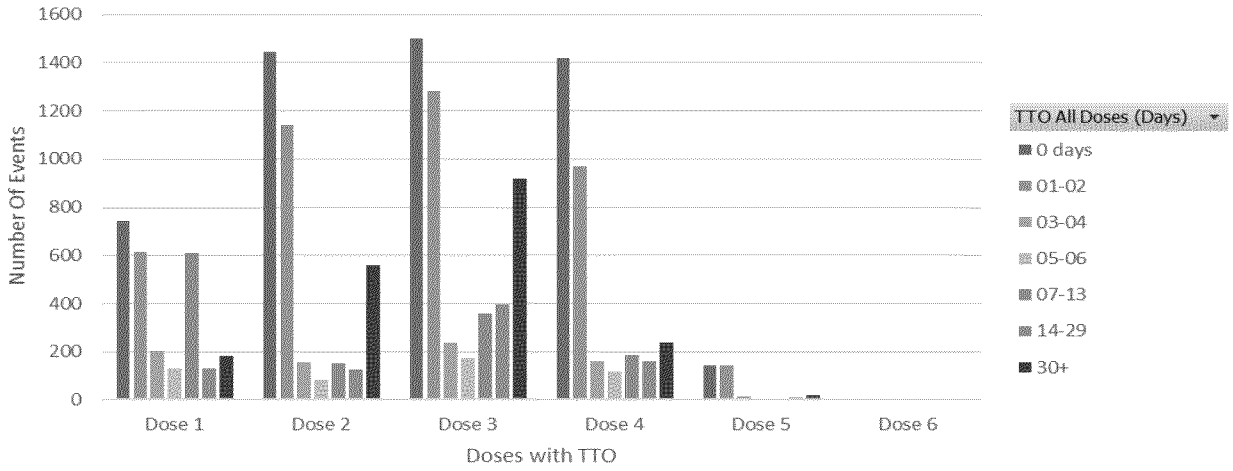
PT	Events (n)	Events (%)
Fatigue	1,625	4.7
Headache	1,460	4.2
Pyrexia	1,456	4.2
Myalgia	1,128	3.3
Arthralgia	877	2.5
Chills	871	2.5
Pain in extremity	852	2.5
Malaise	816	2.4
Nausea	707	2.1
Dizziness	643	1.9

Dose Number and TTO

In this reporting interval, a high proportion of events (57.3%) had missing dose information. When dose number was known, more events (4,862 events) were reported after dose 3 than after dose 2 (3,666 events), followed by dose 4 (3,246 events) and dose 1 (2,611). The higher number of events reported after dose 3 in the elderly may be due to the scale up of booster and dose 3 primary series vaccination. The majority of events were reported within 2 days post-vaccination, regardless of

vaccine dose. However, time to onset was not reported for 42.5% of events. The distribution of events by dose number and TTO is presented in more detail in Figure 16-19.

Figure 16-19. Distribution of Events by Dose Number and Time to Onset for Age ≥ 65 Years elasomeran (Review Period)



About a quarter of reported events (25.9%) had resolved as at the time of report, while 28.7% of reported events had an unknown outcome (Table 16.161).

Table 16.161 Event Outcome for Age ≥ 65 Years elasomeran by Review Period

Event Outcome	Review Period	
	Events (n)	Events (%)
Fatal	440	1.3
Not Recovered/Not Resolved	9,069	26.3
Recovered/Resolved	8,912	25.9
Recovered/Resolved with Sequelae	809	2.3
Recovering/Resolving	5,352	15.5
Unknown	9,889	28.7
Worsened	0	0
Grand Total	**34,471**	**100.0**

Serious Cases in the Elderly

During this reporting interval, there were 2,993 serious cases (10,034 events, 7,133 serious) of which 191 cases were fatal (6.4%). Gender distribution was 54.2% females to 42.1% males (3.8% missing gender), and the median age of elderly patients in the serious reports was 73.0 years (with a range from 65 years to 102 years). Most serious cases were reported by regulatory authorities

(2,449; 81.8%), with the UK (23.4%), Germany (15.4%), and the United States (11.6%) being the three highest contributors.

In serious cases in this reporting period, general disorders and administration site conditions (21.7%), nervous system disorders (16.5%), and musculoskeletal and connective tissue disorders (10.0%) were the top three SOCs while asthenic conditions, Coronavirus infections, and headaches NEC were the top three reported HLTs. The most frequently reported PTs were in line with those seen in the general population and reflect either expected vaccine reactogenicity or active COVID-19 infection. (See Table 16.162 below).

Table 16.162. Top 10 most Frequently reported MedDRA Preferred Terms in Serious Cases in Elderly Age ≥ 65 Years (Review Period and Cumulatively)

Review Period			Cumulative Period		
PT	**# Events**	**% Of Total Events**	**PT**	**# Events**	**% Of Total Events**
Fatigue	337	3.4	COVID-19	4,096	3.0
COVID-19	268	2.7	Pyrexia	3,577	2.6
Headache	268	2.7	Fatigue	3,402	2.5
Pyrexia	243	2.4	Dyspnoea	3,376	2.5
Dizziness	207	2.1	Headache	2,745	2.0
Dyspnoea	192	1.9	Asthenia	2,479	1.8
Myalgia	189	1.9	Nausea	2,111	1.6
Arthralgia	174	1.7	Dizziness	2,107	1.6
Pain in extremity	162	1.6	Death	2,099	1.6
Nausea	155	1.5	Chills	2,056	1.5

Abbreviations: MedDRA = Medical Dictionary for Regulatory Affairs; PT = preferred term.

Further characterization of serious cases of COVID-19 in the elderly is undertaken below.

Serious Cases of COVID-19 in the Elderly (Reporting Period)

There was a remarkable reduction (56.2%) in the number of serious cases and events of COVID-19 (258 cases, 211 events) reported in this reporting period, compared with the prior period (589 cases). These 258 serious cases of COVID-19 represented 2.4% of the 10,686 cases in the elderly in this reporting interval, of which 15 cases had a fatal outcome. The median age of serious cases of COVID-19 in the elderly was 74.0 years, with a range of 65.0 years to 97.0 years. Gender

distribution was 45.0% male and 53.5% female, with four cases (1.6%) missing gender information. A majority of serious cases reporting COVID-19 were received via regulatory authorities (72.5%), with most cases reported from Austria (97; 37.6%) followed by the United States (60; 23.3%), and the UK (29; 11.2%). All 97 serious cases from Austria were reported via regulatory authority, with no reported medical history, unknown outcome, and limited event details. Of the reported 268 events, 144 (53.7%) were in a time frame compatible with vaccine failure (occurrence of COVID-19 despite previous COVID vaccination). Inadequate information limited the MAH to confirm clinical vaccine failure, whether the cases were appropriately and fully vaccinated, taking into account the COVID-19 incubation period and the lag between vaccination and development of protective antibodies.

When dose number was provided, most serious events of COVID-19 in the elderly were reported after dose 3 (71 events), followed by dose 2 (50 events). The outcome of events in serious cases reporting COVID-19 in the elderly was most frequently not reported (58.6%%). When outcome was known, 22.0% of events had resolved, 7.5% of events were resolving, and 6.3% of events had not resolved as of the time of report. In 93 (53.7%) of the 268 events in serious cases of COVID-19, latency was reported as 14 or more days post-vaccination and may represent vaccine failure (see Section 16.3.6.7.5). This should be interpreted with caution since there is inadequate information to determine if the individuals were appropriately and fully vaccinated, taking into account the COVID-19 incubation period and the lag between vaccination and development of protective antibodies.

Fatal Cases in the Elderly

The 191 cases with fatal outcomes (440 events) in the elderly in this reporting interval, occurred in a similar proportion for males (93; 48.7%) and females (94; 49.5%), with four cases (2.1%) missing gender information. and the median age was 77.0 years, ranging from 65.0 years to 100.0 years. The top four reported preferred terms (PT) in fatal cases were death (7.7%), COVID-19 (3.4%), cardiac arrest (2.5%) and pneumonia (2.5%). Most fatal cases were reported from Japan (34; 17.8%) followed by France (21; 11.0%), and Germany (19; 9.9%). About a third of the fatal events did not report a TTO (160 events: 36.4%) during the reporting period. When known, most events occurred after dose 4 (81 events) followed by dose 3 (53 events), dose 2 (43 events), and dose 1 (32 events).

Medical review of the fatal cases did not identify any new safety concerns. In these 191 fatal cases, the patients had multiple comorbidities with strong confounders including respiratory/cardiovascular diseases, diabetes, COVID-19 infection, and malignancy.

Elderly patients have comorbidities and/or unstable health conditions, which are naturally subject to worsening and can lead to fatal outcomes. The frequent comorbidities associated with fatal outcomes were in line with the previous reporting period and comorbidities seen in the entire elderly population in the cumulative database.

Cases in Elderly Patients After Booster dose (>= 3rd dose) of elasomeran

During this reporting period, there was a decline in the number of reported cases in the elderly after booster dose, compared to the prior reporting period. There was a total of 3,400 cases (8,449 events), of which 1,337 (39.3%) were medically confirmed, 1,096 (32.2%) serious cases and 65 (1.9%) cases with fatal outcome were reported in the elderly after a booster dose (defined as the third dose or higher) of elasomeran. Cases reported with booster doses represent 31.8% of all case reports in the elderly in this reporting period. Gender distribution was 38.1% male and 58.9% female, and the median age was 72.0 years (range from 65.0 years to 102.0 years). The most frequently reported event terms after booster were reported in relation to dose 3 (4,862; 57.5%) versus (3,246; 38.4%) after the dose 4. A clustering of events was seen in the period less than three days after each dose (32.9% with dose 3 and 28.2% with dose 4); this is in line with the observation of timing of events after the primary vaccine series. During the reporting period, events occurring after a booster dose were most frequently reported as not resolved (29.2%) or recovered (27.0%), and another 18.1% of events were resolving; outcome was unknown for 20.0% of events.

Serious cases in elderly after booster dose (>= 3rd dose) of elasomeran.

In this reporting period there were 1,096 serious case reports (3,088 events) after elasomeran booster dose, of which 65 cases were fatal. These serious cases occurred in 490 males (44.7%) and 584 females (53.3%), with a median age of 73.0 (range from 65.0 years to 102.0 years). The most frequently reported PTs in serious cases after booster dose were pyrexia, fatigue, and COVID-19. There were 96 events of COVID-19 reported with booster doses in serious cases, representing 3.1% of all events in serious cases in the elderly after a booster dose of elasomeran. Of these 96 events of COVID-19 in serious cases, 74 events were reported as occurring 14 or more days post-vaccination and may represent vaccine failure.

Nearly half of all serious events (49.5%) in the elderly after a booster dose were reported to occur less than three days post-vaccination (dose 4 [23.8%] and dose 5 [5.3%]). This was consistent with expected reactogenicity for elasomeran. However, after dose 3, most serious events reportedly occurred 14 days or more after vaccination.

About twenty-seven per cent (27.4%) of reported event outcomes in serious cases in the elderly after a booster dose had not recovered as of the time of the report, 22.0% were recovering, while 21.2% had recovered. The outcome was unknown for 14.3% of serious events. The demographics, most frequently reported event terms and reporting countries were similar to that reported in the elderly after elasomeran, irrespective of dose.

Cases in Elderly Patients After Receiving Booster with elasomeran/imelasomeran

During this reporting period, 999 cases (3,609 events, of which 755 were serious) were reported in the elderly 65 years and older with elasomeran/imelasomeran, of which 321 (32.1%) were assessed as serious, 227 (22.7%) cases were medically confirmed, and 19 cases (1.9%) reported a fatal outcome. Cases were disproportionately reported in females compared to males (58.9% vs 35.3%, respectively) and were most frequently reported from the UK (45.2%) and the Netherlands (36.9%), followed by Canada (4.2%), Taiwan (3.4%), and Japan (2.4%). These cases reported a median age of 72.0 years (range from 65.0 years to 99.0 years).

In this reporting interval, TTO was not reported for 68.4% of events. Of all 3,609 events, most were reported after the fourth and fifth dose (13.3% and 8.3% respectively). This is expected as most patients receiving the bivalent booster had already received three or four previous doses. The majority of events were reported within less than 3 days post-vaccination, regardless of vaccine dose, and were typically reactogenicity.

Case reports in the elderly represented 13.6% of all elasomeran/imelasomeran cases (5,230 cases) across all age groups in this reporting period, and serious cases in the elderly comprised 22.0% of all elasomeran/imelasomeran serious cases (940 cases) in all age groups during the reporting period.

The most frequently reported events in the elderly who received elasomeran/imelasomeran were representative of expected reactogenicity and were similar to those reported after elasomeran and in the general population. As elasomeran/imelasomeran was more recently authorized, the data are limited.

Serious Cases After Receiving Booster Dose with elasomeran/imelasomeran

In this review period, 321 serious cases (755 serious events) were reported in elderly patients receiving a booster dose with elasomeran/imelasomeran. Of these 321 serious cases, 74 (23.1%) cases were medically confirmed, and 19 cases (5.9%) had fatal outcomes. There were about twice as many cases reported in females (200; 62.3%) compared to males (107; 33.3%), with 14 cases (4.4%) not reporting gender. These serious cases reported a median age of 74.0 years (range: 65.0 years to 99.0 years).

The event terms reported most frequently in serious cases after booster elasomeran/imelasomeran dose(s) in the elderly were consistent with expected reactogenicity, except for abdominal pain upper (14 events) and chest pain (13 events). A review of these cases found these events were strongly confounded by comorbidities, concomitant medications, and advanced age. Most cases contained insufficient information to assess for causality. All but one case of abdominal pain was reported in the United Kingdom; abdominal pain is a listed event in the UK SmPC. The remaining case reporting abdominal pain was reported in Taiwan and was heavily confounded by medical history.

Among serious cases during the reporting period, events were most frequently reported after dose 4 (311 events), followed by dose 5 (185 events). An additional 358 events were missing dose information. Events in serious cases occurred on average within two days of vaccination.

Overview of Fatal Cases with elasomeran/imelasomeran

During the reporting interval, there were 19 cases with fatal outcomes reported among elderly recipients of elasomeran/imelasomeran. Most of these cases were medically confirmed (89.5%) and reported by regulatory authorities (78.9%); 47.4% of cases were reported in Taiwan. About half of all fatal events (51.4%) occurred following dose 5 and 22.9% after dose 4, with 25.7% of events not reporting dose number.

Medical review of the fatal cases did not identify any new safety concerns. Most of the cases (84.2%) were strongly confounded by comorbidities such as cardiovascular disorders, diabetes, malignancies, anaemia, autoimmune disorders, thyroid disease, and chronic respiratory failure, and six of these cases also reported confounding concomitant medications. Summary of review of three cases of interest are discussed below.

[redacted]: A spontaneous report in Taiwan that described a 93-year-old female patient who was found dead six days following administration of elasomeran/imelasomeran (as dose 4).

There was no medical history, concomitant medications, or cause of death reported. Advanced age is noted as a confounder. No other details were provided. According to WHO-UMC causality assessment, this case is assessed as Unassessable, due to insufficient information.

[redacted]: This case was reported by a health authority in Taiwan and described a 92-year-old female patient who died ten days following administration of elasomeran/imelasomeran (as dose 5). Six days following vaccination, the patient reported decreased appetite and feeling abnormal ("poor spirits"), and four days later had "heavy asthma" and died. There was no medical history or concomitant medication reported. An autopsy was performed, and cause of death was determined to be spontaneous cerebral hemorrhage. Advanced age is noted as a confounder. According to WHO-UMC causality assessment, this case is assessed as Unassessable, due to insufficient information.

[redacted]: This case was reported spontaneously in Canada and described a 73-year-old male patient who "collapsed and dropped dead" two days following administration of elasomeran/imelasomeran) (as dose 4). There was no medical history or concomitant medications reported. An autopsy was being performed but cause of death was not yet available at the time of report. Advanced age is noted as a confounder. No other details were provided. According to WHO-UMC causality assessment, this case is assessed as Unassessable, due to insufficient information.

There was no trend observed for reported events. TTO for fatal cases with elasomeran/imelasomeran varied from 0 to 29 days post-vaccination; average TTO was 11.0 days (SD 10.6). Most of the cases with fatal outcome were strongly confounded by medical history and the advanced age of this population.

Cases in Elderly Patients After Receiving Booster with elasomeran/davesomeran

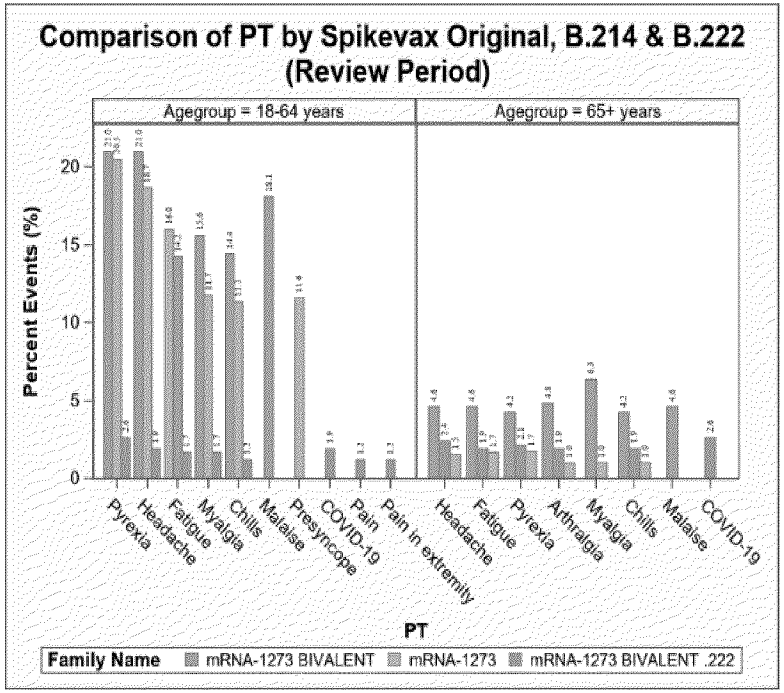
During this reporting period, 710 cases (2,265 events, of which 75 were serious) were reported in the elderly 65 years and older with elasomeran/davesomeran, of which 44 (6.2%) were assessed as serious, 464 (65.4%) cases were medically confirmed, and three cases (0.4%) reported a fatal outcome. Cases were disproportionately reported in females compared to males (51.3% vs 35.1%, respectively), and a majority were reported from the United States (96.2%), followed by Canada (2.1%), and Puerto Rico (1.1%). These cases reported a median age of 73.0 years, with a range from 65.0 years to 100.0 years. A large majority of these cases were reported spontaneously (99.4%).

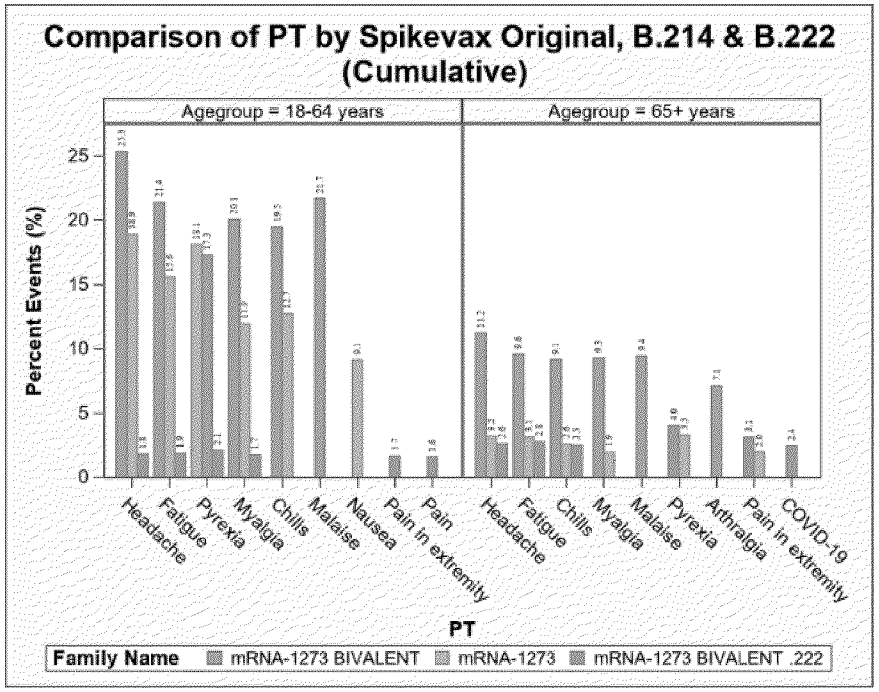
In this reporting interval, most events were reported after the fifth dose (19.4%) and the fourth dose (15.2%). This is expected as most patients receiving the bivalent booster have already received three or four previous doses. There was no dose information provided for 64.1% of reported events. Events were most frequently reported within 3 days of vaccination, regardless of vaccine dose. Case reports in the elderly represented 30.2% of all elasomeran/davesomeran (Original/BA.4/5) cases (2,348 cases) across all age groups in this reporting period, and serious cases in the elderly comprised 37.0% of all elasomeran/davesomeran serious cases (119 cases) in all age groups during the reporting period.

The most frequently reported events in the elderly who received elasomeran/davesomeran were representative of expected reactogenicity and were similar to those reported after elasomeran and in the general population. As elasomeran/davesomeran was more recently authorized, the data are limited.

Comparison of preferred terms (PT) among elderly and non-elderly by elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran showed a higher proportion of PTs were reported in elasomeran among non-elderly compared to elderly in the reporting interval and cumulatively. This was consistent with expected reactogenicity for elasomeran. Of note, is the reporting of COVID-19 infection in the elderly who received elasomeran/davesomeran (Figure 16-20).

Figure 16-20. Overview of Most Frequently Reported MedDRA Preferred Terms (PT) Comparing Elderly (≥65 years) and non-elderly (<65 years) for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran (Review Period and cumulative)





Serious Cases After Receiving Booster Dose with elasomeran/davesomeran)

In this review period, 44 serious cases (75 serious events) were reported in elderly patients receiving a booster dose with elasomeran/davesomeran). Of these 44 serious cases, 45.5% of cases were medically confirmed, and three cases had fatal outcomes.

Cases were disproportionately reported in females (26; 59.1%) than males (18; 40.9%), though overall case counts were low. These serious cases reported a median age of 73.5 years (range from 65.0 years to 90.0 years).

The event terms reported most frequently in the elderly in serious cases after elasomeran/davesomeran were consistent with expected reactogenicity, except for atrial fibrillation (5 events). Medical review of these cases found the event was strongly confounded by concomitant medications and the patients' medical histories, which described comorbid cardiovascular conditions such as underlying ECG abnormalities, hypertension, and recent bypass surgery.

Among serious cases during the reporting period, events were most frequently reported after dose 5 (72 events), followed by dose 4 (28 events). A high proportion (123; 54.7%) of serious cases were missing dose information. Events in serious cases occurred on average within two days of vaccination.

Overview of Fatal Cases with elasomeran/davesomeran

During the reporting interval, there were three cases with fatal outcomes reported among elderly recipients of elasomeran/davesomeran). All three cases were reported spontaneously in the United States, disproportionately in males (66.7%) and none were medically confirmed. One case was reported after dose 5, while the other two cases did not report dose number. Time to onset for fatal cases with elasomeran/davesomeran was not reported. These three cases are described below.

[redacted]: This spontaneous reported case described an 86-year-old female patient who was found dead six days following administration of elasomeran/davesomeran (unknown dose). Her medical history indicated comorbid anxiety, treated with unknown medication, and chronic tobacco use. The patient reportedly experienced cardiac failure and fall at an unknown time after vaccination. Cause of death was reported as cardiac failure. History of smoking and advanced age are confounders. No other information was reported for proper medical assessment. This case is assessed using WHO-UMC causality assessment tool as Unassessable, due to insufficient information.

[redacted]: This case described a 79-year-old male patient who died 14 or 15 days (exact vaccination date unknown) following administration of elasomeran/davesomeran (unknown dose number). Seven to nine days following vaccination, the patient reported dyspnoea and was hospitalized. Clinical course of treatment and cause of death were not provided. Decreased appetite and feeling abnormal ("poor spirits"), and four days later had "heavy asthma" and died. There was no medical history, concomitant medications, cause of death, or details about clinical course of treatment reported. Advanced age is a confounder; this case contained no other information for assessment. This case is assessed using WHO-UMC causality assessment tool as Unassessable, due to insufficient information.

[redacted]: This case described a 79-year-old male patient who died 12 hours following administration of elasomeran/davesomeran (as dose 5). Medical history included hypercholesterolaemia, type 2 DM, and cardiovascular disorders such as CAD, hypertension, and coronary artery bypass. The patient reportedly experienced cardiac arrest the same day as vaccination and was asystolic upon arrival of the ambulance. He was treated with epinephrine and Cardiopulmonary resuscitation at home but died. No autopsy was performed, and no cause of death was provided. Multiple relevant comorbidities and advanced age are strong confounders.

There was no trend observed for reported events in fatal cases. Cases were strongly confounded by comorbidities and the advanced age of this population.

16.3.6.7.6.5. Discussion

Review of the data received during this review period showed that the most frequently reported AEs in the elderly were representative of expected reactogenicity for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and other vaccines, and remarkably, fewer AEs were reported in the elderly compared to the general population. The early data for the bivalents and safety in the elderly are reassuring. Similar age-related reactogenicity had also been reported for the Flu vaccines in the elderly. The high number of reported cases in the elderly from the United States, the UK, and Germany, may be associated with a recent COVID-19 vaccination campaign for elasomeran/imelasomeran and elasomeran/davesomeran Cases reporting COVID-19 still ranked prominently among serious cases in the elderly, including a cluster of cases from Austria which all reported COVID-19 and vaccination failure, but contained little other information for assessment. A majority of the other serious cases of COVID-19 in this reporting period contained insufficient information to ascertain symptomatology or severity of infection.

When reported, more events were reported after the booster dose compared to the primary elasomeran series. This is expected since most of the elderly would be expected to have received their primary elasomeran vaccination series in previous reporting periods.

Although more cases after elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran continue to be reported, there is no observed pattern of event terms or TTO differing from that seen after the primary series of vaccine doses in the elderly. A reduction in the number of cases with fatal outcome was noted during this review period, compared to the prior period. These fatal cases were strongly confounded by comorbid conditions and advanced age and were not suggestive of any safety concerns.

Also reported in the elderly were product administration (accidental underdose) and labeling issues. These may be related to a misunderstanding of the posology of the newly available elasomeran/davesomeran.

16.3.6.7.6.6 Conclusion

After careful review of all new safety data received during the reporting period and cumulatively in the elderly subpopulation, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in the elderly population remains favorable. The risk profile in the elderly will continue to be monitored using routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.7 Subpopulation Analysis: Children < 18 Years (incl adolescent and young children)

16.3.6.7.7.1 Source of the New Information

Information presented below includes analysis performed on cases received by the MAH from 19 Jun 2022 to 17 Dec 2022 for the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 17 Dec 2022, and for the PBRER reporting period (19 Jun 2022 to 17 Dec 2022).

16.3.6.7.7.2. Background Relevant to the Evaluation

In addition to approval in adults over 18 years, elasomeran has received approval under EUA (or similar international public health measures) for age groups 6 months to17 years as of 17 Jun 2022. Prior to this date and during the reporting period, elasomeran received approval under EUA (or similar international public health measures) for age groups 6 years to 11 years. As is the case for

all drugs and vaccines, it is of high importance to keep the safety profile of this pediatric subgroup under close monitoring.

In the context of subpopulation analyzes, ModernaTx, Inc., continues to evaluate topics of interest such as myocarditis and pericarditis identified as being of higher risk n children. This topic is discussed in detail in a Section 16.3.1.2 of this PBRER report.

16.3.6.7.7.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB for the PBRER reporting period (19 Jun 2022 to 17 Dec 2022) for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran using the search criteria "Age groups <18 years", "Age group 0 to 5 months", "Age group 6 months to 5 years", "Age group 6 to 11 years" and "Age group 12 to 17 years." This age group collectively is referred to as the pediatric group.

A review of pediatric cases associated with elasomeran elasomeran/imelasomeran and elasomeran/davesomeran was performed by age group for neonates, infants, children, and adolescents. Data are presented and analyzed for the age groups and for children taking more than two doses (e.g., elasomeran as the primary series and/or booster, elasomeran/imelasomeran booster, or elasomeran/davesomeran booster. If no designation is provided, then data are associated with elasomeran

Pediatric cases are summarized cumulatively and for the reporting period where appropriate.

16.3.6.7.7.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Appendix 11.26 contains details about the serious cases involving children.

Cumulative Overview of Cases in Children <18 Years of Age

Cumulatively, there were 10,080 cases (1,224 serious and 37 fatal cases) with 21,597 events 2,920 serious events) reported in children <18 years of age. Of these total cases, 8,153 cases were medically confirmed. When gender was known more cases were reported in females (51.7%; 5,213 cases) compared to males (42.8%; 4,315), with small proportion of cases (5.5%; 552 cases) having no gender reported. The mean age was 13.8 years (SD: 4.6) and median age was 16.0 years (min: -1.0/max: 17.0). Majority of these cases were received from regulatory authorities (73.5%; 7,404 cases), with highest number of cases reported in United States (50.0%; 5,041 cases), EEA

(22.6%; 2,282 cases), Asia (11.4%;1,153 cases) followed by Latin America (7.0%; 708 cases) and Australia (5.7%; 570 cases).

A cumulative overview of the Top 10 MedDRA PTs by event counts in children < 18 years of age is presented below in Table 16.163. The most frequently reported MedDRA PTs in children < 18 years of age were Product administered to patient of inappropriate age followed by Pyrexia and Headache. It should be noted that PT 'No AE' (4.9%; 1,050 events cumulatively) is not included in order to maintain the most informative display of AEs.

Table 16.163 Cumulative Summary of Top 10 MedDRA Preferred Terms (PTs) by Event count for Children < 18 Years of Age by Frequency

PT	Total Events (N)	Total Events (%)
Product administered to patient of inappropriate age	4,632	21.4
Pyrexia	1,435	6.6
Headache	933	4.3
Fatigue	452	2.1
Nausea	377	1.7
Vaccination site pain	376	1.7
Pain	359	1.7
Vomiting	347	1.6
Myalgia	339	1.6
Chest Pain	336	1.6

MedDRA – Medical Dictionary for Regulatory Affairs, PT- Preferred Term.

Cumulative Overview of Cases in Children < 18 Years of age After a Third Dose or Booster Dose of elasomeran

Cumulatively as of 17 Dec 2022, there were 230 cases (of which 26 were serious and one was fatal) with total of 460 events (82 Serious events) reported in children <18 years of age that received booster dose with elasomeran. Of these total 230 cases, 177 cases were medically confirmed. When gender was known, more cases were reported for females (54.3%;125) compared to males (40.0%; 92 cases), with small proportion of case (5.7%; 13 cases) having no gender reported. The mean age was 11.3 years (SD: 5.5) and median age was 13.0 (min:0.0/ max:17.0).

Overview of Cases for the Reporting Period (19 Jun 2022 to 17 Dec 2022) for Children < 18 Years of Age:

During the reporting period, a total of 2,535 cases (including 426 serious, 12 fatal cases) with total of 6,784 events (887 serious events) were reported, in children <18 years of age. Of these total, 2,182 cases were medically confirmed. When gender was known, slightly more cases were reported in females (48.7; 1,234) compared to males (44.5; 1,127), with small proportion of cases (6.9%;174 cases), having no gender reported. The mean age was 11.0 (SD: 5.6) with a median age of 13.0 (min: 0.0 / max: 17.0). The majority of these cases were received from regulatory authorities (69.2%; 1,753 cases) with highest number of cases reported in Latin America (22.7%; 576 cases), Australia (22.0%; 558 cases), United States (20.5%;519 cases) followed by Asia (17.0%; 432 cases) and EEA (14.5%;367 cases).

Cases were most frequently reported in 12 to17-year-old (60.9%;1,543 cases) followed by 2 to 5-year-old (16.9%; 429 cases) children. The distribution of case reports by age is provided in Table 16.164.

Table 16.164. Distribution of Case Reports by Age group During Reporting Period (19 Jun 2022 to 17 Dec 2022)

Age Group	Review Period	
	# Cases	% of Cases
Months	40	1.6
6 months < 2 Years	170	6.7
02-05	429	16.9
06-11	353	13.9
12-15	753	29.7
16-17	790	31.2
Grand total	**2,535**	**100.0**

During reporting period, the most frequently reported events were 'Pyrexia', 'Expired product administered' and 'Headache'. The events were generally reactogenicity and associated systemic events. Product use related PTs are noted, however these very rarely also had AEs concurrently reported.

There were 170 reports that included an event of Product administered to patient of inappropriate age (170 events, 2.5% in reporting period vs 4,632 events 21.4% cumulative). Of these 170 reports, 169 were non-serious reports and 87 reports included PT No AE. PTs such as Vaccination error, Expired product administered, and Product storage error were otherwise most frequently reported,

often together. The remaining events (<=7 each) generally described reactogenticity and did not demonstrate any unusual pattern. There was only one serious report [redacted] which concerned a 15-year-old male with no medical history provided who experienced Hallucination (medically significant) approximately 1.5 months after elasomeran administered as third dose after primary vaccination (non-serious Product administered to patient of inappropriate age) completed with Pfizer vaccine. The patient also experienced coronavirus infection, with fever rising to 39.2°C and hallucinations. No further information was provided.

The 10 most frequently reported MedDRA PTs following elasomeran administration are provided in Table 16.165. It should be noted that PT 'No AE (7.5%; 506 events during reporting period) is not included in order to maintain the most informative display of AEs.

Table 16.165 Top 10 MedDRA PTs by event counts in Children Under 18 years During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Pyrexia	421	6.2
Expired product administered	270	4.0
Headache	254	3.7
Product storage error	242	3.6
Chest Pain	173	2.6
Medication error	173	2.6
Product administered to patient of inappropriate age	170	2.5
Fatigue	169	2.5
Nausea	153	2.3
Myalgia	149	2.2

During Reporting period, when dose number and TTO could be determined, events were most often reported within the first two days of vaccination (Table 16.166).

Table 16.166 TTO by Dose in Children Under 18 years During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 1	**Subtotal**	**1,556**	**22.9**
	0 days	878	12.9
	01-02	319	4.7
	03-04	54	0.8
	05-06	36	0.5
	07-13	104	1.5

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
	14-29	60	0.9
	30+	105	1.5
Dose 2	**Subtotal**	**1,342**	**19.8**
	0 days	636	9.4
	01-02	422	6.2
	03-04	68	1.0
	05-06	25	0.4
	07-13	42	0.6
	14-29	45	0.7
	30+	104	1.5
Dose 3	**Subtotal**	**203**	**3.0**
	0 days	97	1.4
	01-02	76	1.1
	03-04	1	0.0
	05-06	2	0.0
	07-13	8	0.1
	14-29	19	0.3
	30+	0	0.0
Dose 4	**Subtotal**	**50**	**0.7**
	0 days	29	0.4
	01-02	11	0.2
	03-04	2	0.0
	05-06	1	0.0
	14-29	2	0.0
	30+	5	0.1
Dose 5	**Subtotal**	**1**	**0.0**
	0 days	1	0.0
Unknown	**Subtotal**	**3,632**	**53.5**
	0 days	343	5.1
	01-02	94	1.4
	03-04	15	0.2
	05-06	14	0.2
	07-13	34	0.5
	14-29	24	0.4

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
	30+	54	0.8
	Event onset prior to first dose reported	5	0.1
	Missing	3,049	44.9
Grand total		**6,784**	**100.0**

Adverse Event Outcomes in Children < 18 Years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

The most frequently reported event outcomes in Children < 18 Years of age during reporting period was 'unknown', in (38.3%; 2,598 events), followed by 'Not recovered/Not resolved' in (26.6%; 1,805 events) and 'Recovered/Resolved' in (23.5%; 1,596 events) (Table 16.167).

Table 16.167 Adverse Event Outcomes in Children < 18 years of Age During the Reporting Period (19 June 2022 to 17 Dec 2022)

Event Outcome	Review Period	
	# Events	% of Total Events
Fatal	24	0.4
Not Recovered/Not Resolved	1,805	26.6
Recovered/Resolved	1,596	23.5
Recovered/Resolved with Sequelae	34	0.5
Recovering/Resolving	727	10.7
Unknown	2,598	38.3
Grand total	**6,784**	**100.0**

Details of Reports in the Age group 0-5 months During the Reporting period (19 Jun 2022 to 17 Dec 2022).

During this reporting period, the MAH received 40 cases (11 Serious and no fatal cases) with total of 115 events (including 27 serious events) in children 5 months of age or younger who have been vaccinated with elasomeran. Exposure to elasomeran by other means (eg, maternal exposure/lactation) is described in Section 16.3.5.1 and Section 16.3.5.2.

When gender was known, more cases were reported in females (42.5% ;17 cases) compared to males (35.0%;14 cases), with 9 cases (22.5%) having no gender reported. The mean age was 0.1 years (SD: 0.2) with a median age of 0.1 year (min: 0.0 / max: 0.4). The majority of these cases were received from regulatory authorities (77.5%; 31 cases).

Table 16.168 presents the Top 10 frequently reported events (by PT) for reporting period. It should be noted that PT 'No AE' (3.5%; 4 events) is not included in order to maintain the most informative display of AEs. The three reports with event Product administered to patient of inappropriate age involved different 5-month-old patients who received elasomeran with no resulting AE.

Table 16.168 Top 10 MedDRA PTs by event counts in Children 0-5 months of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT*	# Events	% of Total Events
Pyrexia	8	7.0
Exposure via breast milk	7	6.1
Headache	5	4.3
Chills	4	3.5
Foetal exposure during pregnancy	3	2.6
Product administered to patient of inappropriate age	3	2.6
Medication error	3	2.6
Fatigue	2	1.7
Diarrhoea	2	1.7
Malaise*	2	1.7

* The PTs of Abdominal pain, Rash, Dizziness, Constipation, Faeces discoloured, Lymphadenopathy, Restlessness, Atrial septal defect, Bradycardia neonatal, inflammation, COVID-19 immunization and Wrong product administered, each were also reported twice (1.7%; 2 events each) during Reporting period.

Of the 11 serious cases (30 events) received during this period, 8 involved fetal exposure during pregnancy and are discussed in Section 16.3.5.1. The remaining three cases most likely involved adult patients whose ages were miscaptured because based on the clinical circumstances, the patients are most likely adults (eg, histories of caffeine/alcohol consumption, appendectomy; AE of headache which a 2 day-old would not be able to communicate).

Details of Reports in the Age group 6 months to 5 years of Age During the Reporting period (19 Jun 2022 to 17 Dec 2022).

During this reporting period, the MAH received 599 cases (44 Serious and no fatal cases) with total of 1,585 events (including 95 serious events) in children 6 months to 5 years of age who have been vaccinated with elasomeran. Of the total cases, 532 cases were medically confirmed. When gender was known slightly more cases were reported in females (47.9%; 287 cases) compared to males (42.6%; 255 cases), with small proportion of cases (9.5%; 57 cases) having no gender reported. The mean age was 2.6 years (SD :1.3) with median age of 3.0 years (min:0.5/max: 5.2). The majority of these cases were spontaneous reports (76.0%; 455 cases).

Table 16.169 presents the Top 10 frequently reported events (by PT) for the reporting period. There were 32 non-serious reports (111 total events) that included an event of Product administered to patient of inappropriate age, and of the 32 reports, 26 included PT No AE. PTs Expired product administered, and Product storage error were the next most frequently reported PTs (19 each) and were reported together in 19 cases received from Israel. These were 19 of the 28 reports where PT No AE was reported. The remaining events were reported <=2 each and did not demonstrate any unusual pattern.

It should be noted that PT 'No AE' (22.5%; 357 events) is not included in order to maintain the most informative display of AEs.

Table 16.169 Top 10 MedDRA PTs by event counts in Children 6 months to 5 years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Expired product administered	234	14.8
Product storage error	223	14.1
Product temperature excursion issue	81	5.1
Poor quality product administered	79	5.0
Pyrexia	62	3.9
Medication error	59	3.7
Inappropriate schedule of product administration	55	3.5
Product administered to patient of inappropriate age	32	2.0
COVID-19 Immunization	20	1.3
Rash	16	1.0

The serious reports received during this period generally described events known to occur with elasomeran such as pyrexia, rash, vomiting or those commonly occurring in this population such as diarrhoea. Most serious events were reported once and did not demonstrate any pattern of concern. In some cases, such as [redacted] describing a 6-month-old male who experienced apnea within 24 hours of receiving elasomeran, ankyloglossia provided a plausible and more likely etiology for the event.

There were 10 reports describing serious events of seizure-type activity, and of these, 2 reported patients with a history of seizure disorders, 3 described TTO of 1-2 days post-vaccination but lacked information such as medical history, concomitant medications and clinical management necessary for proper assessment, one report [redacted] described febrile convulsion in a 17 year-old female 6 weeks post-vaccination, and one report [redacted] described a

seizure in a 2 year-old male after exposure via breast milk. Three other reports are presented below.

[redacted] **(WW Identifier** [redacted]**:** This is a regulatory case concerning a 1-year-old male patient with no reported medical history, who was hospitalized due to febrile convulsion. The patient had fever followed by convulsion on the night after receiving the first dose of elasomeran vaccine. The patient presented with cyanosis of limbs and face, both eyes slanted to the right and stiffness of limbs at the hospital. Clinical course, diagnostic tests and treatment details were not provided in the case. The event was resolving at the time of the report.

MAH Comment: Based on the temporal relationship, a causal association is possible, however febrile seizures are common in this age group.

[redacted] **(WW Identifier** [redacted]**):** This spontaneous case concerns a 4-year-old male patient, born prematurely at 24 weeks, who experienced febrile convulsion pyrexia, pain in extremity and vaccination site pain. Febrile convulsion occurred 1 day after vaccination when the patient was observed with unusual breathing with shaking and voided during the episode. The event recurred when he woke up from a nap. His head was hitting the wall, with eyes rolled back and stiffness which lasted for 5-12 mins. He started foaming at the mouth, unresponsive, barely moving and had voided during the episode. Emergency services was called and transported to hospital. Patient symptoms were consistent with complex febrile seizures vs lowered seizure threshold secondary to fever following covid vaccination. He is back to neurological baseline with normal parameters. He's been admitted for observation. On an unknown date Body temperature reported as 38.6.

MAH Comment: Based on the temporal relationship, a causal association is possible, however premature birth is a risk factor and febrile seizures are common in this age group.

[redacted] **(WW Identifier** [redacted]**):** This regulatory authority case concerns a 3.9-year-old male patient, with no medical history reported, with febrile convulsion, seizure and pyrexia less than 24 hours after receiving the second dose of elasomeran. Patient developed fever at night and the febrifuge was given firstly. after the second time of fever, the child developed convulsion with a whey-face, was transferred to the hospital, and has discharged.

WHO-UMC Causality: Based on the temporal relationship, a causal association is possible, however febrile seizures are common in this age group.

Other noteworthy serious cases are presented below.

[redacted] **(WW Identifier** [redacted]**):** This is a report of anaphylaxis in a 9-month-old female. Refer to Section 16.3.1.1 for additional details.

[redacted] **(WW Identifier:** [redacted]**):** This spontaneous case concerns a 4-year-old male with no medical history reported, who experienced meningitis within one week of elasomeran vaccination. Lumbar tap done on an unknown date showed active inflammation with negative bacterial culture and viral screening. No further information on risk factors, detailed clinical course, investigations, treatment of the events was available in the report.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** This Regulatory authority case concerns 3 years old female child, with recent respiratory infection, who experienced unexpected immune thrombocytopenia 7 days after first dose of elasomeran vaccine. The patient had associated hematomas and petechiae, and response to IVIg was reported. Leukemia and Thrombotic Thrombocytopenic Purpura (TTP) were ruled out.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**:** This is a regulatory authority case of product administered to patient of inappropriate age for a 4-year-old female with no medical history reported who experienced vomiting and dizziness requiring hospitalization 11 days after receiving the second dose of the elasomeran vaccine. It was reported that 8 days after vaccination, the patient started to show decreased mobility and 3 days later she experienced vomiting and dizziness. The patient was taken to the hospital and was subsequently admitted for a total of 5 days. CT of the brain showed 'mild brain swelling' and lumbar puncture showed increased pressure (anterior pressure of 27 cm H_2O and posterior pressure of 8 cm H_2O). Various examinations (unspecified) were conducted; however, the cause of increased brain pressure could not be identified. No further details were provided.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history,

concomitant medications, clinical course and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** This is a regulatory authority case concerning a 4-year-old, male patient with no reported medical history who experienced rhinorrhoea, oropharyngeal pain, pyrexia and abdominal pain approximately 4 days after Dose 2 elasomeran. An echocardiogram was performed resulted in suspected Kawasaki like disease, myocardial ischemia, suspected "MIS-C". Due to high fever, high white blood cell count and high C-reactive protein patient was admitted to hospital and treated with antipyretics, aspirin and intravenous immunoglobulin.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** This regulatory authority case concerns a 4-year-old male patient, with no reported medical history, who experienced acute disseminated encephalomyelitis and confusional state approximately 24 days after receiving a dose of elasomeran (reported as booster dose). Hospitalization details including clinical course, diagnostic evaluation, concomitant medications, and treatment given was not reported. The outcome was reported as not recovered.

MAH Comment: Acute Disseminated Encephalomyelitis typically occurs after a viral or bacterial infection the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation. Furthermore, given the extended TTO, this case is considered unlikely related.

Details of Reports in the Age group 6 to 11 Years of Age During the Reporting period (19 Jun 2022 to 17 Dec 2022).

During the reporting period, the MAH received 353 cases (86 serious cases and 2 fatal cases) with total of 728 events (157 serious events) for 6 to11-year-old children who have been vaccinated with elasomeran. Of the total cases, 339 cases were medically confirmed. When gender was known, the number of cases reported in females (48.7%; 172 cases) were slightly higher compared to males (45.9%; 162 cases), with a small proportion of cases (5.4%, 19 cases) having no gender reported. The mean patient age was 8.7 years (SD: 1.8) with median age of 9.0 years (min: 6.0/ max: 11.0). The majority of these cases were received from regulatory authorities (75.9%; 268 cases).

Table 16.170 presents the Top 10 frequently reported events (by PT) for reporting period. There were 25 non-serious report that included an event of Product administered to patient of inappropriate age, and of the 25 reports, 12 were from the Australia Health Authority and also included Vaccination error, the next most frequently reported term in these 25 cases. Only one of the TGA reports also included an additional event: Injection site reaction. Overall, the majority of the 25 reports did not describe an AE and no unusual pattern was identified. It should be noted that PT 'No AE' (9.1%; 66 events) is not included in order to maintain the most informative display of AEs.

Table 16.170 Top 10 MedDRA PTs by event counts in Children 6 to 11 years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Pyrexia	74	10.2
Medication Error	61	8.4
Chest Pain	31	4.3
Product administered to patient of inappropriate age	25	3.4
Wrong product administered	24	3.3
Rash	21	2.9
Expired product administered	20	2.7
Vomiting	18	2.5
Headache	17	2.3
Vaccination error	17	2.3

Serious and Fatal cases in Children 6-11 Years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022

During the reporting period MAH received 86 serious cases (including two fatal cases) with 178 events (157 serious events) in this age group.

Two Fatal cases are summarized below. ([redacted], [redacted]) are summarized below:

[redacted] (WW Identifier AR-[redacted]): This regulatory case concerns a 10-year-old male patient with a prior history of fainting requiring hospitalization, who suddenly died and was diagnosed with a cardiorespiratory arrest. The event occurred approximately 7 days after the third dose of elasomeran. Information regarding clinical evaluation, diagnostic tests, treatment provided, or autopsy reports has not been disclosed.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation., including autopsy results. The prior fainting spell requiring hospitalization suggests a pre-existing serious condition may be contributory. Causality is assessed as conditional.

[redacted] **(WW Identifier AR-**[redacted]**):** This regulatory authority case concerns a 10-year-old male patient, with no medical history reported, who died 5 days after receiving a booster dose of elasomeran. Death was reported as the only event and cause of death was unknown at the time of the report. It was not stated if an autopsy was performed. No further relevant clinical information was available.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation., including autopsy results. Causality is assessed as conditional.

The serious reports received during this period generally described events known to occur with elasomeran such as nausea, vomiting, rash or those commonly occurring in this population. Most serious events were reported once and did not demonstrate any pattern of concern.

During this reporting period, there were 10 cases of myocarditis and 1 case of pericarditis. Refer to Section 16.3.1.2. Cases of chest pain and chest discomfort were reviewed to identify potential cases of myocarditis, myopericarditis, or pericarditis where these more clinically significant events were not reported. There were no cases of chest pain or chest discomfort which yielded evidence of increased troponin, electrocardiogram, echocardiogram, or MRI abnormalities that would help establish a level of diagnostic certainty for myocarditis, myopericarditis, or pericarditis.

Other noteworthy serious cases are presented below.

[redacted] **(WW Identifier** [redacted]**:** This is a regulatory case concerning a 10-year-old female patient with no reported medical history who experienced immune thrombocytopenia approximately two weeks dose 1 elasomeran. The patient developed bleeding and bruising with a platelet count 7000/mm^3. Two weeks later was she was hospitalized with a platelet count of 5000/mm3 and received treatment with IVIg 1g/kg/day for two days with improvement in platelet count two days later to 47000/mm3 and was discharged home. One week later the platelet count was 21000/mm^3 and she was treated with prednisolone. After a week, the platelet count was 226000/mm^3 and the prednisolone dose was reduced.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**:** This is a regulatory case concerning an 11-year-old male patient with no reported medical history, who experienced livedo reticularis which occurred approximately 2 months after receiving the 1st dose of COVID-19 vaccine elasomeran. The patient had a suspected allergy to the excipient Tris contained in the elasomeran vaccine, leading to livedo annularis in arms and legs (generalized reticular pattern). Lymphocyte Transformation Test for Tris was positive; IgE was 1280. Fluocinolone 0.025%+ Neomycin 0.35%, (Fradiomycin) ointment was given as treatment. Outcome was reported as resolving.

MAH Comment: Based on the temporal association and laboratory evaluation, a causal association is possible.

[redacted] **(WW Identifier** [redacted]**):** This regulatory authority case concerns a 9-year-old, female patient with no medical history reported who experienced febrile convulsion, pain, induration and pyrexia 1 day after dose 3 elasomeran vaccine. No information was available regarding the first and second vaccine doses. It was reported that the patient experienced local reaction, seizure, and fever. The diagnosis was febrile seizure.

MAH Comment: Febrile seizures occur commonly in children. Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** Regulatory authority report of a 9-year-old female patient with no medical history reported who cerebrovascular accident 33 days after elasomeran vaccine. It was also reported that the patient "had not received previous dose and another vaccine. Patient received booster dose." The patient had dizziness, right hemiparesis, dysarthria and fall without loss of consciousness or sphincter control. No further information on clinical course, investigations and treatment received was available in the report. Outcome of the event was reported as resolved. The benefit-risk relationship of elasomeran vaccine is not affected by this report.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation. Furthermore, it is unclear which vaccinations she received thus the case is unassessable.

[redacted] **(WW Identifier** [redacted]**):** This regulatory case concerns a 9-year-old, female patient with no reported medical history, who experienced seizure and confusional state the same day of dose 3 elasomeran. Details of concomitant medications, medical history, clinical course, and treatment were not provided. The events have resolved at the time of the report.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

[redacted] **(WW Identifier** [redacted]**):** This is a regulatory authority case concerning a 6-year-old female patient with no reported medical history who experienced epileptic seizure the same day of dose 3 elasomeran vaccine administration. It was reported that the patient experienced a convulsion with loss of consciousness. At the time of the report the patient was hospitalized. No further clinical information was available.

MAH Comment: Based on the temporal association, a causal association is possible, however the report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course, and diagnostic evaluation.

Details of Reports in the Age group 12 to 17 years of Age During the Reporting period (19 Jun 2022 to 17 Dec 2022).

There were 1,543 cases (including 285 serious and 10 fatal cases) with total of 4,356 events (608 serious events) reported in the children of 12–17-year age group, representing 60.9% of cases in children (<18 years) in this reporting period. Of the total cases, 1,297 were medically confirmed. When gender was known, more cases were reported in females (49.1%; 758 cases) compared to males (45.1%; 696 cases), with small proportion of cases (5.8%; 89 cases) having no gender reported. The mean patient age was 15.0 years (SD:1.8), with a median age of 16.0 years (min:12.0/max:17.0). The majority of these cases were received from regulatory authorities (85.0%; 1,311 cases) and in particular, 112 of 113 non-serious events of inflammation were from cases from the Argentina health authority.

There were 110 non-serious reports that included an event of Product administered to patient of inappropriate age. There was only one serious report [redacted], presented here again for completeness, which concerned a 15-year-old male with no medical history provided who experienced Hallucination (medically significant) approximately 1.5 months after elasomeran administered as third dose after primary vaccination (non-serious Product administered to patient of inappropriate age) completed with Pfizer vaccine. The patient also experienced coronavirus infection, with fever rising to 39.2°C and hallucinations. No further information was provided. PT: No AE was included in 51 of the remaining 109 non-serious cases. Of the total 110 reports, 41 from the Australia Health Authority also included Vaccination error, the next most frequently reported term. Overall, the majority of the 110 reports did not describe an AE and no unusual pattern was identified in those that did. The 3 most frequently reported PTs in this age group were 'Pyrexia', and 'Headache' and 'Fatigue' which are consistent with expected events following vaccinations including elasomeran (Table 16.171).

Table 16.171 Top 10 MedDRA PTs by event counts in Children 12 to 17 years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

PT	# Events	% of Total Events
Pyrexia	277	6.4
Headache	227	5.2
Fatigue	146	3.4
Nausea	139	3.2
Chest pain	139	3.2
Myalgia	132	3.0
Vomiting	114	2.6
Inflammation	113	2.6
Product administered to patient of inappropriate age	110	2.5
Dizziness	108	2.5

Serious and Fatal Cases in Children 12-17 Years of Age During the Reporting Period (19 Jun 2022 to 17 Dec 2022)

During the reporting period, MAH received 285 Serious cases (10 fatal cases) with 1,037 events (608 serious events) in this age group.

The ten fatal received cases in this reporting period are summarized below:

[redacted] **(WW Identifier AR-[redacted]):** This regulatory authority case of a 13-year-old female, with history of premature birth, Sjogren's

syndrome, rheumatoid factor 512 IU/ml 6 months prior to vaccination, family history of arterial hypertension, who experienced subarachnoid hemorrhage, intraventricular hemorrhage and fatal cerebral hemorrhage with symptoms first occurring 2 days after first dose of elasomeran. CT informed showed massive ventricular hemorrhage on the right side with dilation of the atrium and temporal horn, slight deviation to the left, of the middle line and hemorrhage of the fourth ventricle. The patient underwent surgery 12 days later for evacuation of a hematoma and hemodynamic decompression. The patient died approximately two weeks after vaccination. The reported cause of death were intraventricular haemorrhage and subarachnoid hemorrhage, cerebral haemorrhage. It is unknown if an autopsy was performed

MAH Comment: The patient has multiple underlying conditions including premature birth, Sjogren's disease/rheumatic disorder and family history of hypertension that could predispose to the reported intracranial events and causality is assessed as unlikely.

[redacted] **(WW Identifier AU-**[redacted]**):** is consumer report from Australia of a 14-year-old female patient, with no medical history reported, who experienced the fatal event of immunization reaction. The event occurred on an unknown date after receiving a dose of elasomeran vaccine. Treatment information was not provided. The reported cause of death was death from an adverse vaccination reaction; however, it is unknown if an autopsy was performed. The event was considered related to the product per the reporter's assessment. No further information was provided.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier AU-**[redacted]**)**: is an HCP report from the Australia health authority of a 14-year-old female patient with no reported medical history, who experienced the fatal events of brain injury with brain herniation, cardiac arrest, multiple organ dysfunction syndrome, headache, dizziness, nausea and pyrexia after receiving a dose of elasomeran on an unknown date. It is not known if an autopsy was performed. No further information was provided.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier** [redacted]**)**: is a consumer report from the Sweden health authority of a 13-year-old male patient, with history of heart surgery at 3 days old, "heart valve operation", thymectomy and liver transplantation, who experienced fatal endocarditis, sepsis and immunodeficiency with death occurring approximately 4 months after the second dose of elasomeran vaccine. The reported cause of death was liver transplantation. It is unknown if an autopsy was performed. No further information was provided.

MAH Comment: There is an extended TTO of about four months and the patient's extensive cardiac and surgical history compounded by likely immunodeficiency from thymectomy provide plausible alternate etiologies for the events, and causality is assessed as unlikely.

[redacted] **(WW Identifier AU-**[redacted]**):** A 15-year-old patient of unknown gender experienced a fatal event of "AE" following immunization' following vaccination with elasomeran and Comirnaty. No further information was provided including vaccination/event dates, medical history, concomitant medications, clinical course or whether autopsy was performed.

MAH Comment: The report is lacking important information for proper assessment including treatment/event dates, details of medical history, concomitant medications, clinical course and diagnostic evaluation, and thus is unassessable.

[redacted] **(WW Identifier AU-**[redacted]**):** A 14-year-old female patient experienced a fatal event of immunization reaction following vaccination with elasomeran. No further information was provided including vaccination/event dates, medical history, concomitant medications, clinical course or whether autopsy was performed.

MAH Comment: The report is lacking important information for proper assessment including details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier PH-PH**[redacted] A 16-year-old female patient experienced diarrhoea and vomiting 5 months after the 2nd dose of the elasomeran with an outcome of death on an unspecified date. No other information was provided such as medical history, concomitant medications, clinical course, treatment, or autopsy results, if performed.

MAH Comment: Minimal information is provided, however given the extended TTO of 5 months, a causal association is unlikely.

[redacted] **(WW Identifier PH-PH[redacted]:** A 15-year-old male patient experienced dyspnoea and COVID-19 on unknown dates after receiving a dose of elasomeran vaccine. The reported cause of death was reported as difficulty of breathing and COVID-19, however, it is unknown if autopsy was performed. No other information was provided such as medical history, concomitant medications, or clinical course.

MAH Comment: The report is lacking important information for proper assessment including treatment/event dates, details of medical history, concomitant medications, clinical course, and diagnostic evaluation. Given that COVID-19 is attributed as cause of death, a causal association with elasomeran is unlikely.

[redacted] **(WW Identifier IT-[redacted])** is a consumer report concerning a 16-year-old male with no medical history reported, who reportedly got sick and died (PT Illness) after an unspecified dose of elasomeran vaccine. It was reported that after the ModernaTx, Inc. vaccine, the patient began to get sick. Death occurred on an unknown date. The reported cause of death was Illness. The exact course of event of illness (began to get sick) which led to the fatal outcome was not disclosed. It is unknown if an autopsy was performed. No further clinical information including medical history, concomitant medications and vaccination dates was provided.

MAH Comment: The report is lacking important information for proper assessment including description of the AE, treatment/event dates, details of medical history, concomitant medications, clinical course and diagnostic evaluation, and the case is unassessable.

[redacted] **(WW Identifier: SE-[redacted]):** is a consumer report concerning a 13-year-old male patient with prior cardiac surgery 3 days after birth and liver transplant at 6 months of age who experienced serious events of sepsis, hepatic failure, renal failure, cardiac arrest, cerebrovascular accident, brain injury and endocarditis on an unknown date after 2 doses elasomeran and subsequently died from endocarditis nearly 4 months after Dose 2 and 5 months after Dose 1. Death occurred on hospital day 67 after supportive care was discontinued. Causes of death were reported also as endocarditis and sepsis.

MAH Comment: The minimal information provided suggests that the patient experienced complications due to endocarditis which is known to occur in children with a history of prior cardiac surgery. WHO-UMC causality is assessed as unlikely

The serious reports received during this period generally described events known to occur with

elasomeran such as pyrexia, myalgia, vomiting and headache. Most serious events were reported once and did not demonstrate any pattern of concern.

There were 80 events of syncope (78 serious) of which 50 serious events of syncope containing minimal information were from the Australia health authority, 8 serious events of syncope containing minimal information were from the Argentina health authority, and 11 serious events of syncope from a literature report containing minimal case level information.

During this reporting period, there were 41 cases of myocarditis and 22 cases of pericarditis and 8 myopericarditis cases. Refer to Section 16.3.1.2. Cases of chest pain and chest discomfort were reviewed to identify potential cases of myocarditis, myopericarditis, or pericarditis where these more clinically significant events were not reported. Most cases of chest pain or chest discomfort yielded no evidence of increased troponin, electrocardiogram, echocardiogram, or MRI abnormalities that would help establish a level of diagnostic certainty for myocarditis, myopericarditis, or pericarditis. One noteworthy report is presented below

[redacted] **(WW Identifier** [redacted]**:** This is a health authority report from an HCP which describes a 12-year-old male patient who experienced chest tightness (PT: Chest pain) and was hospitalized 4 days after dose 2 elasomeran and 74 days after dose 1 elasomeran. No medical history or concomitant medications were reported. The patient had normal fibrin D-dimer and elevated troponin (129.9 ng/dL) on day 3 and elevated CRP and cardiac enzyme "at Leptomeningeal disease" on day 4. After admission, the symptoms subsided spontaneously. Follow-up troponin-I and ECG showed no ischemic change with improved "lab data". Echocardiography revealed good cardiac function. The patient was subsequently discharged.

MAH Comment: Based on the clinical presentation and plausible temporal association, WHO-UMC causality is assessed as possible with further information such as medical history and concomitant medications necessary to exclude disease or other drugs and attribute a more compelling causal association.

Other noteworthy serious cases are presented below.

[redacted]**(WW Identifier:** [redacted] is a regulatory authority report with follow-up on a 13-year-old female with no medical history or concomitant medications reported, who experienced thrombocytopenia, neutropenia, COVID-19, gingival bleeding, iron deficiency, haematoma, serum ferritin decreased, epistaxis, fatigue, platelet morphology abnormal and HMB 1 month and 19 days after vaccination with Dose 2 of elasomeran and requiring

hospitalization. The outcome of the events was reported as unknown.

MAH Comment: Important data needed for proper evaluation are missing including full medical history, detailed diagnostic evaluation, and clinical course. Evaluation is confounded by concurrent COVID-19. The case is unassessable.

[redacted] **(WW Identifier** [redacted] **):** This was received from a health authority describing a 17-year-old-female with no reported medical history or concomitant medications who received elasomeran Dose 2 and approximately 9 months later experienced endocarditis. No treatment information was provided.

MAH Comment: While minimal information is provided, the extended TTO of 9 months following vaccination makes a causal association unlikely.

[redacted] **(WW Identifier:** [redacted] is a regulatory authority report concerning a 16-year-old female with medical history of factor V Leiden heterozygote and concomitant use of drospirenone, who experienced the serious (reported as medically significant) events of HMB, menstruation irregular and dysmenorrhoea almost two months after dose 2 elasomeran.

MAH Comment: Minimal information is provided, however the history of factor V Leiden heterozygote and concomitant drospirenone offer more likely alternate etiologies for the events which are considered unlikely related.

Reports in Children < 18 years Who Received Booster with elasomeran/imelasomeran During Reporting period (19 Jun 2022 to 17 Dec 2022)

During the reporting period, 27 cases (22 medically confirmed, 2 serious, and no fatal cases) with 63 events (4 serious events) were reported in Children < 18 years of age who received elasomeran/imelasomeran. When gender was known, more cases were reported in males (48.1%;13 cases) compared to females (37.0%;10) with small proportion of cases (14.8%;4) having no gender reported. The mean patient age was 12.3 years (SD: 5.7) with median age of 15.0 years (min :0.0 /max :17.0). The majority of these cases were reported in children 12-17-years of age (77.8%; 21 cases).

Of the 27 cases, 25 were non-serious and involved product use issues with no AE reported, or describe events known to occur with elasomeran such as fever, pain and malaise. One of the 25 non-serious cases and one serious case likely involved adult patients whose age was miscaptured.

The other serious case [redacted] is a regulatory authority report concerning a 16-year-old male with no reported medical history, who experienced the medically significant event of dizziness, tension headache, and palpitations within one day of elasomeran with no indication of hospitalization. Given the plausible TTO, a causal association is possible with the events likely representing reactogenicity.

Reports in Children <18 years Who Received Booster with elasomeran/davesomeran During Reporting period (19 Jun 2022 to 17 Dec 2022)

During this reporting period, 65 Cases (of which 57 were medically confirmed, 3 serious and no fatal cases) with 160 events (5 serious events) were reported in children <18 years of age who received elasomeran/davesomeran. When gender was known slightly more cases were reported in males (38.5%; 25 cases) compared to females (33.8%; 22 cases), and (27.7% ;18 cases) having no gender reported. The mean age was 9.4 years (SD :4.9) with median age of 11.0 (min:0.0/max:17.0). The majority of these cases were reported in children 12-17 years of age (46.2%; 30 cases).

Of the 65 cases, 62 were non-serious and involved product use issues with no AE reported, described events known to occur with elasomeran or contained insufficient information to draw further conclusions.

Three serious cases ([redacted], [redacted], [redacted]) are summarized below.

[redacted] **(WW Identifier** [redacted]**:** This regulatory authority case concerns a 17-year-old female patient with no reported medical history who experienced chest pain (reported as medically significant) 1 day dose 4 elasomeran/davesomeran_bivalent vaccine. There was no dyspnea, no palpitation, no fever, or cough. No abnormality was found on electrocardiogram and blood tests. There is no indication that the patient was actually admitted

MAH Comment: Based on the temporal association, a causal association is possible and very probably reactogenicity.

[redacted] **(WW Identifier** [redacted]**):** Concerns a 14-year-old male with no medical history reported, who experienced serious pyrexia and chest pain 1 day after elasomeran/davesomeran_vaccination as Dose 4. One day after vaccination, the patient reportedly was admitted for complaints of chest pain, chest distress, suspected cardiogenic chest pain with pain index of 8 points. Troponin value was slightly elevated on the first day and back to normal

values afterward. Creatine phosphokinase was elevated at 195 IU/L with other labs unremarkable. An ECG was performed and reported as abnormal but actual results were not provided. After one day patient was transferred to another hospital and discharged within 3 days with chest pain reported as resolved.

MAH Comment: According to the Brighton Collaboration case definition this case is considered Level 2 for myocarditis. According to the CDC case definition this case is considered Probable, and according to the WHO causality assessment this case is considered possible. The report is lacking important information including medical history, concomitant medications, actual ECG results.

[redacted] **(WW Identifier:** [redacted]**:** Concerns a 13-year-old male with no medical history reported, who experienced chest pain, dizziness and pyrexia one day after elasomeran/davesomeran vaccination as Dose 3. Laboratory results provided showed normal Troponin and negative D-dimer, but elevated CRP with other lab results unremarkable. Electrocardiogram was reported as normal. Patient had high blood pressure and elevated heart rate and was subsequently discharged.

MAH Comment: According to the Brighton Collaboration case definition this case is considered Level 5 – Not a case of myocarditis. According to the CDC case definition this case is considered "Not a case". Given that this is not considered a case of myocarditis the WHO causality assessment was not conducted. Events reported by the patient more likely represent reactogenicity events.

16.3.6.7.7.5. Discussion

Over three-quarters (83.2%) of cases reported in children under the age of 18 years during this reporting period were non-serious and most of the cases (1,543; 60.9%) were reported in adolescents 12 – 17 years. In the 0- 5 months age group, there were 40 cases with most commonly reported events of pyrexia, exposure via breast milk and headache. In 6 months to 5 years (599 cases) product use related events were mostly reported. Among 6 to 11 years age group there were 353 cases where vaccine was administered (as opposed to exposure through breast milk) with AEs typical of reactogenicity predominating. In the12-17-year age group the most frequently reported events of pyrexia, headache and fatigue were in line with reactogenicity of elasomeran, however events of myocarditis/pericarditis/myopericarditis (71 events, 1.6 %) (myocarditis is an Important Identified Risk for elasomeran) continue to be received in the 12–17-year-old age group.

Reports of events following booster doses with elasomeran/imelasomeran and elasomeran/davesomeran were mainly non-serious, involved product use issues or described events associated with vaccine administration or those commonly occurring in this population.

The MAH has observed a marked decrease in the events of Product administered to patient of inappropriate age received during this period (170 events, 2.5%) compared to all prior intervals (4462 events, 30.1%), driving the cumulative reporting rate downwards (4,632 events 21.4%). The vast majority of reports were non-serious and very often did not have associated AEs. When AEs were infrequently reported, they were typically reactogenicity, or other events that did not demonstrate any unusual pattern. With the approval of conditional marketing authorization in adolescents and now in children 6 months-11 years, use will no longer be considered inappropriate in this age group. With greater global awareness and vaccine availability, the MAH expects an increasing amount of information to be received in coming months about the safety of the product in this subpopulation to enable the MAH to further inform vaccination practice.

Overall, the reports received during this period generally described events that were representative of reactogenicity and other systemic events such as pyrexia, headache, fatigue, malaise, and chills and were similar across age groups.

16.3.6.7.7.6 Conclusion

After careful review of all new safety data received during the reporting period and cumulatively, for the children <18 years, the benefit-risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran remains favorable. The safety of vaccination in children <18 years will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.8 Bivalent Variant Use

16.3.6.7.8.1 Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTx, Inc. cumulatively from 20 Dec 2020 to 17 Dec 2022 and for the reporting period of 19 Jun 2022 to 17 Dec 2022 for elasomeran, elasomeran/imelasomeran booster and elasomeran/davesomeran booster.

16.3.6.7.8.2. Background Relevant to the Evaluation

The MAH received a request from a regulatory authority to summarize cases involving elasomeran, elasomeran/imelasomeran booster and elasomeran/davesomeran booster. Specifically, the regulatory authority requested:

"The MAH is requested to ensure a transparent presentation of cases reported from the newly approved variant vaccines, as well as a continuous comparison of the safety issues identified with the evidence available for the original vaccine – cumulative and booster. Any differences in occurrence of safety issues, when comparing the variant updated vaccines with the original monovalent elasomeran or, indeed, when comparing the two different variants updated bivalent elasomeran vaccines, should be discussed."

Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations (eg, immunocompromised) and/or as a booster dose, including authorization for two bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) continue to expand.

16.3.6.7.8.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB cumulatively from 18 Dec 2020 to 17 Dec 2022 and for the reporting period 19 Jun 2022 through 17 Dec 2022, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The MAH has continued its review and reporting of cases involving booster doses of elasomeran and of the 2 bivalent vaccine boosters (elasomeran/imelasomeran and elasomeran/davesomeran). For cases reporting a third dose with elasomeran, reporting sources rarely identify this third dose as either booster or as part of the primary series in immunocompromised patients. Further, prior vaccination information (i.e., manufacturer) is often not provided. This absence of differentiation confounds the MAH's ability to identify and report clear safety patterns involving booster doses of elasomeran. In comparison, administration information provided by the reporting sources about the 2 bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) supports their use as boosters. Attribution of events to specific doses is provided, when available. Otherwise, analysis is presented in a consolidated manner for ≥ 3 doses of elasomeran.

The MAH is receiving information globally after new authorizations for bivalent boosters. When relevant to vaccine exposure, results are designated as being associated with elasomeran) as the primary series and/or booster, elasomeran/imelasomeran booster and elasomeran/davesomeran booster. If no designation is provided, then data are associated with elasomeran.

16.3.6.7.8.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Refer to Appendix 11.27 for details of the summaries in this section.

Overview of Cases: elasomeran

The majority of case reports were from regulatory authorities (76.0% cumulatively and 84.3% for the reporting period).

Cumulatively, the MAH has received 658,759 cases (2,516,669 events, of which 418,715 events were serious). Of the cumulative reported cases, 310,791 cases were medically confirmed, 134,884 cases were serious, and 6,569 cases had fatal outcomes. The majority of cases were reported in females (444,791; 67.5%) compared to males (186,791; 28.4%) with mean age of 48.9 years (SD: 17.8; median: 48.0 years). A total of 27,177 cases (4.1%) had unknown/unreported gender.

During this reporting period, the MAH received 80,461 cases (327,956 events, of which 37,235 events were serious). Of the total cases during this reporting period, 30,538 cases were medically confirmed, 15,335 cases were serious, and 373 cases had fatal outcomes. The majority of cases were reported in females (53,192; 66.1%) compared to males (23,536; 29.3%) with mean age of 45.0 years (SD: 16.8; median: 44.0 years). A total of 3,733 cases (4.6%) had unknown/unreported gender.

Cumulatively and during the reporting period, the majority of cases received for elasomeran have been non-serious (Table 16.172).

Table 16.172. Post-authorization Cases Received Cumulative and Reporting Period- (elasomeran)

Seriousness	Review Period		Cumulative	
	Cases (N)	Cases (%)	Cases (N)	Cases (%)
Non-Serious	65,126	80.9	523,875	79.5
Serious	15,335	19.1	134,884	20.5
Total	**80,461**	**100.0**	**658,759**	**100.0**

Cumulatively and during the reporting period for cases reported to the MAH for elasomeran with age information, the majority of cases have been reported in adults ≥ 18 years of age (Table 16.173).

Table 16.173. Distribution of Cases by Age Group and Gender-Cumulative and Reporting Period (elasomeran)

Age Group	Review Period			Cumulative N (%)
	Female N (%)	Male N (%)	Unknown N (%)	
Children (<12 years old)	476 (0.9)	431 (1.8)	85 (2.3)	1,525 (0.2)
Adolescents (12-17 years old)	758 (1.4)	696 (3.0)	89 (2.4)	8,552 (1.3)
Adults (≥18 years old)	49,510 (93.1)	21,167 (89.9)	2,251 (60.3)	597,180 (90.7)
Unknown	2,449 (4.6)	1,243 (5.3)	1,308 (35.0)	51,510 (7.8)
Total	**53,192 (100.0)**	**23,536 (100.0)**	**3,733 (100.0)**	**658,759 (100.0)**

Cumulatively, the majority of all cases for elasomeran have been reported by the EEA (42.9%) and the United States (39.2%) and the majority of serious cases have been reported by the EEA (35.9%), United States, (33.4%), and UK (18.8%). During the reporting period, reports from the EEA accounted for 66.6% of non-serious cases and 69.5% of serious cases.

For the calculation of Time To Onset (TTO) and the attribution of Dose Number to individual events, an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a specific Dose Number was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number. Furthermore, for each event, TTOs were calculated by Dose Number. Therefore, when the Dose Number was "Unknown" for an event, TTO could not be calculated, and the event has a missing TTO.

Event distribution by dose number and seriousness are described in Table 16.174 below. The majority of doses administered cumulatively and during the review period have involved the primary series (ie, Dose 1 and Dose 2 and [for certain subpopulations] Dose 3), when dose information was reported by the source. During this reporting period, event distribution showed

that a greater number of events for elasomeran were associated with Dose 2 than with other doses. The section below (Overview of Cases: elasomeran Booster) provides a summary of cases and events for recipients of 3 or more doses.

Table 16.174 Distribution of Events by Dose Number and Seriousness -Cumulative and Reporting Period (elasomeran)

Dose	Review Period		Cumulative
	Non-Serious	Serious	
	Events N (%)	Events N (%)	Events N (%)
Dose 1	39,023 (13.4)	3,808 (10.2)	758,268 (30.1)
Dose 2	51,740 (17.8)	6,786 (18.2)	606,530 (24.1)
Dose 3	40,169 (13.8)	6,582 (17.7)	202,370 (8.0)
Dose 4	4,456 (1.5)	2,068 (5.6)	11,467 (0.5)
Dose 5	272 (0.1)	452 (1.2)	923 (0.0)
Dose 6	7 (0.0)	0 (0.0)	17 (0.0)
Dose 7	1 (0.0)	1 (0.0)	10 (0.0)
Unknown	155,053 (53.3)	17,538 (47.1)	938,084 (37.3)
Grand total	**290,721 (100.0)**	**37,235 (100.0)**	**2,517,669 (100.0)**

Table 16.175 provides the cumulative distribution of events by dose and time to onset. Excepting the events with "Unknown" dose (ie, not reported by the source), substantially more events were reported after Dose 1 compared to Dose 2 and Dose 3.

Table 16.175 Distribution of Events by Dose Number and Time to Onset (TTO) Cumulative and Reporting Period (elasomeran)

		Review Period		Cumulative	
Dose Number	TTO (days)	Events (N)	Events (%)	Events (N)	Events (%)
Dose 1	**Subtotal**	**42,831**	**13.1**	**758,268**	**30.1**
	0 days	17,005	5.2	294,478	11.7
	01-02	12,950	3.9	200,491	8.0
	03-04	1,903	0.6	37,423	1.5
	05-06	1,801	0.5	35,335	1.4
	07-13	6,102	1.9	139,590	5.5
	14-29	1,455	0.4	29,905	1.2
	30+	1,615	0.5	21,046	0.8
Dose 2	**Subtotal**	**58,526**	**17.8**	**606,530**	**24.1**

		Review Period		Cumulative	
Dose Number	**TTO (days)**	**Events (N)**	**Events (%)**	**Events (N)**	**Events (%)**
	0 days	27,875	8.5	253,469	10.1
	01-02	19,168	5.8	219,254	8.7
	03-04	1,604	0.5	21,008	0.8
	05-06	814	0.2	9,885	0.4
	07-13	1,601	0.5	20,662	0.8
	14-29	1,679	0.5	20,621	0.8
	30+	5,785	1.8	61,631	2.4
Dose 3	**Subtotal**	**46,751**	**14.3**	**202,370**	**8.0**
	0 days	17,041	5.2	80,949	3.2
	01-02	16,441	5.0	78,787	3.1
	03-04	2,080	0.6	9,403	0.4
	05-06	1,220	0.4	4,883	0.2
	07-13	3,347	1.0	12,822	0.5
	14-29	2,306	0.7	6,970	0.3
	30+	4,316	1.3	8,556	0.3
Dose 4	**Subtotal**	**6,524**	**2.0**	**11,467**	**0.5**
	0 days	3,017	0.9	5,759	0.2
	01-02	1,987	0.6	3,556	0.1
	03-04	294	0.1	519	0.0
	05-06	192	0.1	258	0.0
	07-13	337	0.1	500	0.0
	14-29	271	0.1	341	0.0
	30+	426	0.1	534	0.0
Dose 5	**Subtotal**	**724**	**0.2**	**923**	**0.0**
	0 days	330	0.1	437	0.0
	01-02	273	0.1	339	0.0
	03-04	28	0.0	36	0.0
	05-06	6	0.0	10	0.0
	07-13	20	0.0	26	0.0
	14-29	25	0.0	27	0.0
	30+	42	0.0	48	0.0
Dose 6	**Subtotal**	**7**	**0.0**	**17**	**0.0**
	0 days	1	0.0	1	0.0
	01-02	1	0.0	1	0.0

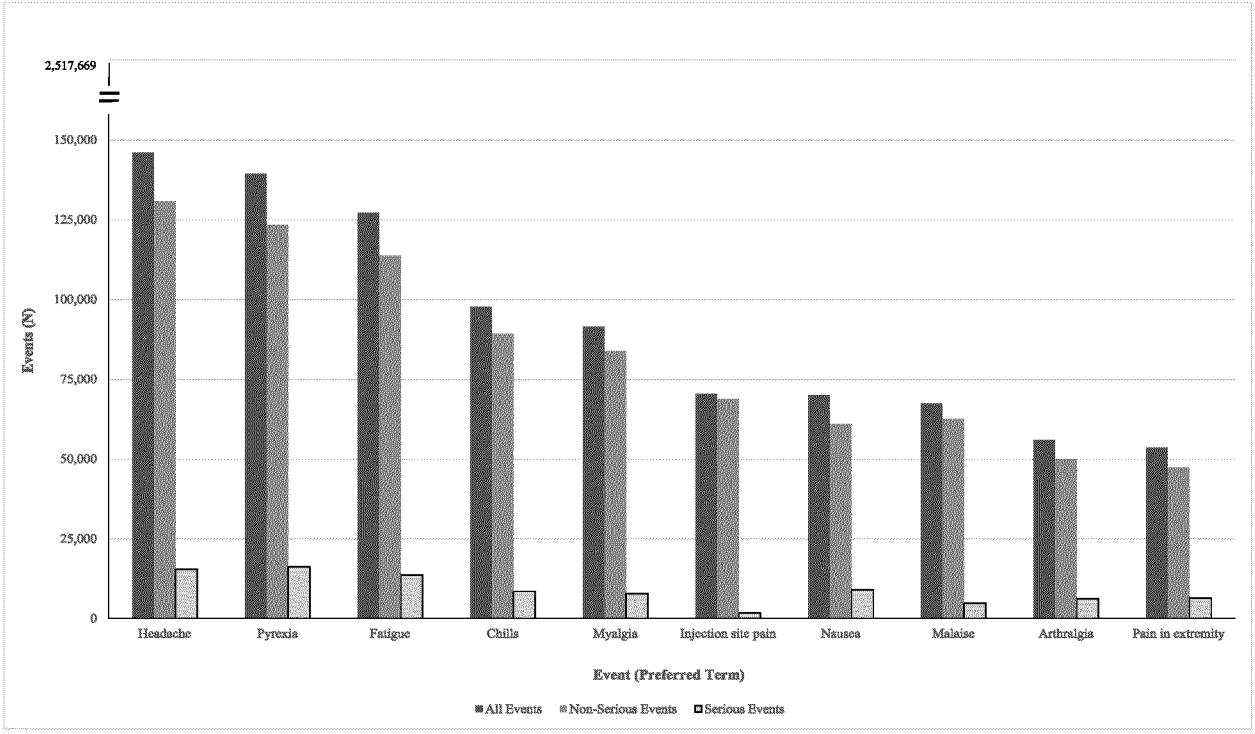
		Review Period		Cumulative	
Dose Number	**TTO (days)**	**Events (N)**	**Events (%)**	**Events (N)**	**Events (%)**
	05-06	0	0	10	0.0
	07-13	5	0.0	5	0.0
Dose 7	**Subtotal**	**2**	**0.0**	**10**	**0.0**
	0 days	0	0	8	0.0
	30+	2	0.0	2	0.0
Unknown	**Subtotal**	**172,591**	**52.6**	**938,084**	**37.3**
	0 days	18,320	5.6	150,617	6.0
	01-02	7,361	2.2	136,447	5.4
	03-04	1,482	0.5	15,885	0.6
	05-06	998	0.3	10,654	0.4
	07-13	2,370	0.7	35,047	1.4
	14-29	2,278	0.7	14,163	0.6
	30+	10,297	3.1	27,603	1.1
	Event onset prior to first dose reported	8,429	2.6	17,218	0.7
	Missing	121,056	36.9	530,450	21.1
Grand Total		**327,956**	**100.0**	**2,517,669**	**100.0**

Interval and Cumulative Spontaneous Adverse Reactions by SOC, HLT, and PT

Overview of Events

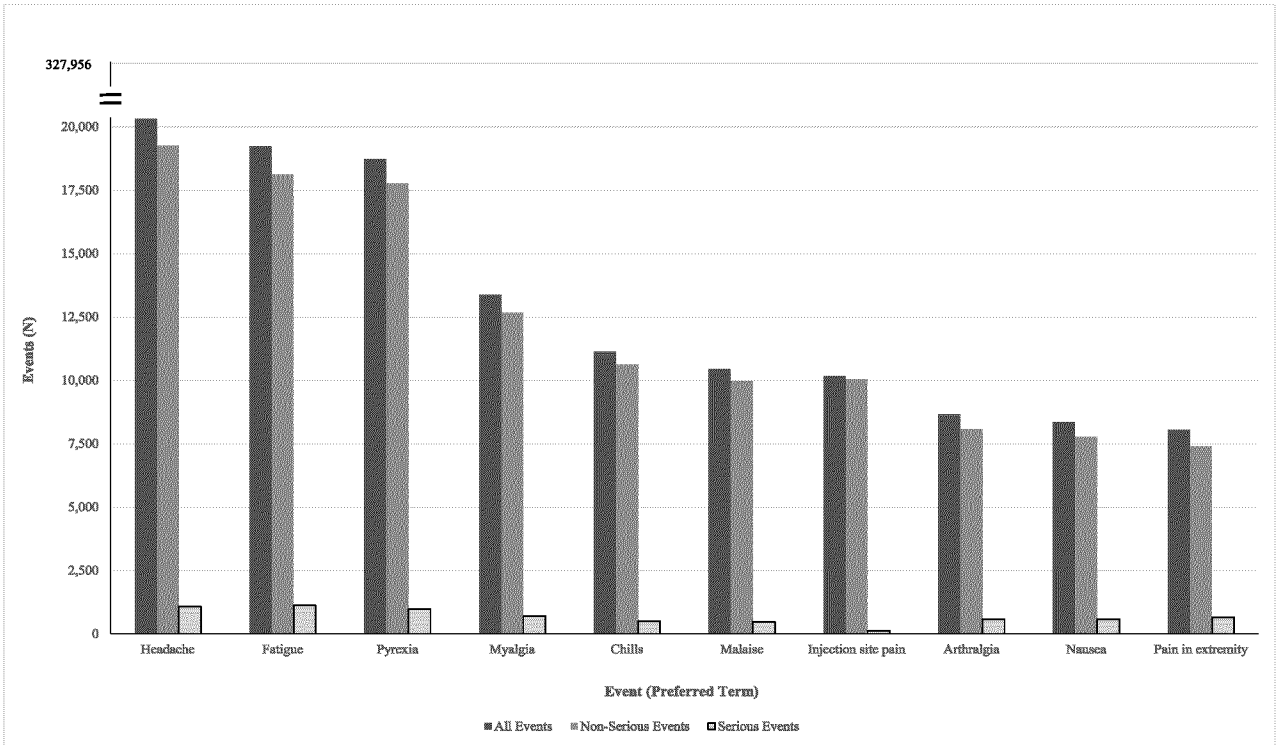
The most frequently reported events for elasomeran are presented cumulatively in Figure 16-21. Among all events cumulatively (N=2,517,669), the most frequently reported serious and non-serious events were headache (15,358 serious events, 0.6%; 130,681 non-serious events, 5.2%), pyrexia (16,087 serious events, 0.6%; 123,373 non-serious events, 4.9%), and fatigue (13,569 serious events, 0.5%; 113,615 non-serious events, 4.5%) which are consistent with the expected reactogenicity events associated with elasomeran.

Figure 16-21. Most Frequently Reported Events Reported for elasomeran (Cumulative)



The most frequently reported events for elasomeran during the reporting period are presented in Figure 16-22. Among all events during the reporting period (N=327,956), the most frequently reported serious and non-serious events were headache (1,070 serious events, 2.9%; 19,256 non-serious events, 6.6%), fatigue (1,118 serious events, 3.0%, 18,126 non-serious events, 6.2%), and pyrexia (967 serious events, 2.6%; 17,759 non-serious events, 6.1%) which are consistent with the expected reactogenicity events associated with elasomeran.

Figure 16-22. Most Frequently Reported Events Reported for elasomeran (Review Period)



Overview of Serious Cases During the Reporting Period – elasomeran

Of the 80,461 cases during the reporting period, 15,335 cases were serious, and 373 cases had fatal outcomes. There were 327,956 events, of which 37,235 were serious. Outcomes for serious events during the reporting period included 778 fatal events, 6,726 events resolved, 6,313 events resolving, 2,058 events resolved with sequelae, 12,712 events not resolved, and 8,648 events had missing/unknown data.

For serious events whose associated doses were reported, most occurred after receiving Dose 2 (18.2%) compared to Dose 3 (17.7%) and Dose 1 (10.2%). A substantial proportion of serious events (47.1%) were reported without associated doses.

Overview of Cases with Fatal Outcomes – elasomeran

Cumulatively, a total of 6,569 cases (17,751 events, all serious) had fatal outcomes. The majority of cases were in males (3,752 cases, 57.1%) compared to females (2,642 events, 40.2%) with mean age of 70.8 years (SD: 17.0; median: 73.0 years). A total of 175 cases (2.7%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (3,005 events,

16.9%), COVID-19 (696 events, 3.9%), and dyspnoea (534 events, 3.0%). The majority of cases with fatal outcomes were reported from the United States (63.5%), EEA (18.3%), and Asia (13.9%). The majority of events (69.3%) were reported after Dose 1 and Dose 2. During the reporting period, a total of 373 cases (778 events, all serious) had fatal outcomes. The majority of cases were in males (202 cases, 54.2%) compared to females (155 cases, 41.6%) with a mean age of 64.2 years (SD: 20.1; median: 68.0 years). A total of 16 cases (4.3%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (82 events, 10.5%), COVID-19 (19 events, 2.4%), and myocarditis and cardiac arrest (18 events, 2.3% for each term). The majority of cases were reported from Asia (132 cases, 35.4%) and the EEA (116 cases, 31.1%). The majority of cases (60.4%) were reported with unknown association to dose number. Events with fatal outcomes are summarized in Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

Overview of Cases: Elasomeran Booster

Cumulatively, the MAH has received 70,647 cases (214,787 events, of which 68,016 events were serious) involving recipients of >2 doses of elasomeran. Of the cumulative reported cases, 20,424 cases were medically confirmed, 22,050 cases were serious, and 542 cases had fatal outcomes. The majority of cases were reported in females (45,518; 64.4%) compared to males (22,591; 32.0%) with the mean age of 49.7 years (SD: 16.1; median: 49.0 years). A total of 2,538 cases (3.6%) had unknown/unreported gender.

During this reporting period, the MAH received 16,923 cases (54,008 events, of which 9,103 events were serious) involving recipients of >2 doses of elasomeran. Of the total cases during this reporting period, 5,123 cases were medically confirmed, 3,880 cases were serious, and 100 cases had fatal outcomes. The majority of cases were reported in females (11,054; 65.3%) compared to males (5,555; 32.8%) with mean age of 50.7 years (SD: 15.7; median: 50.0 years). A total of 314 cases (1.9%) had unknown/unreported gender.

Cumulatively and during the reporting period, the majority of cases involving recipients of >2 doses of elasomeran have been non-serious (Table 16.176).

Table 16.176 Post-authorization Cases Involving Recipients of >2 Doses of elasomeran Cumulative and Reporting Period

Seriousness	Review Period		Cumulative	
	Cases (N)	Cases (%)	Cases (N)	Cases (%)
Non-Serious	13,043	77.1	48,597	68.8
Serious	3,880	22.9	22,050	31.2
Total	**16,923**	**100.0**	**70,647**	**100.0**

Cumulatively and during the reporting period for recipients of >2 doses of elasomeran, the majority of cases have been reported in adults ≥ 18 years of age (Table 16.177).

Table 16.177 Distribution of Cases by Age Group and Gender Involving Recipients of >2 Doses of elasomeran Cumulative and Reporting Period

Age Group	Review Period			Cumulative N (%)
	Female N (%)	Male N (%)	Unknown N (%)	
Children (<11 years old)	30 (0.3)	27 (0.5)	7 (2.2)	147 (0.2)
Adolescents (12-17 years old)	10,711 (96.9)	5,367 (96.6)	224 (71.3)	66,157 (93.6)
Adults (≥18 years old)	277 (2.5)	143 (2.6)	81 (25.8)	4,260 (6.0)
Unknown	11,054 (100.0)	5,555 (100.0)	314 (100.0)	70,647 (100.0)
Total	**30 (0.3)**	**27 (0.5)**	**7 (2.2)**	**147 (0.2)**

Cumulatively, the majority of all cases have been reported by the EEA (47.2%), UK (26.0%) and United States (16.3%) and the majority of serious cases have been reported by the UK (52.9%) and EEA (30.0%). During the reporting period, the EEA accounted for 75.8% of non-serious cases and 53.9% of serious cases.

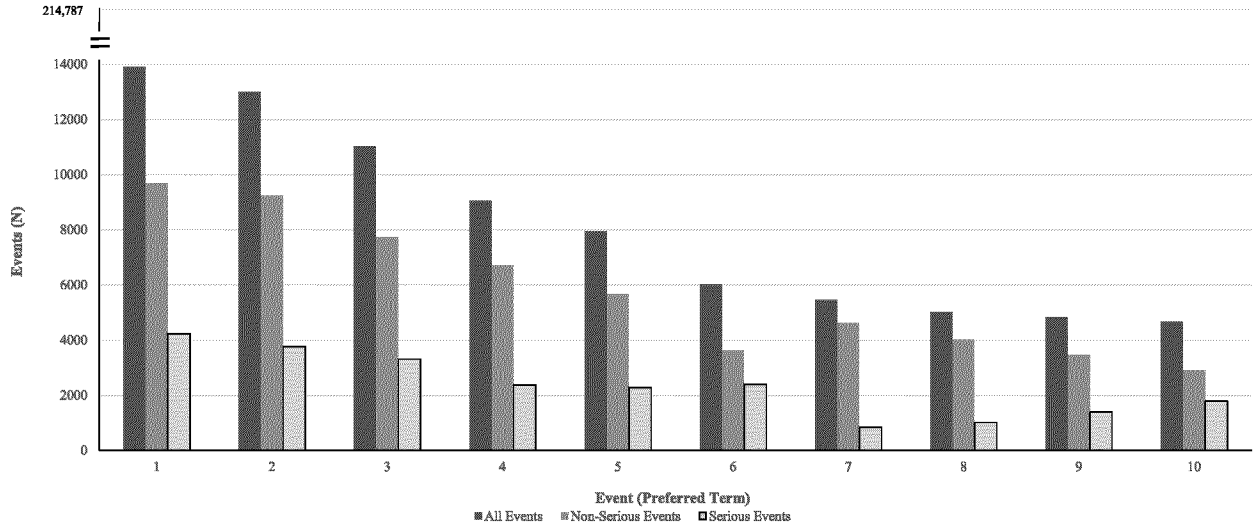
Interval and Cumulative Spontaneous Adverse Reactions by SOC, HLT, and PT

Overview of Events – elasomeran) >2 Doses

The most frequently reported events reported for recipients of > 2 doses of elasomeran are presented cumulatively in Figure 16-23. Among all events cumulatively (N=214,787), the most frequently reported serious and non-serious events were headache (4,229 serious events, 2.0%;

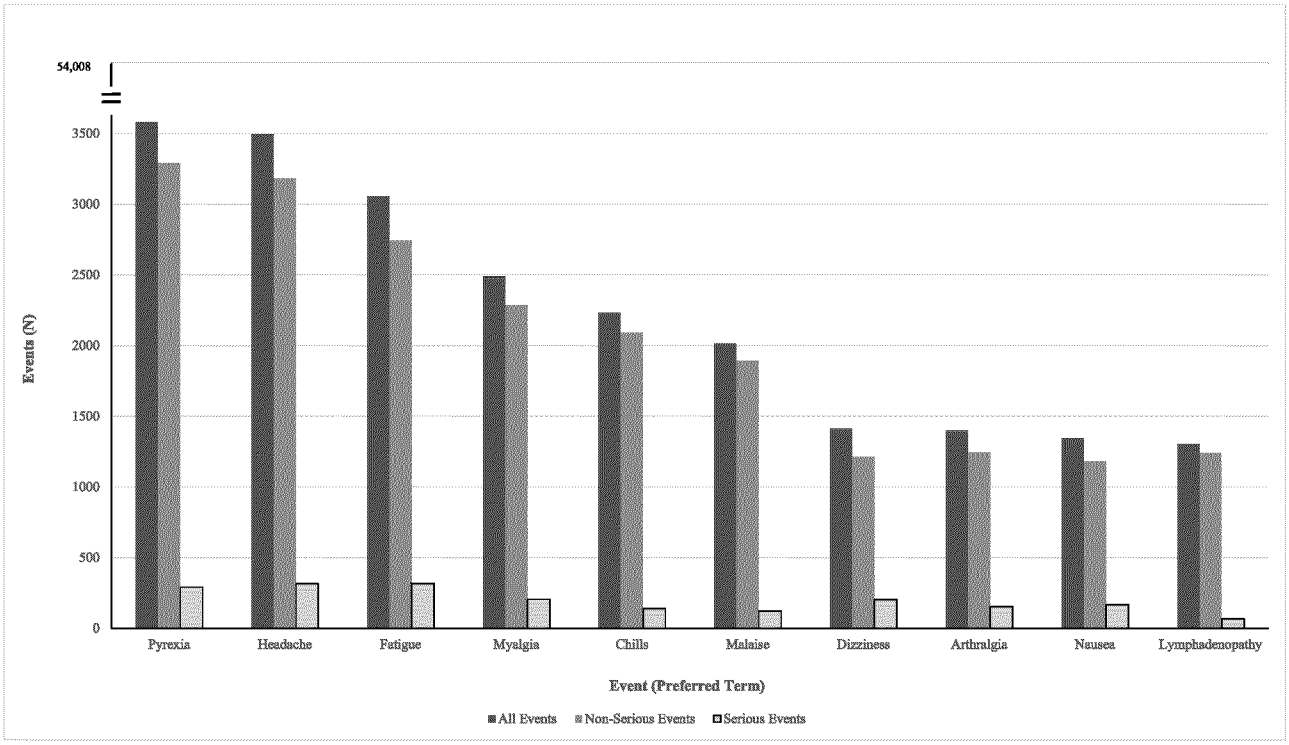
9,690 non-serious events, 4.5%), pyrexia (3,764 serious events, 1.8%; 9,240 non-serious events, 6.1%), and fatigue (3,303 serious events, 1.5%; 7,737 non-serious events, 1.5%).

Figure 16-23. Most Frequently Reported Events Reported for Recipients of >2 Doses of elasomeran (Cumulative)



The most frequently reported events during the reporting period for recipients of > 2 doses of elasomeran are presented in Figure 16-24. Among all events during the reporting period (N=54,008), the most frequently reported serious and non-serious events were pyrexia (290 serious events, 0.5%; 3,291 non-serious events, 6.6%), headache (313 serious events, 0.6%; 3,182 non-serious events, 5.9%), and fatigue (316 serious events, 0.6%; 2,741 non-serious, 5.1%).

Figure 16-24. Most Frequently Reported Events Reported for Recipients of >2 Doses of elasomeran (Review Period)



During the reporting period, a total of 6,508 events were reported for recipients of >2 doses of elasomeran among which the 3 most frequently reported events by PT were pyrexia (647 events, 9.9%), headache (530 events, 8.1%), and fatigue (401 events, 6.2%). During the reporting period, a total of 726 serious events were reported for recipients of >2 doses of elasomeran among which the 3 most frequently reported serious events by PT were arthralgia (30 events, 4.1%), fatigue (25 events, 3.4%), and headache (25 events, 3.4%) which are consistent with the expected reactogenicity events associated with elasomeran.

Overview of Serious Cases During the Reporting Period – elasomeran >2 doses

Of the 16,923 cases during the reporting period for recipients of >2 doses of elasomeran, 3,880 cases were serious, and 100 cases had fatal outcomes. There were 54,008 events, of which 9,103 were serious. Outcomes for serious events during the reporting period included 201 fatal events, 1,664 events resolved, 1,963 events resolving, 727 events resolved with sequelae, 3,391 events not resolved, and 1,157 events had missing/unknown data.

Overview of Cases with Fatal Outcomes

Cumulatively, a total of 542 cases (1,362 events, all serious) had fatal outcomes. The majority of cases were in males (328 cases, 60.5%) compared to females (211 events, 38.9%) with mean age of 70.7 years (SD: 16.4; median: 73.0 years). A total of 3 cases (0.6%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (174 events, 12.8%), cardiac arrest (49 events, 3.6%), and cardiorespiratory arrest (42 events, 3.1%). The majority of cases with fatal outcomes were reported from Asia (40.4%), EEA (27.3%), and United States (22.1%).

During the reporting period, a total of 100 cases (201 events, all serious) had fatal outcomes. The majority of cases were in males (69 cases, 69.0%) compared to females (30 cases, 30.0%) with a mean age of 68.7 years (SD: 18.0; median: 70.0 years). A total of 1 case (1.0%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (17 events, 8.5%), myocarditis (11 events, 5.5%), and pyrexia (9 events, 4.5%). The majority of cases were reported from Asia (56 cases, 56.0%) the EEA (22 cases, 22.0%), and the United States (10 events, 10.0%).

Events with fatal outcomes are summarized in Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

Overview of Cases: elasomeran/imelasomeran Booster

Elasomeran/imelasomeran received authorization for use in selected global regions in Sep 2022 and within the review period of this PBRER; therefore, the data received by the MAH during the review period constitute the cumulative data.

Since Sep 2022, a limited number of cases have been reported to the MAH. Important to note is that a substantial number of cases (2,552, 48.8%) were reported to the MAH without information about age and 90.3% of events have been reported to the MAH without information regarding dose number. This limits the MAH's ability to present certain summaries as in other sections of this report.

The majority of case reports were from regulatory authorities for the reporting period (78.9%).

During the reporting period, the MAH has received 5,234 cases (21,578 events, of which 2,130 events were serious) involving the elasomeran/imelasomeran booster. Of the reported cases, 1,271 cases were medically confirmed, 940 cases were serious, and 38 cases had fatal outcomes.

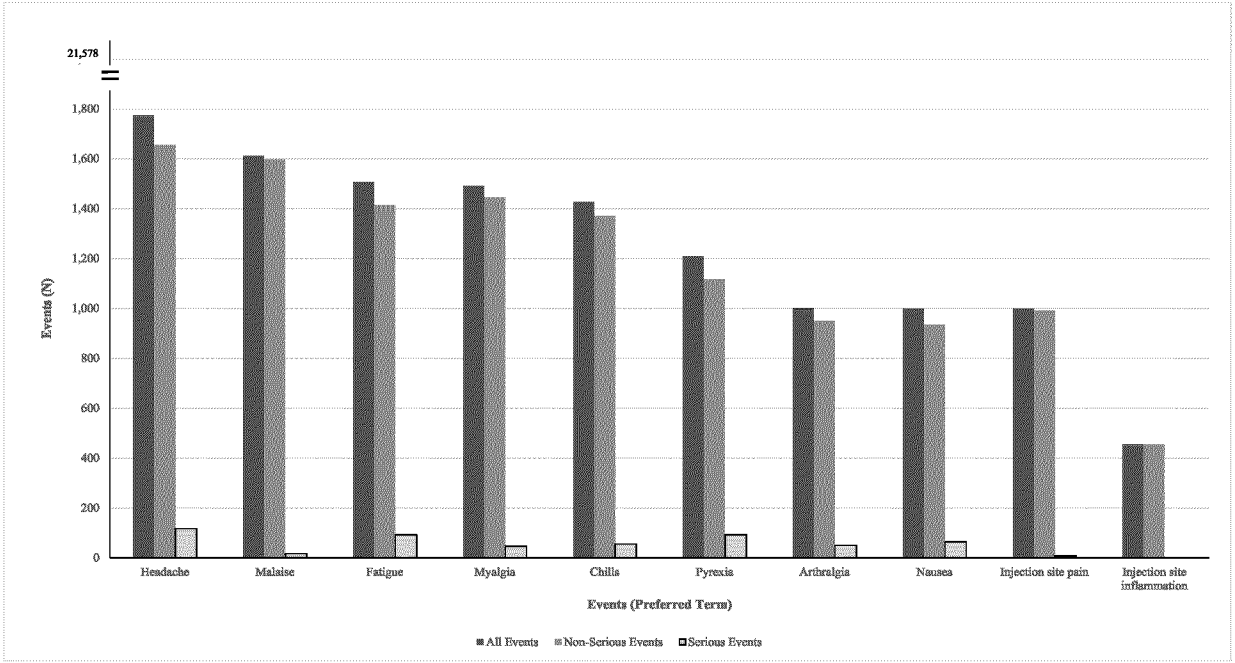
The majority of cases were reported in females (3,129, 59.8%) compared to males (1,591; 30.4%) with mean age of 58.9 years (SD: 14.9; median: 60.0 years). A total of 514 cases (9.8%) had unknown/unreported gender. Of the reported serious cases, the majority of serious cases were reported in females (587, 62.4%) compared to males (317; 33.7%) with mean age of 61.1 years (SD: 16.9; median: 64.0 years). A total of 36 cases (3.8%) had unknown/unreported gender.

During the reporting period, the majority of all cases have been reported from Europe (60.3%), UK (20.3%), and Asia (11.0%). Among the 940 serious cases reports, the majority were reported from the UK (50.5%) and Europe (33.8%).

During the reporting period, for events reported as being associated with a known dose number (2,089 events), the majority (1,743 events, 83.4%) occurred within 2 days after administration of the elasomeran/imelasomeran) booster. Of note, a total of 19,489 events were reported without an associated dose number. Among serious events reported as being associated with a known dose number (1,253 events), the majority (1,051 events, 83.9%) occurred within 2 days after administration of elasomeran/imelasomeran. Of note, a total of 1,899 serious events were reported without an associated dose number.

The most frequently reported events during the reporting period are presented in Figure 16-25. Among all events (N=21,578), headache (7.7%), malaise (7.4%), and myalgia (6.7%) were the most frequently reported non-serious events and headache (0.5%), fatigue (0.4%), and pyrexia (0.4%) were the most frequently reported serious events among 940 serious cases, which are consistent with the expected reactogenicity events associated with elasomeran/imelasomeran).

Figure 16-25. Most Frequently Reported Events During the Review Period



The event outcome most frequently reported outcome during the reporting period was Not recovered/Not Resolved in 31.7% non-serious events and 30.7% of serious events (Table 16.178).

Table 16.178 Event Outcome (Reporting Period) elasomeran/imelasomeran

Event Outcome	Review Period	
	Non-Serious Events, n (%)	Serious Events, n (%)
Fatal	69 (0.3)	69 (2.2)
Not Recovered/Not Resolved	6,836 (31.7)	654 (30.7)
Recovered/Resolved	5,798 (26.9)	553 (26.0)
Recovered/Resolved with Sequelae	48 (0.2)	29 (1.4)
Recovering/Resolving	6,212 (28.8)	589 (27.7)
Unknown	2,615 (12.1)	236 (11.1)
Grand Total	**21,578 (100.0)**	**2,130 (100.0)**

Fatal Cases (Reporting Period) - elasomeran/imelasomeran

During the reporting period a total of 38 cases (69 events, all serious) had fatal outcomes. More cases involving males (20 cases, 52.6%) were reported than for females (14 cases, 36.8%) with

mean age of 76.5 years (SD: 14.6; median: 76.0 years). A total of 4 cases (10.5%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (11 events, 15.9%), myocardial infarction (4 events, 5.8%), and the following events each occurring with a frequency of 2 event (2.9%): abdominal pain, acute myocardial infarction, asthma, cardiac arrest, condition aggravated, fatigue, hypoxia, sepsis, and tachycardia. The most cases with fatal outcomes were reported from Asia (16 cases, 42.1%) and EEA (12 events, 31.6%). Among events for which dose number was reported (38 events), the 18 events (47.4%) occurred within 2 days after administration of elasomeran/imelasomeran booster.

Events with fatal outcomes are summarized in Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

Overview of Cases: elasomeran/davesomeran

Elasomeran/davesomeran received authorization for use primarily in the United States in Sep 2022 followed by selected regions thereafter within the review period of this PBRER; therefore, the data received by the MAH during the review period constitute the cumulative data.

Since September, a limited number of cases have been reported to the MAH. Important to note is that a substantial number of cases (801, 34.1%) were reported to the MAH without information about age and 76.0% of events have been reported to the MAH without information regarding dose number. This limits the MAH's ability to present certain summaries as in other sections of this report.

The majority of case reports were spontaneous reports for the reporting period (99.3%).

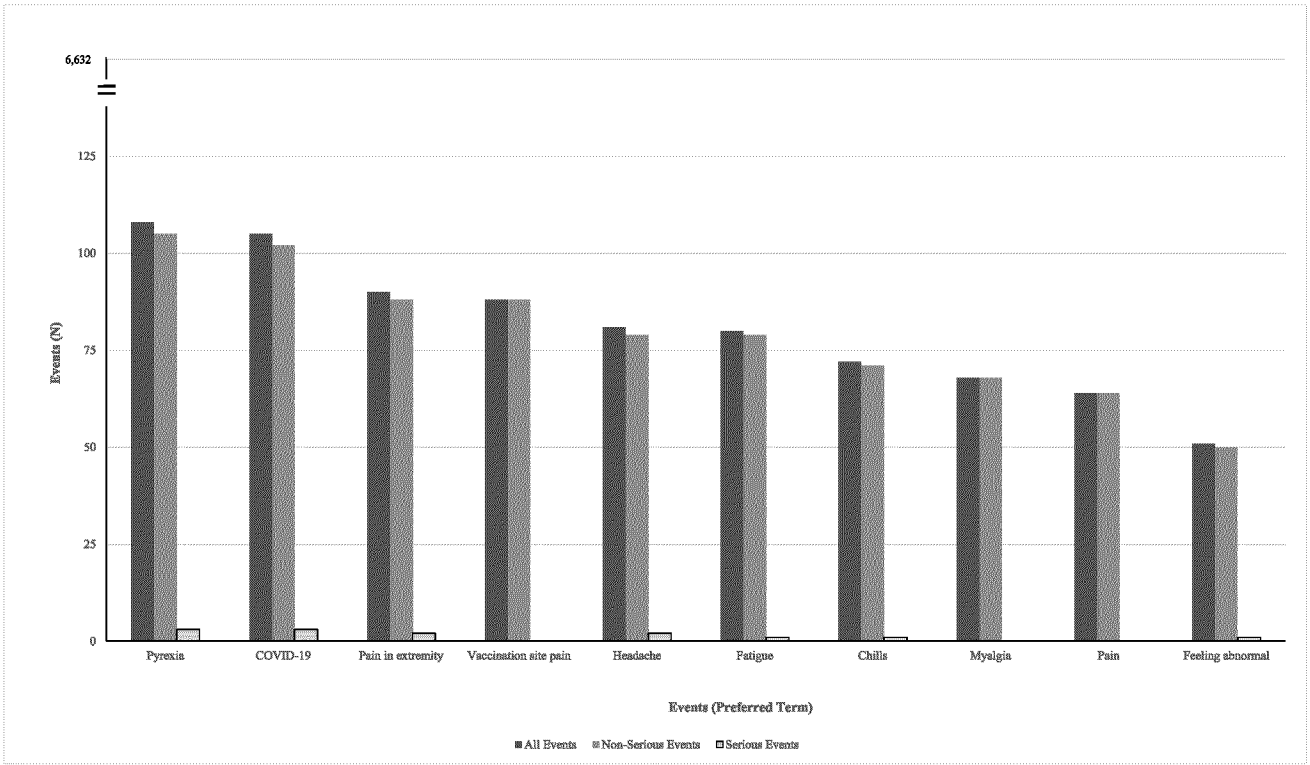
During the reporting period, the MAH has received 2,348 cases (6,632 events, of which 181 events were serious) involving the elasomeran/davesomeran booster. Of the reported cases, 1,709 cases were medically confirmed, 119 cases were serious, and 12 cases had fatal outcomes. More cases were reported in females (951, 40.5%) compared to males (686; 29.2%) with mean age of 57.7 years (SD: 19.7; median: 63.0 years). A total of 711 cases (30.3%) had unknown/unreported gender. Of the reported serious cases, more serious cases were reported in females (58, 48.7%) compared to males (52; 43.7%) with mean age of 62.1 years (SD: 16.8; median: 66.0 years). A total of 9 cases (7.6%) had unknown/unreported gender.

During the reporting period, the majority of all cases (2,101, 89.5%) have been reported from the United States. Among the 119 serious cases reports, the majority were reported from the United States (92.4%).

During the reporting period, for events reported as being associated with a known dose number (1,594 events), the majority (1,405 events, 88.2%) occurred within 2 days after administration of the elasomeran/davesomeran booster. Of note, a total of 5,038 events were reported without an associated dose number. Among serious events reported as being associated with a known dose number (182 events), the majority (150 events, 82.4%) occurred within 2 days after administration of elasomeran/davesomeran booster. Of note, a total of 267 serious events were reported without an associated dose number.

The most frequently reported events during the reporting period that were associated clinically with administration of elasomeran/davesomeran booster are presented in Figure 16-26. Among all events (N=6,632), pyrexia (105 events, 1.6%%), COVID-19 (102 events, 1.6%), and pain in extremity (88 events, 1.3%) were the most frequently reported non-serious events while serious events accounted for ≤ 3 events (< 0.05%) in each of those most frequently reported PTs. Events coded as "No AE" (23.3% of all events during the review period) were often associated with events involving product administration errors (e.g., accidental underdose, wrong product administered, etc.). Among all events, the most frequently reported serious events were syncope (8 events, 0.12%), atrial fibrillation (7 events, 0.11%%), and loss of consciousness (7 events, 0.11%). Both syncope and loss of consciousness may be related to Immunization Stress-Related Responses (ISRR). Immunization Stress-Related Responses is used to describe the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom. Individual responses to stress vary from person to person and may change according to time or context. Immunization Stress-Related Responses may manifest as acute stress responses, vasovagal reactions (syncope/ loss of consciousness) or dissociative neurological symptom reactions [135].

Figure 16-26. Most Frequently Reported Events During the Review Period - elasomeran/davesomeran booster



The event outcome most frequently reported outcomes during the reporting period were Not recovered/Not Resolved for non-serious events (8.6%) and serious events (21.0%) (Table 16.179). Of note, events reported without outcome accounted for 80.5% of non-serious events and 53.6% of serious events.

Table 16.179 Event Outcome Reporting Period - elasomeran/davesomeran booster

Event Outcome	Review Period	
	Non-Serious Events, n (%)	Serious Events, n (%)
Fatal	0 (0)	12 (6.6)
Not Recovered/Not Resolved	558 (8.6)	38 (21.0)
Recovered/Resolved	505 (7.8)	25 (13.8)
Recovered/Resolved with Sequelae	11 (0.2)	3 (1.7)
Recovering/Resolving	181 (2.8)	6 (3.3)
Unknown	5,196 (80.5)	97 (53.6)
Grand Total	**6,451 (100.0)**	**181 (100.0)**

Fatal Cases (Reporting Period) - elasomeran/davesomeran) booster

During the reporting period a total of 12 cases (12 events, all serious) had fatal outcomes. The majority of cases involved males (7 cases, 58.3%) were reported than for females (4 cases, 33.3%) with mean age of 67.8 years (SD: 20.2; median: 79.0 years). A total of 1 case (8.3%) had no gender reported. The most frequently reported events by PT with fatal outcome were death (5 events, 41.7%), myocardial infarction (2 events, 16.7%), and the following events each occurring with a frequency of 1 event (8.3%): abdominal pain, cardiac arrest, cardiac failure, pulmonary thrombosis, and thrombosis. The most cases with fatal outcomes were reported from the United States (11 cases, 91.7%). Among events for which dose number was reported (2 events), both events occurred within 2 days after administration of elasomeran/davesomeran booster.

Events with fatal outcomes are summarized in Appendix 11.27. Assessments of events with fatal outcome are presented with their associated medical topics, as applicable, to provide clinical context.

16.3.6.7.8.5. Discussion

Review of the post-marketing safety data for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and for both bivalents showed that the majority of reported events were reported in females compared to males, and the majority of reports are in individuals >18 years of age, and more specifically >50 years of age.

It is important to note that this distribution of reported cases by gender for each of the vaccines is similar to the overall distribution of reported cases by gender for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in general in the GSDB. Overall, cumulative as of 17 Dec 2022, a total of 448,846 (67.4%) reports for females are included in the GSDB, with 189,053 (28.4%) reports for males, and 28,399 (4.3%) reports missing sex information. According to the literature, Zucker et al., [185] stated that women experience ADRs nearly twice as often as men, yet the role of sex as a biological factor in the generation of ADRs is poorly understood. In a scoping review conducted by Brabete et al [186] in order to identify sex- and gender-related factors that impact the lifecycle management of drugs processes, the authors concluded that observed sex differences in the number of reported ADRs can be linked to sex- or gender-related factors.

Sex-related factors refer to biological differences between women and men, whereas gender-related factors refer to social, behavioral, or cultural differences. They also mentioned that in addition to sex-related factors that affect both ADR occurrence and reporting, there are also

gender-related factors such as gender roles, access to resources and opportunities, adherence to gender norms, degrees of commitment to dominant femininities and masculinities, and institutionalized inequities that reinforce sex and gender groups in all cultures and contexts. Women are more interested in and report much more active seeking of health-related information and receive more informal health-related information from close family members, other kin, and friends/workmates than men do [187]. Review of the safety data also showed that for all three vaccines, when dose number and TTO was reported, more events happened after Dose 1 (758,368; 47.9%) and Dose 2 (606,588; 38.3%) than any other dose, and within less than 7 days (1,259,718; 79.6%).

The most common reported events for all three vaccines are consistent with the expected reactogenicity events that have been associated with administration of elasomeran. The majority of the fatal cases reported to the global; safety database for all three vaccines were reported in elderly individuals (>65 years of age) (3,536; 73.0%), and after Dose 1 (2,152; 44.4%). Elderly individuals are also considered part of the frail population. Frail patients are considered at higher risk of complications due to coronavirus disease 2019 (COVID-19) infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. The most frequently reported event terms in fatal cases closely match those seen both in the elderly population and in the general population as a whole. Fatal cases are in general strongly confounded by multiple comorbidities and the advanced age in the elderly.

The large scale of use of elasomeran (and other COVID-19) vaccines through EUA and related mechanisms is without historical precedent. As of the end of the reporting period, a total of 1,315,589,716 doses of elasomeran had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered. Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 408,226,293 individuals received a first dose, 275,197,667 received a second dose, 166,419,347 received a third dose, and 62,984,506 received

a fourth dose, with third and fourth doses including both original elosameran and elosameran bivalent booster dose formulations.

With this large number of doses of elosameran (Original and bivalents) that has been administered worldwide, reported cases included in the MAH's GSDB in the large majority are associated with expected reactogenicity events. The MAH has a comprehensive and systematic approach to evaluating all available safety information, including that pertaining to the administration of the bivalent vaccines as well as new age indications that have been authorized since the beginning of this pandemic. The MAH has monitored safety concerns included in the RMP, as well as AESI, and any other additional medical topic that may trigger in the conduct of the Observe/Expected analysis of the post-marketing safety data in each MSSRs as well as PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elosameran (and other COVID-19) vaccines and boosters, the MAH has found that review of the safety data in all subpopulations, including individuals with AI/ID, immunocompromised individuals, frail individuals, use in pregnancy and while breastfeeding, children, among other, reported in the GSDB indicates that the general pattern of commonly reported AEs is comparable to the general population, rather than as a result of vaccine exposure.

16.3.6.7.8.6 Conclusion

The data provided in this PBRER describe the safety profile of elosameran, elosameran/imelasomeran and elosameran/davesomeran, in the reporting period and cumulatively. A comparison with the cumulative data shows no new safety concerns or change in safety profile of the vaccines and the benefit-risk evaluation remains positive.

Based on the analysis of all the safety data received cumulative and during the reporting period of this PBRER, ModernaTx, Inc. considers that cases reported after vaccination with elosameran/imelasomeran and elosameran/davesomeran) to be consistent with the known safety profile of elasomeran. The MAH will continue to monitor AEs reported after use of any of the elasomeran vaccines using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.7.9 Histiocytolic necrotizing lymphadenitis

16.3.6.7.9.1 Source of the New Information

Information presented below includes a cumulative analysis performed on cases received by the MAH from 18 Dec 2020 to 17 Dec 2022 for elasomeran, elosameran/imelasomeran and

elosameran/davesomeran for cases of histiocytic necrotizing lymphadenitis (HNL, aka Kikuchi-Fujimoto Disease [KFD]), per request from a health authority.

16.3.6.7.9.2. Background Relevant to the Evaluation

A health authority requested the MAH to perform a cumulative review of all cases concerning elasomeran and HNL from all sources, including any relevant articles from the literature and to discuss possible mechanism(s) of action.

A histologically distinct form of subacute necrotizing lymphadenitis was first described in Japan in 1972 by Kikuchi and independently by Fujimoto and colleagues. Although apparently more common in Asia and Asian people, the disease has been reported in many areas of the world, including Europe, the United States, and Australia [188].

Kikuchi-Fujimoto disease occurs most often in young women (mean age, 30 years; female/male ratio, 4:1). No laboratory study is pathognomonic for this pathology. Laboratory abnormalities associated with KFD include mainly an inflammatory syndrome with moderate granulocytopenia observed in 25-58% of cases. The most common clinical manifestation is cervical adenopathy with or without fever, but some authors report generalized lymph node enlargement (1.3-22.2%); additional findings may include fever, sore throat, weight loss, sweats, chills, myalgia, arthralgia, splenomegaly, and skin rash [189]. About half of the cases may be associated with painful lymphadenopathy. Leukopenia is reported in 25-50% of the cases and leukocytosis in less than 5% of the cases [190]. Laboratory abnormalities may include leukopenia, an elevated serum transaminase level, and an elevated serum lactate dehydrogenase level. In almost all cases, the course is benign and followed by complete recovery within 1 to 3 months [191]. Recurrence of disease may occur but is infrequent, and fatalities are exceptional.

The diagnosis is confirmed based on histopathological examination of the lymph nodes biopsy and immunohistochemical testing. It shows typically on microscopic examination as a partially preserved architecture with follicular hyperplasia. Three forms have been described in the literature: necrotic form (more than 50% of cases), proliferative form (30%), and xanthogranulomatous form (<20%) [192]. Histological examination, especially seen in sub-Saharan Africa, also helps to exclude the main differential diagnoses such as infectious lymphadenitis (particularly tuberculosis) and lymphomas. Immunohistochemical analysis reveals CD3+ cells as the majority of the cells present in the pathological areas of the lymph node. The cell population is predominantly composed of CD68+ histiocytes, while the lymphocyte population represents 20-50% of the total cell population, mainly CD8+ cytotoxic T-lymphocytes.

These heterogeneous results may be a reflection of the different immunological staging of KFD.

KFD has been reported in rare patients infected with the human immunodeficiency virus (HIV). Pathogenesis of the lesion is probably related to an impaired immune function [193]. It has been hypothesized that KFD is predominantly linked to apoptosis mediated by cytolytic lymphocytes. Felgar et al [194] found evidence of apoptosis (DNA fragmentation, using the in situ-end labeling technique, Iressa Survival Evaluation in Lung Cancer) in lymphocytes and histiocytes within and in surrounding areas of necrosis. They found also an increase in CD8+ and TIA1+ lymphocytes, whereas CD56+ cells were present in few numbers. These authors concluded that their findings corroborated a viral (still unknown) or autoimmune (perhaps initiated by a viral infection) pathogenesis in KL.

The etiology of KFD is still unknown. Two main theories have been postulated, but although the clinical and histopathological features point to a viral etiology, this hypothesis has not been proven yet. Generally, the diagnosis is made based on a lymph node excisional biopsy. Its recognition is crucial mainly because this disease can be mistaken for other disorders, including SLE or malignant lymphoma [195]. A KFD-like lesion occurring in a patient with silicone lymphadenopathy suggested that KFD may represent a non-specific autoimmune-like reaction.

As mentioned above KFD is thought to either occur as a response to a viral infection or due to an underlying autoimmune disorder [196]. The discovery of histiocytes and CD8-positive cells in KFD-affected lymph nodes supports the viral origin. Numerous studies have attempted to show an association between KFD and different viruses. In a study by Cho et al [197] polymerase chain reaction (PCR) was used to check 50% of lymph node tissues identified with KFD for the presence of human herpesvirus (HHV-6, 7, and 8) but the study could not establish a link between KFD and HHV-6, 7, or 8. Hudnall et al [198] examined 30 lymph nodes affected by KFD and demonstrated that HHV-1, varicella zoster virus, and HHV-8 DNA were not detectable, and HHV-2, CMV, HHV-6, and HHV-7 were occasionally detected. This contrasts with another study by Zhang et al [199] which identified an association between parvovirus B19 and KFD. According to the study by Hudnall et al., it was unlikely that these viruses served as the etiology of KFD.

It has also been demonstrated that autoimmune disorders may play a role in the pathogenesis of KFD. Imamura et al [200] first suggested that KFD might be a lupus-like autoimmune condition triggered by viral infection, given that histologic features of KFD in some cases may be difficult to distinguish from systemic lupus erythematosus (SLE)-associated lymphadenitis. Although at diagnosis KFD is not associated typically with serologic evidence of autoimmune disease, in 2

cases reviewed by Dorfman and Berry [189], SLE subsequently developed and led to a recommendation that patients with KFD be observed carefully for development of SLE. Several cases of KFD occurring in association with SLE have been described [201]. A study by Sopeña et al [202] detected autoimmune conditions, including SLE, thyroiditis, leukocytoclastic vasculitis, Sjogren's syndrome, Still's disease, and Wegener's granulomatosis, associated with KFD. These findings were also reported in another study by Kucukardali et al [203] who reported 32 cases of KFD associated with SLE. Of these instances, 18 had KFD and SLE at the same time, six developed SLE later, and four had a pre-existing condition that was indicative of SLE. Goldblatt et al [204] discussed three Asian women who had KFD, and none of the three patients had symptoms or signs typical of SLE at the time of their diagnosis and testing for ANA was negative for all three patients however, after receiving a diagnosis of KFD, all three patients experienced symptoms of SLE and a positive ANA test within a 3-14-month window. Although the link between KFD and SLE has been reported, the exact association remains unclear. Thus, KFD pathogenesis may be a consequence of an aberrant T-cells and histiocyte immune response to an immunogenic antigen [205]. A study conducted by Ferreras et al [206] which was based on a search in the Spanish AEs database and the European AEs database (Eudravigilance) looking for any drug and the diagnosis of "HNL" according to MedDRA as of 02 Jun 2022. In the Spanish AEs database, they identified two reports, one related to methotrexate and one to elasomeran. In the Eudrovigilance 14 KFD AEs related to COVID-19 vaccines were identified, including 11 related to Comirnaty vaccination, two after Vaxzervria, and one after elasomeran vaccination.

Cases of KFD associated with COVID-19 infection have also been reported [207]. Taking into account the possible viral origin, it seems logical to think that COVID-19 may also induce the onset of KFD, as do the numerous viruses already described as possible causative agents. It is very uncommon for KFD to occur after vaccination, and only rare cases in the literature of KFD associated with other vaccines can be found, mainly after human papillomavirus vaccine, influenza and Japanese encephalitis virus vaccination. Although the causal relationship between vaccination and KFD is not proven, according to Ferreras et al. the T-lymphocyte-mediated immune response at the lymph node level could contribute to the development of KFD.

There are two hypothesized mechanisms for the development of autoimmune diseases following vaccination, it includes molecular mimicry, wherein vaccines trigger an immune response against self-antigens, and bystander activation, wherein vaccines release self-antigens from host tissues and activate antigen-presenting cells and dormant autoreactive T-helper cells.

Following on the autoimmunity hypothesis for KFD, it has been suggested that the cytoplasm of

lymphocytes and histiocytes seen in KFD has a tubular reticular structure, similar to that seen in autoimmune diseases, such as SLE. It is also suggested that patients with a genetic component, especially HLA-DPA1 and HLA-DPB1 (more frequent in Asians), develop an immune response that is mainly composed of T-cells, especially cytotoxic T-cells.

Kashiwada et al [191] presents in their article that given that mRNA vaccines induce a rapid and localized infiltration of neutrophils, monocytes, and dendritic cells at the site of administration and in the draining lymph node promptly after vaccination. COVID-19 mRNA vaccine rapidly induces CD8+ T-cells as well as antibody production, contributing to vaccine efficacy, it is possible that the mRNA vaccine-induced a CD8+ T-cell-related immune response in the draining lymph node, resulting in the development of KFD localized to the ipsilateral axillary lymph node. However, a causal relationship between KFD and COVID-19 vaccine has never been proven, and further pathophysiological analysis is warranted, according to the authors.

16.3.6.7.9.3 Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively to 17 Dec 2022 for valid case reports of histiocytic necrotizing lymphadenopathy (HNL, aka Kikuchi-Fujimoto Disease [KFD]) received from HCP, HA, consumers, and literature worldwide reported for elasomeran using the following MedDRA PTs: "histiocytic necrotizing lymphadenopathy".

The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17].

Literature Search Methodology

The MAH performed a focused search of PubMed for elasomeran and KFD to retrieve relevant literature during this reporting period. As part of the search strategy, the MAH selected appropriate key terms and applied appropriate filters (eg, All Fields, MeSH Terms, Text Word, Date-Publication, etc) so that relevant articles would be retrieved. The exact search criteria are specified in Appendix 12.1d.

A total of 17 literature articles were retrieved using these search criteria. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran.

16.3.6.7.9.4 Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

For more details on HNL cases please refer to Appendix 11.28.

Overview of Cases

Cumulative there were 4 cases (4 events) of HNL/KFD identified in the MAH GSDB. Out of those, 3 cases (3 events) were considered serious cases. There were no cases reporting a fatal outcome, and all 4 cases reported an outcome of recovering/ resolving.

There were 3 reports involving males (75%), and 1 report involving a female (25%). For those reports where age was provided it ranged between 45 to 47 years of age.

There were 2 reports from Spain, 1 from Korea, and one from Qatar. Three reports were from the literature and one from a regulatory authority.

After assessing causality of all four reports, they were all considered to be unlikely related to the vaccine. See information below in (Table 16.180).

Table 16.180 Elasomeran Cases Reporting Histiocytic necrotizing lymphadenitis – Cumulative to 17 Dec 2022

Case ID/ WW ID	Country	Report Type	Dose #	TTO	WHO Causality	MAH Assessment
[redacted]	[redacted]	Regulatory Authority	Dose 3	73	Unlikely	This is a regulatory case concerning a 47-year-old male patient with no medical history reported, previously received Comirnaty, who 2 months and 14 days after receiving the 3rd dose of COVID-19 vaccination with elasomeran, experienced HNL (Kikuchi disease). A biopsy was conducted, and the report showed HNL. No further information regarding the clinical course and treatment of the event was provided, as well as medical history, concomitant medications or any other laboratory test conducted. According to the WHO causality assessment this case is considered unlikely based on the prolonged TTO between vaccination and the occurrence of the events. There is also important information missing in this report.

Case ID/ WW ID	Country	Report Type	Dose #	TTO	WHO Causality	MAH Assessment
[redacted]	[redacted]	Literature-Non-Study	Unknown		Unlikely	Literature case report for a 45-year-old man with a history of [redacted] stage A2, on [redacted] treatment and HHV-8 associated multicentric Castleman disease, presented multiple infiltrated erythematous nodular lesions on the forehead, cheek, arms and trunk, without lymphadenitis. Skin lesions appeared 2 days after receiving an unknown dose of mRNA-based COVID-19 vaccine (ModernaTx, Inc.) and due to clinical suspicion of lymphoma, a skin biopsy was performed. Histopathological study showed epidermis with basal hydropic degeneration and dyskeratosis. The dermis presented a perivascular and periadnexal lymphohistiocytic infiltrate with karyorrhectic debris without neutrophils next to plasma cells. Real-time PCR revealed 30 copies of Epstein-Barr Virus (EBV)/100,000 cells and no HHV-6. HNL is characterized for cervical adenopathy with or without fever; additional findings may include fever, sore throat, weight loss, sweats, chills, myalgia, arthralgia, splenomegaly, and skin rash. According to the authors "the temporal association between the administration of the COVID-19 vaccine and the appearance of skin lesions is a clue to suspicion" but they fail to present in their analysis the fact that this is an immunocompromised individual, with [redacted]nd Castleman's disease as concurrent comorbidities, who presented with multiple infiltrates but without lymphadenitis. Several publications do not support the author's statement that [redacted] patients may present exclusively with skin involvement, and on the contrary those publications do

Case ID/ WW ID	Country	Report Type	Dose #	TTO	WHO Causality	MAH Assessment
						include case reports where lymphadenitis is present in all the cases. Pathogenesis of the lesion has been considered that is probably related to an impaired immune function. Additionally, the most commonly detected infectious agent in HNL is EBV, and this patient had a Real-time PCR that revealed 30 copies of EBV/100,000 cells. Based on all these concurrent comorbidities and findings, this report is considered unlikely related to elasomeran.
[redacted]	[redacted]	Literature-Non-Study	Dose 1	10	Unlikely	This literature report is for a female patient in her twenties, with no relevant medical history (described as previously healthy), who was hospitalized with headache and fever (38.5°C) 10 days after the first dose of elasomeran (ModernaTx, Inc.). Laboratory testing revealed the following: ESR, 120 mm/h; and CRP, 4.3 mg/dl (<0.30 mg/dl). cerebrospinal fluid analysis found no pathogens; she was diagnosed with aseptic meningitis. She had an intermittent fever for 20 days, hair loss, and necrotizing cervical lymphadenitis. Laboratory analysis revealed the following: ANA, 1:1280; anti-Ro antibody >240 U/ml (<7 U/ml); anti-La antibody >320 U/ml (<7 U/ml); and positive direct Coombs test. Symptomatic improvement was achieved with prednisolone 15 mg and naproxen 500 mg BID. Chilblain lupus developed on the fingertips during steroid tapering. She was diagnosed with systemic lupus erythematosus. According to an article by Hudnall, several features of HNL suggest that the cause is likely to be infectious or autoimmune. The clinical manifestations of fever, chills, lymphadenitis, rash, arthralgia, and

Case ID/ WW ID	Country	Report Type	Dose #	TTO	WHO Causality	MAH Assessment
						myalgia in young women is certainly suggestive of an infectious or autoimmune disease. Imamura et al first suggested that KFD might be a lupus-like autoimmune condition triggered by viral infection. Indeed, the histologic features of KFD in some cases may be difficult to distinguish from systemic lupus erythematosus (SLE)-associated lymphadenitis. Although at diagnosis KFD is not associated typically with serologic evidence of autoimmune disease, in 2 cases reviewed by Dorfman and Berry, SLE subsequently developed and led to a recommendation that patients with KFD be observed carefully for development of SLE. This case is considered unlikely related to elasomeran due to the concurrent comorbidities of aseptic meningitis and the diagnosis of SLE.
[redacted]	[redacted]	Literature-Non-Study	Dose 3	30	Unlikely	Literature reports for a 46-year-old, male patient with medical history of smoking and regular alcohol use and with history of being on vacation four weeks prior to hospital admission in [redacted] and came back to [redacted] who 1 month after the third dose of elasomeran experienced fever while in India, for one month which was mild initially and then started to worsen. It was reported that he took many antibiotics with no improvement, including cefixime, azithromycin, augmenting, and ceftriaxone. He was in contact with a coronavirus disease 2019 (COVID-19)-positive patient in India, his COVID-19 antigen test was negative. One week before the presentation, patient noticed a swelling on the left side of the neck (supraclavicular region). The swelling was tender and associated with fever without any specific

Case ID/ WW ID	Country	Report Type	Dose #	TTO	WHO Causality	MAH Assessment
						timing, resolved with paracetamol, and no night sweats. Patient also reported a loss of appetite with a 2 kg weight loss in the previous month. Ultrasound scan showed multiple lymph nodes in the left supraclavicular region, and multiple jugular lymph nodes were noted bilaterally and left supraclavicular region with enlarged round lymph nodes with preserved fatty hilum and normal vascularity. A biopsy of the left supraclavicular lymph node was done. Light microscopic examination revealed distorted lymph node with patchy necrotic areas showing a moth-eaten appearance. These necrotic areas consisted of amorphous eosinophilic material admixed with karyorrhectic debris, showing a lymph node with patchy necrotic areas (hematoxylin and eosin, ×40) and showing the eosinophilic necrotic area with karyorrhectic debris on the left side surrounded by sheets of plasmacytoid histiocytes and lymphocytes on the right side. Viral and mycotic test were negative. Patient was diagnosed with KFD. This report is heavily confounded by the patient's exposure to COVID-19, by his long travel out of country, the extensive use of antibiotics, as well as the prolonged TTO between vaccination and the events.

16.3.6.7.9.5. Discussion

The etiology of KFD is still unknown. Two main theories have been postulated, but although the clinical and histopathological features point to a viral etiology, this hypothesis has not been proven yet. Generally, the diagnosis is made based on a lymph node excisional biopsy. Its recognition is crucial mainly because this disease can be mistaken for other disorders, including SLE or malignant lymphoma [195]. A KFD-like lesion occurring in a patient with silicone lymphadenopathy suggested that KFD may represent a non-specific autoimmune-like reaction.

A cumulative review of the safety data in the MAH's GSDB for reports of related HNL events received after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran identified 4 cases (4 events) for individuals between the ages of 45 to 47 years old. There were no reports received for individuals <45 years of age. All cases were considered unlikely related to the vaccine based on the information available which included important confounding factors like associated comorbidities (HIV, Castleman's Disease, SLE), exposure to COVID-19, etc.

Based on the cumulatively estimated total doses of elasomeran administered worldwide (772,908,958 doses) the reporting rate for cases of HNL after administration of elasomeran is 0.0005 cases per million doses administered. In addition, all four reported cases were considered unlikely related to the vaccine.

Evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

16.3.6.7.9.6 Conclusion

The data provided in this PBRER describe sufficiently the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in the reporting period and cumulatively. The cumulative data shows no new safety concerns or change in safety profile of the vaccine and the benefit-risk evaluation remains positive. The MAH considers that at this time there is no need to update the product information or the RMP for elasomeran.

Based on the analysis of all safety data available as of 17 Dec 2022, the MAH considers that for cases included under the histiocytic necrotizing lymphadenitis PTs (Table 16.180), information provided in the majority of the reports is inadequate to provide evidence of causality between elasomeran exposure and HNL. The MAH will continue to monitor events of HNL using routine surveillance.

16.4 Characterization of Risks

Table 16.181 Important Identified/Important Potential Risks

Important Identified Risk	Myocarditis
Potential Mechanism	Myocarditis is an under-diagnosed cardiac disease resulting from any one of a broad range of infectious, immune, and toxic causes. Most cases of myocarditis are caused by infectious agents, toxic substances, drugs or autoimmune disorders. Hence, it is increasingly recognized that myocarditis is an inflammatory condition of the myocardium triggered by various factors rather than a distinct cardiovascular disease. Infectious causes include viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa. Non-infectious triggers have been identified such as toxins, auto immunes disease and hypersensitive reactions. Numerous medications like antipsychotics (e.g., clozapine), antibiotics (penicillin, ampicillin, sulfonamides, tetracyclines), and antiphlogistic (e.g., mesalamine) can induce hypersensitivity eosinophilic myocarditis. Myocarditis has been reported following many different vaccines including flu vaccine, however the smallpox vaccine has the strongest association. During the influenza epidemic of the winter 1998-1999 there were several reports of patients who had preceding flulike symptoms and fever and developed cardiac involvement between 4 and 7 days after the onset of influenza symptoms [208]. Evaluation of the post-authorization safety data suggest a very rare risk of myocarditis following COVID-19 vaccination, the mechanisms involved in such vaccine-related myocarditis are not clear based on the data currently available.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and the post-authorization safety.
Characterization of risk	In Study mRNA-1273-P301 (Part A), there were 15,184 participants exposed to the elasomeran vaccine, and 15,166 participants in the placebo arm. There were no reported TEAEs of Myocarditis follow-up period after vaccination. No cases have been reported in Part B of the study (CSR mRNA-1273-P301 addendum 1 (Safety from open-label phase [Part B]). Using post-authorization safety data, an evaluation of all the cases identified as cases of Myocarditis, utilizing the WHO-UMC causality assessment and the newly developed DRAFT Myocarditis Brighton Collaboration case definition (30 May 2021) was conducted. A total of 77 cases were identified. Analysis of the 77 cases that reported events of myocarditis using the WHO-UMC standardized case causality assessment revealed that there were 20 reports (8% of the Myocarditis cases) classified as "Possible" events, 11 reports were classified as "Conditional", 17 reports were classified as "Unlikely", and 29 were classified as "Unassessable". Of the "Possible" 20 cases, there were 18 males and 2 females. Their ages were between 18 and 52 years of age. The reported TTO was between 0 days and 10 days (Median= 3 days). The 20 reports that were classified as "Possible" according to the WHO-UMC causality assessment, were evaluated according to the Myocarditis Brighton Collaboration case definition. Out of the 20 possible reports,

Important Identified Risk	Myocarditis
	there were 2 classified as Level 1 (Definitive case); 12 classified as Level 2 (Probable case); and 6 were classified as Level 4 (a reported event of myocarditis with insufficient evidence to meet level 1,2 or 3 of the case definition). As of DLP of this PBRER, there were 3,534 cases of Myocarditis reported.
Risk factors and risk groups	Myocarditis related to SARS-CoV-2 infection has been reported since the beginning of the pandemic. Multiple studies have reported the prevalence of cardiac complications in adults after being diagnosed with COVID-19, which included heart failure (23%–33.3%), myocardial injury/myocarditis (8%–27.8%), arrhythmia (16.7%), and thromboembolism (31%–40%) [33]. Among these, high mortality rates (51%–97%) have been described in several cases series. Although the incidence of myocarditis in the vaccinated population is higher than in unvaccinated individuals, the risk of myocarditis due to COVID-19 and its fatal outcome is much lower among vaccinated people. Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The annual prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. Myocarditis related to SARS-CoV-2 infection has been reported since the beginning of the pandemic. Multiple studies have reported the prevalence of cardiac complications in adults after being diagnosed with COVID-19, which included heart failure (23%–33.3%), myocardial injury/myocarditis (8%–27.8%), arrhythmia (16.7%), and thromboembolism (31%–40%) [33]. Among these, high mortality rates (51%–97%) have been described in several cases series. Although the incidence of myocarditis in the vaccinated population is higher than in unvaccinated individuals, the risk of myocarditis due to COVID-19 and its fatal outcome is much lower among vaccinated people. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men [209]. Patients are usually between the ages of 20 and 50. Acute myocarditis and hyperthyroidism are also common diseases that often present in young, otherwise healthy patients. The spontaneous reports included in the GSDB included 4 cases that reported previous COVID-19 infection (5.9%) with these reports in the 18 to 39 years of age group. There were 5 reports of previous Myocarditis/ Pericarditis medical history (5.9%), 14 reports of cardiovascular conditions (16.5%), 5 with Thyroid conditions (5.9%), and 12 (14.1%) had previous medical histories of allergy-type conditions including history of anaphylaxis.
Preventability	Myocarditis presents with a spectrum of symptoms ranging from mild dyspnea or chest pain that spontaneously resolves without treatment to cardiogenic shock and sudden death. The major long-term consequence is dilated cardiomyopathy (DCM) with chronic heart failure. Common

Important Identified Risk	Myocarditis
	viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated [210]. Very rare cases of myocarditis and pericarditis have been observed following vaccination with elasomeran. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. For patients presenting with myocarditis or pericarditis after the 1st dose CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, it could consider proceeding with 2nd dose [211]. Current SmPC and Package information Leaflet (PIL) adequately covers the information on this risk awareness to the health-care professionals, caregivers and vaccinees.
Impact on the benefit-risk balance of the product	Based on the analysis of all the safety data, there have been very rare reports of myocarditis occurring after vaccination with Moderna COVID-19 Vaccine. Causal association between elasomeran and myocarditis is considered of at least a reasonable possibility. The majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended [43].
Public health impact	Myocarditis associated with vaccines typically occur at a low incidence, which results in a low public health impact. Although the potential clinical consequences of the occurrence of myocarditis is serious, this is a risk known to healthcare professionals and can be managed with early diagnosis with supportive treatment. Most observed cases have been of mild severity, and spontaneously resolved.

Important Identified Risk	Pericarditis
Potential Mechanism	Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterized by chest pain, pericardial friction rub, changes in the electrocardiogram (ECG) and occasionally, a

Important Identified Risk	Pericarditis
	pericardial effusion. Generally, the diagnosis requires 2 of these 4 features. Epidemiologic data on the incidence of acute pericarditis are lacking, likely because this condition is frequently inapparent clinically, despite its presence in numerous disorders [212]. However, it appears to be the most common form of pericardial disease and a relatively common cause of chest pain. It is diagnosed in approximately 0.1% of patients hospitalized for chest pain and in 5% of patients admitted to the ED for chest pain unrelated to acute myocardial infarction (MI). Although acute pericarditis occurs in all age groups and in men and women, it presents most often in men 20 to 50 years of age. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases. Other common causes include infection, renal failure, myocardial infarction (MI), post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from the CTs and post-authorization safety data.
Characterization of risk	In study mRNA-1273-P301 (Part A), in the safety set, there were 15,184 participants exposed to the elasomeran vaccine, and 15,166 participants in the placebo arm. There were four TEAE of "Pericarditis" in P301: Two TEAEs in the Placebo arm, and two in the Vaccine arm of the safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the >18 to <65 years of age. The events in the vaccination arm were reported in a male in his 60s' and a female in her 50s'. In Part B, one case of acute pericarditis (verbatim: "acute infective pericarditis") was reported in a male in his 60s' in the placebo group; the event occurred 24 days after a COVID-19 diagnosis. In addition, one case of pericardial effusion was reported as an SAE (resolving) in a 20s' years old male in the placebo–elasomeran group. No participant in the elasomeran group experienced pericarditis (CSR mRNA-1273-P301 addendum 1 (Safety from open-label phase [Part B]). A review of the spontaneous reports from the Company's global safety identified 68 case reports with the PTs of Pericarditis. All of the aforementioned reports were considered serious reports. As a difference with the Myocarditis reports, most of the Pericarditis reports (64.7%) involved persons >50 years of age. There was not an important difference between the reported genders, with 51% males, and 47% females. There was not an important difference in the TTO for the pericarditis cases with 16% reporting a TTO less than 1 day, 18 % for each 2 to 3 days and 4 to 7 days. The majority of the reports reported a TTO of more than 8 days following last vaccination. Occurrence following dose 1 was very similar (37% of reports) to the one seeing following dose 2 (41%). Dose number was not reported in 22% of the cases. Evaluation of all the 68 cases identified as cases of Pericarditis, utilizing the WHO-UMC causality assessment, there were 18 reports that were classified as "Possible" according to the WHO-UMC causality assessment. Of these "Possible" 18 cases, there were 9 males and 9

Important Identified Risk	Pericarditis
	females. Their ages were between 28 and 82 years of age (Median= 51.5). 8 reports were after the 1st dose, 9 after the 2nd dose of the elasomeran vaccine, and 1 did not provided dose information. The reported TTO was between 1 days and 23 days (Mean 11.3 days). The rest of the 68 cases that reported Pericarditis, 11 cases (16.2%) were classified as "Conditional"; 21 cases (30.8%) were classified as "Unassessable/ Unclassifiable"; and 18 (26.5%) were classified as "Unlikely". The post-marketing reporting rate for pericarditis (without myocarditis) was 2.16 per 100,000 person-years based on a 21-day risk window following each dose of vaccine administered.
Risk factors and risk groups	Acute pericarditis occurs when the bilayer pericardial sac becomes inflamed. In most cases, the cause of pericarditis is idiopathic or is assumed to be due to a viral infection for which the antecedent virus is not identified. There are several less common infectious and non-infectious causes of pericarditis, but most patients with acute pericarditis present with a history suggestive of recent or concurrent viral illness. Most cases resolve with no long-term sequelae. While pericardial effusions might develop as a result of pericarditis, they are usually minor and rarely result in cardiac tamponade [213]. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years [214]. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65 [215]. Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.
Preventability	Pericarditis may be caused by many disorders (e.g., infection, MI, trauma, tumors, metabolic disorders) but is often idiopathic. Symptoms include chest pain or tightness, often worsened by deep breathing. Cardiac output may be greatly reduced if cardiac tamponade or constrictive pericarditis develops. Diagnosis is based on symptoms, a friction rub, electrocardiographic changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram [216]. Pericarditis may result in one of two serious complications: cardiac tamponade and chronic constrictive pericarditis. Cardiac tamponade is considered a medical emergency and, if left untreated, can quickly become fatal. Very rare cases of myocarditis and pericarditis have been observed following vaccination with elasomeran. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Important Identified Risk	Pericarditis
	Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, could consider proceeding with 2nd dose [211].
Impact on the benefit-risk balance of the product	Based on the analysis of all the safety data, it shows that there have been very rare reports of pericarditis occurring after vaccination with Moderna COVID-19 Vaccine. Although causality cannot be established at this time, the majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of pericarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended.
Public health impact	Pericarditis associated with vaccines typically occur at a low incidence, which results in a low public health impact. Although the potential clinical consequences of the occurrence of pericarditis are serious, this is a risk known to healthcare professionals.

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Potential Mechanism	Research points to disease enhancement being triggered by one of two major mechanisms although other mechanisms may also contribute. The first and least well characterized is when priming by the initial infection results in a Th2 biased immune response mediated more by myeloid lineage cells, including neutrophils and eosinophils with immune complex formation and complement activation. While this inflammatory phenotype may be preferred for parasitic infections it is not ideal for viruses, for which an adaptive T-cell and antibody mediated Th1 type response is preferable. This "Th2 biased" phenotype is most associated with enhanced disease as resulting from the formalin-inactivated measles and respiratory syncytial virus (RSV) vaccines. In these cases, post-vaccination exposure of previously naïve vaccines resulted in an immune response characterized by high interleukin (IL) 4, 5 & 13 levels and localized tissue inflammation associated with neutrophil and eosinophil infiltration, immune complex deposition and pulmonary inflammation and obstruction. The second and far better characterized mechanism is antibody dependent

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
	enhancement. This results from the generation of binding but poorly neutralizing antibodies induced by heterologous antigens generated either by heterologous viral strains (e.g., dengue), by chemically disrupted antigens (e.g., formalin-inactivated RSV and measles) or by epitope altering mutations such as feline infectious peritonitis. These antibodies bind to but do not neutralize the virus and facilitate Fc receptor mediated entry of viable virus into macrophages. This can result in an accelerated and more marked viremia and more severe disease. This scenario is the one associated with dengue virus and its virus and vaccine-associated ADE. ADE for dengue can also result from sub-neutralizing concentrations of neutralizing antibodies, such as that seen in infants as maternal antibodies wane. It is likely that in many cases there are components of both mechanisms in enhanced disease.
Evidence source(s) and strength of evidence	As of 17 Dec 2022, SARS-CoV-2 vaccines have not been associated with VAED in preclinical studies or in any ongoing or completed clinical studies for mRNA-1273, nor in any post-marketing reports received in the GSDB. Even with the potential for new variants/serotypes of SARS-CoV-2, to provoke sub-neutralizing antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as it was the case for SARS-CoV-2 variant Omicron, which demonstrates a drop in neutralizing antibody titres in patients who have received two doses of a mRNA COVID-19 vaccine. Despite this drop in neutralization, enhancement of disease has not been reported. Infection with other variants of SARS-CoV-2 have also been shown to impact antibody binding to SARS-CoV-2 and its variants post-vaccination through imprinting, but no disease enhancement has been reported in these cases either. Cross reactivity has been observed between SARS-CoV-1 and SARS-CoV-2, which results in improved vaccine-induced immune responses by provoking the generation of broadly- neutralizing antibodies against a wide variety of coronaviruses.
Characterization of risk	Not applicable as no evidence of harm has been identified.
Risk factors and risk groups	This is a potential risk and no increased risk to elasomeran has been established. Therefore, no risks groups or risks factors can be identified. However, the generation of binding but poorly neutralizing antibodies in individuals may result in an accelerated and more marked viremia and more severe disease.
Preventability	Information is not available as the risk remains theoretical.
Impact on the benefit-risk balance of the product	In addition to possible early efficacy, the Data Safety Monitoring Board has monitored Phase 3 mRNA-1273-P301 study for vaccine harm. Based on these analyses no vaccine harm was identified. This risk is further evaluated in the ongoing Phase 3 mRNA-1273-P301 through continued trial follow-up as well as pharmacovigilance activities.
Public health impact	The public health impact of elasomeran in worsening COVID-19 disease

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
	is unknown but this could impact the benefit-risk should this event be reported in a significant number of vaccinees.

Missing information	Use in Pregnancy and While Breast-Feeding
Evidence source	Use of Moderna COVID-19 vaccines during pregnancy is an area of missing information in the Risk Management Plan (RMP); no CTs were conducted among pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications in this population. There have been no specific safety concerns identified for COVID maternal immunization. Epidemiological studies have not indicated any increased risk of adverse perinatal outcomes including spontaneous abortion, preterm birth, small for GA birth, stillbirth, or neonatal intensive care admission after COVID-19 vaccination during pregnancy. More specifically, a case-control study case-control study from Norwegian registries of 13 956 women with ongoing pregnancies (958 vaccinated) found adjusted odds ratios of 0.91 (0.75 to 1.10) for COVID-19 vaccination in the previous three weeks following a spontaneous abortion and 0.81 (0.69 to 0.95) for vaccination in the previous five weeks, showing no risk of early pregnancy loss after COVID-19 vaccination. Another important perinatal outcome of interest after maternal vaccination is risk of fetal anomalies. Given the importance of timing in pregnancy and risk of fetal anomalies, a large cohort study evaluated the association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies and found no difference in incidence of congenital anomalies among people who received at least one dose of COVID-19 vaccine versus unvaccinated people. Importantly, after control for potential confounders such as hemoglobin A1c level in the first trimester and age at delivery, vaccination within the highest risk period for teratogenicity was not associated with presence of congenital anomalies identified by ultrasonography (adjusted odds ratio 1.05, CI: 0.72 to 1.54). Additional studies have not found an increased risk of congenital anomalies among pregnant people received COVID-19 vaccines including elasomeran during pregnancy. There have also not been specific safety concerns identified for vaccinated breast-feeding women and/or their breastfed children. Epidemiological studies have not indicated any increased risk of side-effects in the mother or the breastfed child after vaccination with elasomeran, or decreased milk production. More specifically, a large series of 17,525 women vaccinated with a COVID-19 vaccine of which 6,815 were lactating women (2,596 received elasomeran), 7,809 pregnant, and 2,901 women of reproductive age planning to get pregnant,

Missing information	Use in Pregnancy and While Breast-Feeding
	found that there was no difference in rate of AEs by vaccine type across all groups and the AEs were transient, mild and consistent with reactogenicity events. Regarding the side-effects among infants exposed to breastmilk from mothers who had been vaccinated with elasomeran, studies show no increased risk in short-term adverse effects. In the large case series by [84], only 3% and 4.4% of breastfeeding mothers reported to have concerns about the infant after the first dose and second dose, respectively. Few infant events are reported; and the most common side-effects seen among nursing children are transient, non-serious poor sleep and irritability. Regarding impact of vaccination on breastmilk production, most studies have shown that only a small percentage of lactating vaccine recipients report a transient reduction in breastmilk production post-vaccination. The literature also demonstrates robust secretion and transfer of maternal SARS-CoV-2 antibodies (mainly Immunoglobulin (Ig) A and IgG) induced by vaccination through breast milk, and some studies have showed these antibodies have neutralizing activity indicating potential passive protection to the infant, although the effectiveness is not yet established.
Anticipated risk/consequence of the missing information	Targeted populations of the indication will include women of childbearing potential, thus, the use of elasomeran in pregnant and breastfeeding women may happen. Pregnancy outcome data will be collected in enhanced pharmacovigilance. An observational cohort pregnancy study will inform on the risk of adverse outcome in women who were exposed to elasomeran during pregnancy.
Missing information	**Long-Term Safety**
Evidence source	Per protocols, the clinical development program has a safety follow-up period of 12 months in the ongoing Phase 1 study 20-0003, Phase 2a Study mRNA-1273-P201 and, 24 months in the Phase 3 study mRNA-1273-P301. In the Phase 3 Study mRNA-1273-P301 the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183◦days (range: 1 to 218 days), or approximately 6 months. The follow-up time is through Day 209 for the Phase 1 study DMID 20-0003 and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.
Anticipated risk/consequence of the missing information	The long-term safety profile continues to be characterized through continued trial follow-up, active surveillance for safety, a European post-authorization safety study, and routine pharmacovigilance.

Missing information	Use in Immunocompromised subjects
Evidence source	Immunocompromised and/or Immunosuppressed people were excluded from CTs, thus this subpopulation constitutes missing information in the MAH's Risk Management Plan (RMP). The MAH has been monitoring

Missing information	Use in Immunocompromised subjects
	the safety profile in this subpopulation through routine pharmacovigilance. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, countries are recommending a booster dose (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in immunocompromised individuals, especially now with the bivalent vaccines. The third dose of elasomeran recommended for immunocompromised patients is 100 ug dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 ug dose. In general, public health and professional groups recommend COVID-19 vaccination for patients immunocompromised. These recommendations highlight the likely potential benefits of COVID vaccines in this population with the potential risk of more severe COVID infections, sequelae, and impact on underlying immune-mediated diseases. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals immunocompromised after vaccination with elasomeran, and they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran. Analyzes have found a higher risk of hospitalization or death from COVID-19 in those with a variety of immunocompromising conditions, including rheumatic diseases, hematological malignancies, solid organ transplants, and HIV. Factors that increase the risk of severe COVID-19 in the general population, such as older age, chronic kidney disease, cardiovascular disease, and other comorbidities, are significant drivers of risk in immunocompromised individuals. Moreover, some immunodeficiencies seem to increase the risk above and beyond traditional risk factors.
Anticipated risk/consequence of the missing information	After careful review of all new safety data received during the reporting period for the safety topic of Use in Immunocompromised individuals, the benefit-risk profile for elasomeran remains favorable. Review of the safety data in immunocompromised subjects reported in the GSDB indicates that the general pattern of commonly reported AEs in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population, rather than as a result of vaccine exposure. The MAH continues to evaluate "Use in Immunocompromised subjects" in reports of elasomeran and Bivalent Boosters via routine

Missing information	Use in Immunocompromised subjects
	pharmacovigilance activities as well as through post-authorization safety studies. Throughout the world all the EUA received for elasomeran includes recommendations for additional doses for immunocompromised subjects Use of elasomeran in immunocompromised subjects is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.

Missing information	Interactions with other vaccines
Evidence source	The MAH has monitored interactions with other vaccines in each Monthly Safety Summary Report (MSSRs) as well as in PSURs since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found: Review of the safety data on individuals receiving concurrent vaccines with elasomeran reported in the GSDB indicates that the general pattern of commonly reported AEs are consistent with expected reactogenicity events and are comparable to events observed in the general population receiving other widely used vaccines. Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show an increase in reporting of AEs. Health authorities consider that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial. Use of elasomeran with other vaccines, including childhood immunization vaccines is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran.
Anticipated risk/consequence of the missing information	Extended use of the elasomeran vaccines in conjunction with other vaccines has provided extensive safety information for "Interactions with other vaccines" no longer be considered missing information. Concomitant use of other vaccines with elasomeran is included in the Summary of Products Characteristics: High dose quadrivalent influenza vaccine can be concomitantly administered with elasomeran. The MAH continues to evaluate "Interaction with other vaccines" in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies. Concomitant use of the vaccine with the influenza vaccine is already included in the product's labeling, and the use of with other vaccine is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of elasomeran. There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile

Missing information	Interactions with other vaccines
	of the product with respect to Interaction with other vaccines' as long-term safety is being kept as missing information.

Missing information	Use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
Evidence source	Frail patients are considered at higher risk of complications due to coronavirus disease 2019 (COVID-19) infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. Since frail subjects with unstable health conditions and comorbidities were excluded from the registration trials, ModernaTx, Inc. is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Frailty refers to a state of vulnerability to stressors characterized by a decreased physiological reserve, resulting in poor health outcomes compared to individuals of the same chronological age. There is growing evidence supporting the safety profile of the COVID-19 vaccine in immunocompromised patients, such as HIV-infected patients, diabetics, and patients with cardiopulmonary diseases, is similar to that in the general population. Presently, the US Centers for Disease Control and Prevention, British Society for Immunology, and various other governmental and professional societies and organizations endorse COVID-19 vaccination in the immunocompromised population. Overall, recommendations for use in patients with immunocompromising medical conditions and immunosuppressing medications on the efficacy of the vaccine may support the extrapolation into the frail subpopulation indicating potential benefits to outweigh theoretical risks. The frail population was the first subpopulation group vaccinated with elasomeran and other COVID-19 vaccines given that this population was recognized to have the potential for more severe complications due to COVID-19 infection. This same recommendation is still in place for vaccination against SARS-CoV2 and its variants. [120] in a prospective, multicenter, national VAX4FRAIL study (NCT04848493) which evaluated vaccines in a large trans-disease cohort of patients with solid or hematological malignancies, and/or neurological, and/or rheumatological diseases demonstrated that frail patients who are candidates for mRNA COVID-19 vaccination should be reassured about the safety profile of vaccine strategy. They noted that AEs were in line with the reporting from the healthy cohort of subjects and national observatories, no evidence of worsening of the underlying disease was reported, and no concern on the adherence to the treatment program of the disease itself emerged from the prospective multicenter national study. [121] is an observational cohort study examining approximately 325 frail patients with rheumatic and musculoskeletal diseases and taking immunomodulatory therapy; 51% received BNT-162b2 and 49% were vaccinated with elasomeran. The most common diagnoses were

Missing information	Use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	inflammatory arthritis (38%), systemic lupus erythematous (28%) and overlap connective tissue disease (19%). Observed AEs were mild local and systemic reactions consistent with expected vaccine reactogenicity and occurred at a similar frequency as in the non-frail population. Thus far, there have been no specific safety concerns identified for use of elasomeran in frail subjects with unstable health conditions and comorbidities. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals when compared to the general population after vaccination with elasomeran, and they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran. As of the DLP of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in frail individuals. Serious events and fatalities reported after vaccination are heavily confounded or may have been caused by underlying medical conditions. Otherwise, the general pattern of commonly reported AEs in those considered frail individuals or with unstable health conditions and comorbidities is comparable to the general population.
Anticipated risk/consequence of the missing information	The MAH has monitored Use in frail subjects with unstable health conditions and comorbidities in each MSSRs as well as PSURs since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found: Review of the safety data in frail subjects with unstable health conditions and comorbidities reported in the GSDB indicates that the general pattern of commonly reported AEs in those frail subjects with unstable health conditions and comorbidities is comparable to the general population, rather than as a result of vaccine exposure. The MAH continues to evaluate Use in frail subjects with unstable health conditions and comorbidities in reports of elasomeran and Bivalent Boosters via routine pharmacovigilance activities as well as through post-authorization safety studies. Use of elasomeran in frail subjects with unstable health conditions and comorbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines and no longer constitutes missing information in the safety profile of elasomeran.

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders
Evidence source	Use of elasomeran in individuals with autoimmune and inflammatory disorders (AI/ID) is an area of missing information in the Risk Management Plan (RMP). Because there was limited data from CTs on the use of elasomeran in individuals with AI/ID, the MAH has been closely monitoring the safety profile of elasomeran in this population

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders
	through routine pharmacovigilance. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, countries are recommending a booster dose (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in immunocompromised individuals, especially now with the bivalent vaccines. The third dose of elasomeran recommended for immunocompromised patients is 100 ug dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 ug dose. In general, public health and professional groups recommend COVID vaccination for patients with autoimmune or inflammatory disorders (AI/ID). These recommendations highlight the likely potential benefits of COVID vaccines in this population with the potential risk of more severe COVID infections, sequelae, and impact on underlying immune-mediated diseases. Of note, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine and may be a risk factor for more severe COVID-19 disease. As it has been described before in previous PBRER, exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID vaccines. Given that each AI/ID has a different immune pathophysiology, makes it difficult to generalize observed flare rates across different AI/ID conditions. Despite the limitations noted above, study findings indicate that the safety profile of elasomeran among individuals with AI/ID is reassuring and disease flares are limited. The published literature continues to support the benefit-risk profile of the use of elasomeran in individuals with autoimmune and inflammatory diseases. As of the DLP of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in individuals with AI/ID. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. In addition, there have been non-serious, serious and fatal reports of COVID-19 in this subpopulation, perhaps reflective of reduced immunogenicity/effectiveness of the vaccine in this population, the surges of variants and subvariants, waning immunity, and

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders
	policy and behavior changes. Otherwise, the general pattern of commonly reported AEs in those with a medical history of AI/ID is comparable to the general population.
Anticipated risk/consequence of the missing information	The MAH has monitored Use in individuals with AI/ID in each MSSRs as well as PSUR since EUA (18 Dec 2020) at the request of the EMA and other HAs. Over the years of analysis and the large scale of use of elasomeran (and other COVID-19) vaccines and boosters, the MAH has found: Review of the safety data individuals with AI/ID reported in the GSDB indicates that the general pattern of commonly reported AEs in those with a medical history of autoimmune/ inflammatory disorder is comparable to the general population, rather than as a result of vaccine exposure. Exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID vaccines. This has been recognized by professional and public health organizations; yet, given the risk of the potential consequences of COVID infection, some are recommending vaccination with monitoring and management of any potential flare or exacerbation occurring after vaccination. In addition, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine, and/or make them more susceptible to infections. Use of elasomeran in individuals with AI/ID is embedded in clinical practice and included in the SmPC and relevant health guidelines. The MAH continues to evaluate Use in individuals with AI/ID in reports of elasomeran and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorization safety studies.

16.5 Effectiveness of Risk Minimization Measures

There are no additional risk minimization measures in place for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Routine risk minimization activities are sufficient to manage the safety of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

17 BENEFIT EVALUATION

17.1 Important Baseline Efficacy and Effectiveness Information

Epidemiology and Natural History of COVID-19 disease

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome (MERS-CoV) and severe acute

respiratory syndrome (SARS-CoV). Coronaviruses infect humans, other mammals and avian species, including livestock and companion animals. Four CoVs are causes of the common cold and represent the only significant CoVs to infect humans prior to the 21st century. Before 2019, novel coronaviruses had resulted in two major respiratory illness outbreaks during the 21st century: SARS, which occurred during 2002–04; and Middle East respiratory syndrome (MERS), which began in 2012 [217].

As of 11 Dec 2022, over 645 million confirmed cases and over 6.6 million deaths have been reported globally [218].

As the name suggests, SARS-CoV-2 is primarily a respiratory infection, with manifestations ranging from asymptomatic infection to death due to pneumonia or to related organ failure as a consequence of primary pulmonary infection. The initial steps of coronavirus infection involve the specific binding of the coronavirus spike (S) protein to the cellular entry receptors, which have been identified for several coronaviruses and include human aminopeptidase N (APN; HCoV-229E), ACE2; HCoV-NL63, SARS-CoV and SARS-CoV-2) and dipeptidyl peptidase 4 (DPP4; MERS-CoV. The expression and tissue distribution of entry receptors consequently influence viral tropism and pathogenicity [219]. The replication cycle of the SARS-CoV-2 virus infection into the host cell can be divided into several key steps: (a) attachment and cell entry, (b) transcription of viral replicase, (c) genomic transcription and replication, (d) translation of structural proteins, and (e) virion assembly and release [220].

A cluster of pneumonia cases of unknown cause was reported in the city of Wuhan, China, by health officials on 31 Dec 2019. Sequencing of the fluid samples collected from the cluster of those patients with pneumonia identified the causal agent as a novel coronavirus [221] and soon the virus was named as SARS-CoV-2. By 07 Jan 2020, the China National Institute of Viral Disease Control and Prevention had confirmed the genetic sequence of SARS-CoV-2 and that the virus was associated with the previously reported pneumonia cluster in Wuhan. On 20 Jan 2020, the US CDC activated its emergency operations center in response to the emerging public health threat of COVID-19. On 30 Jan 2020, WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern, and 6 weeks later, on 11 Mar 2020, WHO characterized the COVID-19 epidemic as a pandemic[222]; however, widespread community transmission was already occurring in many locations [223].

On 11 Mar 2020, the WHO officially declared the outbreak a pandemic, and governments across the world began implementing strategies to slow the infection spread, including social distancing

and complete lockdown [223]. On 16 Mar 2020, no more new cases were reported in China, but by 19 Mar 2020 the death toll surpassed 10,000 worldwide [223]. Italy quickly became the new emerging epicenter with peak daily new cases reported at 6,557 on 21 Mar 2020 [223]. The infection quickly spread in the US, with at least 100,000 cumulative cases by 27 Mar 2020, and over 2,700 deaths. On 29 Mar 2020, the global number of cases surged to >600,000, including more than 29,000 deaths [223]. On 29 Mar 2020, Spain recorded 838 new deaths in 24 hours [223]. By the end of Mar 2020, few countries with unreported cases remained. The death toll in the US surpassed that in China, and the international community had begun an unprecedented lockdown [224] [225].

By 09 Feb 2021, a spike in the death toll was reported with 910 deaths and 40,000 cases in China alone [225]. On 15 Feb 2021, Egypt and France reported deaths due to COVID-19 [225]. By the end of Feb, 11 additional European countries reported cases with 82,000 confirmed infections and 2,800 people killed worldwide [225].

Globally, the number of new weekly cases remained stable (+2%) during the week of 5 to 11 Dec 2022 as compared to the previous week, with over 3.3 million new cases reported. The number of new weekly deaths increased by over 10% as compared to the previous week, with over 9700 new fatalities reported. As of 11 Dec 2022, over 645 million confirmed cases and over 6.6 million deaths have been reported globally [218].

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids in three principal ways: 1) inhalation of respiratory droplets and aerosol particles; 2) deposition of respiratory droplets and aerosol particles on mucous membranes in the mouth, nose, or eye by direct splashes and/or sprays; and, 3) touching mucous membranes with hands that have been soiled either directly by respiratory fluids or indirectly by touching surfaces with virus on them [226]. Transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic individuals has also been documented and may account for an estimated 59% of transmission [227]. Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state, liver disease, obesity, pregnancy, sickle cell disease, solid organ transplant, and stroke or cerebrovascular disease [228]. Smokers and individuals with substance use disorders are also at increased risk for severe COVID-

19 [228].

Most individuals with COVID-19 have mild symptoms or moderate illness. Approximately 10% to 15% of COVID-19 cases progress to severe disease, and approximately 5% become critically ill (WHO 2021b). Long-term sequelae in COVID-19 patients with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae [229,230]. Myocardial injury has reported among patients with severe COVID-19 [231]. Additionally, some patients develop serious medical complications such as myocardial inflammation, ventricular dysfunction, pulmonary function abnormalities, and acute kidney injury [232-236] [237] While more serious long-term health complications appear to be less common, they have individual, global health, and severe socioeconomic consequences.

Like all RNA viruses, SARS-CoV-2 is prone to mutation. Multiple viral variants have been detected, most of which appear to have little if any biological significance. However, a small number of 'variants of concern' (VOC) appear to influence SARS-CoV-2 transmissibility and possibly also host immune responses. Since the outbreak of the COVID-19 caused by the 2019 novel CoV began in Wuhan, in Dec 2019, the WHO proposed labels for global COVID-19 variants of concern (VOC) and variants of interest (VOI) (WHO 2021b). According to WHO, currently circulating VOC is the Omicron variant. Delta was originally documented in Oct 2020 in India and Omicron first documented in various countries in Nov 2021.

There is currently no circulating VOI (WHO 2021b). Latest VOCs have largely replaced other co-circulating SARS-CoV-2 variants. Delta reached almost 90% of all viral sequences submitted on Global Initiative on Sharing Avian Influenza Data (GISAID) by Oct 2021, and Omicron is currently the dominant variant circulating globally, accounting for >98% of viral sequences shared on GISAID after Feb 2022.

Among the 15 EU/EEA countries with an acceptable sequencing volume in the period from 13 May 2022 to 12 Jun 2022, the Omicron VOC remains the dominant variant circulating globally, accounting for 97% of sequences reported. Among Omicron lineages submitted, BA.2 represents 39%, while BA.2.12.1 represents 28%, BA.5 represents 6%, and BA.4 represents 3%. For epidemiological week 20 (15 May 2022 to 21 May 2022) and week 21 (22 May 2022 to 28 May 2022), there was a 4% decline in the number of BA.2 sequences, while there were increases of 4%, 3%, and 2% in BA.5, BA.2.12.1, and BA.4 sequences respectively.

World Health Organization created a case definition to identify VOC: A SARS-CoV-2 variant that

meets the definition of a Variant of Interest (VOI) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance: Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR Increase in virulence or change in clinical disease presentation; OR Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

As transmission of these VOCs has been sustained, this has led to significant intra-VOC evolution. Since its designation as a VOC by WHO on 26 Nov 2021, viruses' part of the Omicron complex has continued to evolve, leading to descendent lineages with different genetic constellations of mutations. Each constellation may or may not differ in the public health risk it poses, and each lineage that includes substitutions in key sites may need further investigation to assess whether its characteristics diverge or not from those that define the VOC they stem from.

In light of the widespread transmission of the Omicron VOC across the globe and the subsequent expected increased viral diversity, WHO has added a new category to its variant tracking system, termed "Omicron subvariants under monitoring" to signal to public HAs globally, which VOC lineages may require prioritized attention and monitoring. According to WHO, the main objective of this category is to investigate if these lineages may pose an additional threat to global public health as compared to other circulating viruses.

The SARS-CoV-2 virus has continued to evolve globally, and 5 VOCs have been identified to date: namely Alpha, Beta, Gamma, Delta, and Omicron. The Omicron variant has become the epidemiologically dominant variant in multiple countries in 2022 and Omicron subvariants with additional spike protein mutations (BA.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, BN.1 and XBB.1) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). According to the NOWCAST report from the Center of Disease Control and Prevention in the US (12 Nov 2022–17 Dec 2022) the BQ.1.1, BQ.1, BA.5, and XBB.1.5 subvariants comprised approximately 35.3%, 23.3%, 16.1%, and 7.2%, respectively, of the SARS-CoV-2 sequences analyzed. On 17 Jun 2022, the WHO issued an interim statement on the composition of current COVID-19 vaccines. Due to the continued evolution of SARS-CoV-2 viruses and the associated increasing potential for immune escape from currently authorized COVID-19 vaccines based on the ancestral (Wuhan-Hu-1) strain, WHO recommended that inclusion of Omicron VOC in an updated vaccine composition may be considered to achieve "broader immunity against circulating and emerging variants, while retaining protection against severe disease and death."

The general consensus reached amongst the regulators was aligned with WHO recommendation that an inclusion of an antigenically distinct variant, primarily Omicron (but to a lesser extent, Beta) should be considered as an additional component for a modified variant vaccine to be used going forward. The bivalent approach was favored over the monovalent approach however, a monovalent Omicron could also be considered.

The MAH developed a portfolio of modified, bivalent booster vaccines, which contain equal amounts of the mRNA sequence for the spike protein of ancestral SARS-CoV-2 and of a VOC. The first developed bivalent booster was mRNA-1273.211 (also referred to as ".211"), which contains 25 µg of mRNA-1273 and 25 µg of the Beta spike mRNA sequence, and was evaluated in Study P205 Part A. mRNA-1273.214 elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. Supportive data from the first bivalent vaccine (mRNA-1273.211) demonstrate a durable neutralizing antibody response to multiple variants, suggesting improved antibody persistence with bivalent vaccines.

At the request of FDA, based on the outcome of the 28 Jun 2022 Vaccines and Related Biological Products Advisory Committee (VRBPAC), the MAH developed a modified, bivalent booster; elasomeran/davesomeran (also referred to as ".222") vaccine, based on the addition of Omicron BA.4/BA.5 sublineage in combination with the prototype ancestral strain, 25 µg each, 50 µg total. The bivalent elasomeran/davesomeran (Original/ Omicron BA.4/BA.5) produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine.

As of 17 Dec 2022, previously circulating VOCs and current Omicron subvariants under monitoring (www.who.int/activities/tracking-SARS-CoV-2-variants) [238] are presented in Table 17.1 and Table 17.2:

Table 17.1 Previously circulating Variants of Concerns

WHO label	Pango lineages*	GISAID clade	Next strain clade	Additional amino acid changes monitored*	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	United Kingdom,	18 Dec 2020

WHO label	Pango lineages*	GISAID clade	Next strain clade	Additional amino acid changes monitored*	Earliest documented samples	Date of designation
					Sep 2020	
Beta	B.1.351 B.1.351.2 B.1.351.3	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May 2020	18 Dec 2020
Gamma	P.1 P.1.1 P.1.2 P.1.4 P.1.6 P.1.7	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov 2020	11 Jan 2021
Delta	B.1.617.2 AY.1 AY.2 AY.3 AY.3.1	G/478K.V1	21A	+S:417N	India, Oct 2020	VOI: 04 Apr 2021 VOC: 11 May 2021
Omicron*	B.1.1.529	GRA/484A	21K, 21L 21M, 22A, 22B, 22C, 22D	+S:R346K +S:L452X +S:F486V	Multiple countries, Nov 2021	VUM: 24 Nov 2021 VOC: 26 Nov 2021

*Includes all descendent lineages.

Table 17.2 Omicron subvariants under monitoring

Pango lineage# (+ mutation)	GISAID clade	Next strain	Relationship to circulating VOC lineages	Spike genetic features	Earliest documented samples
BF.7*	GRA	22B	BA.5 sublineage	BA.5 + S:R346T	24 Jan 2022
BQ.1$	GRA	22E	BA.5 sublineage	BQ.1 and BQ.1.1: BA.5 + S:R346T, S:K444T, S:N460K	07 Feb 2022
BA.2.75§	GRA	22D	BA.2 sublineage	BA.2.75: BA.2 + S:K147E, S:W152R, S:F157L, S:I210V, S:G257S, S:D339H, S:G446S, S:N460K, S:Q493R reversion CH.1.1: BA.2.75 + S:L452R, S:F486S	31 Dec 2021
XBBμ		22F	Recombinant of BA.2.10.1 and BA.2.75 sublineages, i.e. BJ1	BA.2+ S:V83A, S:Y144-, S:H146Q, S:Q183E, S:V213E,	13 Aug 2022

Pango lineage# (+ mutation)	GISAID clade	Next strain	Relationship to circulating VOC lineages	Spike genetic features	Earliest documented samples
			and BM.1.1.1, with a breakpoint in S1	S:G252V, S:G339H, S:R346T, S:L368I, S:V445P, S:G446S, S:N460K, S:F486S, S:F490S XBB.1.5: XBB + S:F486P (see rapid risk assessment)	

Includes descendent lineages

* Additional mutations outside of the spike protein: N: G30-, S33F, ORF9b: M26-, A29I, V30L

$ additional mutation outside the spike protein: ORF1a: Q556K, L3829F, ORF1b: Y264H, M1156I, N1191S, N: E136D, ORF9b: P10F

§ additional mutations outside of the spike protein: ORF1a: S1221L, P1640S, N4060S, ORF1b: G662S, E: T11A

μ additional mutations outside of the spike protein: ORF1a: K47R, ORF1b: G662S, S959P, E: T11A, ORF8: G8*

Nature of the Benefit

Early in 2020, the WHO declared COVID-19 to represent a Public Health Emergency of International Concern, denoting its highest level of public health emergency. Globally, the number of new weekly cases remained stable (+2%) during the week of 5 to 11 Dec 2022 as compared to the previous week, with over 3.3 million new cases reported. The number of new weekly deaths increased by over 10% as compared to the previous week, with over 9700 new fatalities reported. As of 11 Dec 2022, over 645 million confirmed cases and over 6.6 million deaths have been reported globally [218]. These figures are considered underestimates. As per estimates, COVID-19 deaths in 2021 imply a 1.7-year reduction in life expectancy at birth and a 1.1-year reduction in life expectancy at age 65 for the total US population relative to pre-pandemic levels [239]. Like other respiratory viruses, SARS-CoV-2 spreads efficiently. Indeed, the most recent circulating variants, omicron and its sub lineages, have significantly enhanced transmissibility compared with the progenitor SARS-CoV-2 virus that was responsible for the start of the pandemic. Continued challenges in achieving global COVID-19 vaccine coverage, limitations in durability of vaccine protection, and viral evolution all contribute to the ongoing challenges in controlling this pandemic.

It is widely acknowledged that the lynchpin to control this pandemic is vaccination. Efforts to control the pandemic through other public health measures (e.g., social distancing, mask wearing) are helpful but not sufficient. The use of therapeutic agents to prevent or treat SARS-CoV-2

infections are similarly important but secondary to the role of primary prevention through vaccinations as a means of controlling and mitigating the impact of this pandemic.

Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, and there is an urgent public health need for rapid development of novel prophylactic therapies, including vaccines, to prevent the spread of this disease. ModernaTx, Inc's. scalable mRNA/LNP technology platform allowed for a rapid response to the pandemic and was used to develop elasomeran, a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2.

Elasomeran, an LNP-encapsulated mRNA vaccine expressing the prefusion stabilized spike glycoprotein, is enzymatically manufactured, directs vaccine antigen production in vivo, thus avoiding the need for the lengthy processes to optimize the production and in vitro characterization of the target antigen as required with traditional vaccines. This approach provides potential benefits in terms of reducing time from discovery to production. Additionally, production of the antigen in vivo likely mimics the expression of the antigen during the course of a natural infection.

mRNA does not interact with the genome, is nonreplicating, delivers only the genetic elements required for expression of the encoded protein, and is only a transient carrier of information and does not persist in the body.

During translation, mRNA serves as the template for the synthesis of the intended proteins. mRNA vaccines targeting SARS-CoV-2 represent the first vaccines employing this technology. They offer the potential to vaccinate against any encoded protein antigen with potential use in both prophylactic and therapeutic vaccines.

Moderna COVID-19 Vaccine is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 months of age and older.

Efficacy and immunogenicity against COVID-19 disease are currently being evaluated in 21 ongoing CTs including 11 sponsored by ModernaTx, Inc. Primary analysis for efficacy was demonstrated in adults 18 years and older in Study mRNA-1273-P301. The primary end point was the efficacy of the elasomeran vaccine in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second injection in the per protocol population, among participants who were seronegative at baseline."COVID-19 cases were defined as occurring in participants who had at least two of the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or as occurring in those who had

at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if the participant was hospitalized) that was positive for SARS-CoV-2 by reverse-transcriptase–polymerase chain reaction (RT-PCR) test" [240]. Vaccine efficacy was assessed in the full analysis population (randomized participants who received at least one dose of mRNA-1273 or placebo), the modified intention-to-treat population (participants in the full analysis population who had no immunologic or virologic evidence of COVID-19 on day 1, before the first dose), and the per protocol population (participants in the modified intention-to-treat population who received two doses, with no major protocol deviations). Participants were evaluated in the treatment groups to which they were assigned. Vaccine efficacy was defined as the percentage reduction in the hazard ratio for the primary end point (mRNA-1273 vs. placebo). A stratified Cox proportional hazards model was used to assess the vaccine efficacy of mRNA-1273 as compared with placebo in terms of the percentage hazard reduction [240].

The primary efficacy endpoint in Study mRNA-1273-P301 was met, elasomeran prevented COVID-19 starting 14 days after the second injection of vaccine, based on a total of 95 adjudicated cases accrued (5 cases in the elasomeran group and 90 cases in the placebo group). For the primary analysis, 196 cases of COVID-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1,000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1,000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the elasomeran vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo. Findings were similar across key secondary analyzes, including assessment starting 14 days after dose 1 (225 cases with placebo, vs. 11 with elasomeran , indicating a vaccine efficacy of 95.2% [95% CI, 91.2 to 97.4]), and assessment including participants who were SARS-CoV-2 seropositive at baseline in the per protocol analysis (187 cases with placebo, vs. 12 with elasomeran; one volunteer assigned to receive elasomeran was inadvertently given placebo], indicating a vaccine efficacy of 93.6% [95% CI, 88.6 to 96.5]). Between days 1 and 42, seven cases of COVID-19 were identified in the elasomeran group, as compared with 65 cases in the placebo group.

A key secondary end point evaluated the efficacy of elasomeran at preventing severe COVID-19. Thirty participants in the trial had severe COVID-19; all 30 were in the placebo group (indicating vaccine efficacy of 100% [95% CI, could not be estimated to 1.0]), and one death among these participants was attributed to COVID-19. The vaccine efficacy to prevent COVID-19 was consistent across subgroups stratified by demographic and baseline characteristics: age groups

(18 to <65 years of age and ≥65 years), presence of risk for severe COVID-19, sex, and race and ethnic group (non-Hispanic White and communities of color). Among participants who were positive for SARS-CoV-2, by serologic or virologic testing, at baseline (337 in the placebo group and 343 in the elasomeran).

The mRNA-1273-P301 study population included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID-19. The efficacy of elasomeran was consistent for the primary efficacy endpoint in study participants with and without risk factors for severe COVID-19, in older and younger adults, in males and females, and in White participants and those from communities of color. There was a limited number of participants in each ethnic group in the subgroup analysis who contributed to the primary efficacy endpoint, and therefore efficacy analyzes were not performed for each specific racial and ethnic subgroup.

Importantly, analysis of the 04 May 2021 dataset also showed that elasomeran 100 µg was 98.2% effective in preventing severe COVID-19, with 106 adjudicated cases of severe COVID-19 in the placebo group and 2 adjudicated cases in the elasomeran group. Subgroup analyzes of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection. Additionally, elasomeran was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of elasomeran (VE of 92.8% based on Hazard Ratios).

Elasomeran also demonstrated protection against asymptomatic SARS-CoV-2 infection. The VE to prevent asymptomatic SARS-CoV-2 infection was 63.0% (95% CI 56.6%, 68.5%) and VE to prevent SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0% (95% CI 79.5%, 84.2%).

Study mRNA-1273-P301 demonstrated that the 100 µg dose level was highly immunogenic through Day 57 as measured by both bAb and nAb in both SARS-CoV-2 baseline-negative and baseline-positive individuals. In SARS-CoV-2 baseline-positive participants, antibody levels at Day 29 were similar to those observed at Day 57 in baseline-negative participants, indicating that the first injection of elasomeran acts like a booster in participants with previous SARS-CoV-2 infection.

The final efficacy analysis of the primary endpoint for Part A (04 May 2021) was performed on 799 adjudicated first occurrences of COVID-19 starting at least 14 days after the second injection in the Per protocol (PP) Set.

The follow-up period for the final blinded efficacy analysis provided a median of 148 days (approximately 5.3 months, where 1 month=28 days) from randomization to the PDV for participants who completed their PDV on or before the data cut-off date. Additionally, the median duration of follow-up from the PDV to the data cut-off was 67 days, during which time blinded follow-up continued for participants who did not complete their PDV on or before to the data cut-off. Together, these provide a total follow-up duration of approximately 7.6 months from randomization (or approximately 6.5 months from the second injection).

The results of this analysis were consistent with the results of the interim and primary efficacy analyzes, confirming persistent, high efficacy over a substantially larger case database and over the median 5.3-months blinded observation period of Part A. For the final efficacy analysis, the VE point estimate (95% CI) was 93.2% (91.0%, 94.8%; $p < 0.0001$) and the 95% CI was observed to be within the 95% CIs for the interim and primary efficacy analyzes. In the final analysis of efficacy (database lock of 04 May 2021), 108 participants had adjudicated severe COVID-19 starting 14 days after second injection in the PP Set (106 cases in the placebo group and 2 cases in the elasomeran group); the VE point estimate (95% CI) based on the hazard ratio was 98.2% (92.8%, 99.6%), confirming and extending the findings of the primary analysis of 25 Nov 2020 based on a median of 148 days (final analysis) versus 78 days (primary analysis) of efficacy follow-up after randomization. Among these participants, 3 deaths in the placebo group were attributed to COVID-19.

The observed efficacy in each subgroup was consistent with the high efficacy observed for the primary endpoint across the entire population, and the lower bound of the 95% CI of the individual subgroup analyzes exceeded 30%, one of the success criteria for the interim efficacy analysis. Results were consistent across subgroups (VE point estimates within the 95% CI for the overall dataset) stratified by age groups ($\geq$ 18 to < 65 years, $\geq$ 65 years, $\geq$ 65 years to < 75 years, and $\geq$ 75 years); age and health risk ($\geq$ 18 to < 65 years and not at risk, $\geq$ 18 to < 65 years and at risk, and $\geq$ 65 years), sex (male and female), ethnicity (Hispanic or Latino and not Hispanic or Latino); presence of risk for severe COVID-19 at screening; and race and ethnicity. With respect to the subgroup analysis for race and ethnicity, limited numbers of participants in each ethnic group contributed to the primary efficacy endpoint. Therefore, the race and ethnicity data were pooled into a "communities of color" group for this analysis to ensure that the subpopulations in the study

would be large enough for meaningful analysis. The VE of elasomeran across major demographic and baseline characteristic subgroups was consistent with that of the primary efficacy endpoint analysis.

Studies mRNA-1273-P201 and mRNA-1283-P101 provided evidence of persistence of immune response through Day 209, 6-months after the second injection of elasomeran, although antibody levels at Day 209 were lower than peak values.

The immunogenicity of the elasomeran vaccine was evaluated in DMID Study mRNA-1273-P101/20-0003/NCT04283461 and mRNA-1273-P201 and is supportive of the efficacy of the vaccine to prevent COVID-19 as demonstrated in the pivotal mRNA-1273-P301 Phase 3 study. In DMID Study mRNA-1273-P101/20-0003/NCT04283461 (Phase 1), 2 doses of 100 µg or higher generated the highest titers of neutralizing or binding antibody and this observation was the basis for selecting the 100-µg dose for use in the pivotal mRNA-1273-P301 Phase 3 study. Importantly, the antibody levels after 2 doses of elasomeran exceeded those in a pool of convalescent sera. Neutralizing activity was observed for the 100-µg elasomeran dose as of day 36, which was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata. Additionally, in DMID Study mRNA-1273-P101/20-0003, Th1-directed CD4+ T-cells were observed to be induced across age groups, with limited indication of a Th2-directed response and similar responses were observed among all age groups for the 100-µg dose. In the dose-confirming study, mRNA-1273-P201, generally comparable neutralizing and binding antibody responses were measured in the serum of participants who received either 50 µg or 100 µg doses of elasomeran administered 28 days apart.

Efficacy in adolescents 12 through 17 years of age

mRNA-1273-P203 is an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in adolescents ages 12 to 17 years in the US (NCT04649151). Participants with a known history of SARS-CoV-2 infection were excluded from the study.

A total of 3,732 participants were randomly assigned to receive doses of either 100 µg of mRNA 1273 vaccine or a placebo control in a 2:1 randomization ratio (2,773 participants aged ≥12 to < 16 years and 959 participants aged ≥ 16 to < 18 years.

An efficacy analysis was performed in 3,236 participants who received at least Dose 1 of either Moderna COVID-19 Vaccine (n=2,163) or placebo (n=1,073) and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set). In the mITT set, 48.5% were female, 11.2% were Hispanic or Latino; 83.9% were White, 2.8% were African American, 6.3% were Asian, and 0.9% other races. Between participants who received Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as the presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive nasopharyngeal (NP) swab or saliva sample for SARS-CoV-2 by RT-PCR (reverse transcription polymerase chain reaction). Listed symptoms were fever (temperature > 38ºC/≥ 100.4ºF), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.

There were 2 COVID-19 cases in the Moderna COVID-19 vaccine group and 13 cases in the placebo group, with a vaccine efficacy of 92.7% (95% CI of 67.8% to 99.2%) (Table 17.3).

Table 17.3 Efficacy analysis: COVID-19* in participants 12 to 17 years of age starting 14 days after Dose 1–modified intent-to-treat set

Moderna COVID-19 Vaccine			Placebo			% Vaccine efficacy (95% CI)†
Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	Participant (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	
2,163	2	3.828	1,073	13	52.473	92.7 (67.8, 99.2)

* COVID-19: Presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.
† Vaccine efficacy defined as 1 — ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Immunogenicity in adolescents 12 through 17 years of age

In mRNA-1273-P203, an analysis was conducted of SARS-CoV-2 50% neutralizing titers and seroresponse rates (SRR) 28 days after Dose 2 in a subset of adolescents aged 12 through 17 in mRNA-1273-P203 and in participants aged 18 through 25 in mRNA-1273-P301 (Part A) who had no immunologic or virologic evidence of prior COVID-19 at baseline. Non-inferior immune

responses and SRR were demonstrated in a comparison of immune responses in adolescents aged 12 through 17 years compared with those of participants aged 18 through 25 (Table 17.4).

Table 17.4 Summary of geometric mean titer and seroresponse rate–comparison of adolescents aged 12 through 17 to participants aged 18 through 25–per protocol immunogenicity subset

Assay	Time point	Moderna COVID-19 Vaccine		12 through 17 years/18 through 25 years	
		12 through 17 years n=340	18 through 25 years n=305		
		GLSM (95% CI)*	GLSM (95% CI)*	GMR (95% CI)†	Met Noninferiority objective (Y/N)‡
SARS-CoV-2 neutralization assay–ID50 (titer)§	28 days after Dose 2	1401.7 (1276.3, 1539.4)	1301.3 (1177.0, 1438.8)	1.08 (0.94, 1.24)	Y
		Seroresponse % (95% CI)	Seroresponse % (95% CI)	Difference in seroresponse rate % (95% CI)#	
		98.8 (97.0, 99.7)	98.6 (96.6, 99.6)	0.2 (-1.8, 2.4)	

GLSM = Geometric least squares mean
GMR = Geometric mean ratio
n = Number of subjects with non-missing data at the corresponding timepoint
* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
† The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in mRNA-1273-P203 and young adults in mRNA-1273-P301 [Part A]) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
‡ Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%.
§ SARS-CoV-2 50% inhibitory dose (ID50) neutralization titers were determined using a SARS-CoV-2 Spike-Pseudo-typed Virus Neutralization Assay. Quantification of SARS-CoV-2 neutralizing antibodies utilizes lentivirus particles expressing SARS-CoV-2 Spike protein on their surface and contains a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by relative luminescence units (RLU). Neutralization is measured as the serum dilution at which RLU is reduced by 50% (ID50) relative to mean RLU in virus control wells virus but after subtraction of mean RLU in cell control wells.
Seroresponse due to vaccination specific to pseudovirus neutralizing antibody ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits

Efficacy in children 6 through 11 years of age

The pediatric study is an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in children ages 6 through 11 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4,011 participants were randomized 3:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for effectiveness and safety until

1 year after the second dose.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cut-off date of 06 Oct 2021 was performed in 3,556 participants who received two doses (0.25 mL at 0 and 1 month) of either the Moderna COVID-19 Vaccine (n=2,678) or placebo (n=878) and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to Treat Set [mITT]). Between participants who received the Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics. The median length of follow-up for efficacy for participants in the study was 50 days post Dose 1.

The efficacy information in children 6 through 11 years of age is presented in Table 17.5:

Table 17.5 Efficacy analysis: COVID-19 and SARS-CoV-2 infections in participants 6 through 11 years of age starting 14 days after dose 1–modified intent-to-treat set

	Moderna COVID-19 Vaccine N=2,672		Placebo N=877		% Vaccine Efficacy (95% CI)*
	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
COVID-19 Cases-Definition 1[a]	0	0	13	152.027	100.0 (89.3, NE)
COVID-19 Cases-Definition 2[b]	3	11.399	14	163.810	93.0 (75.1, 98.7)
SARS-CoV-2 Infections (regardless of symptoms)[c]	16	60.958	26	306.853	80.1 (61.5, 90.0)
Asymptomatic SARS-CoV-2 Infections[d]	13	49.529	12	141.625	65.0 (16.1, 85.3)

N = Number of participants at risk at 14 days after Dose 1 for specific efficacy endpoint.

NE = Not estimable

* Vaccine efficacy defined as 1-ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

[a] Participant must have experienced at least two of the following systemic symptoms: fever (≥38°C / ≥100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS- CoV-2 by RT-PCR.

[b] Presence of at least one symptom from a list of COVID-19 symptoms and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature >38°C / ≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.

[c] A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV- 2 status at baseline binding antibody against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline.

[d] Absence of symptoms and infections as detected by RT-PCR or serology tests: absent of COVID-19 symptoms and at least 1 of the following: binding antibody level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.

Immunogenicity in children 6 through 11 years of age

An analysis evaluating SARS-CoV-2 50% neutralizing titers and SRR 28 days after Dose 2 was conducted in subset of children aged 6 through 11 (n=134) in the pediatric study and in participants aged 18 through 25 (n=296) in the adult study (NCT04796896). Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The GMR of the neutralizing antibody titers in children 6 through 11 years of age compared to the 18- to 25-year-olds was 1.5 (95% CI: 1.3, 1.8). The difference in seroresponse rate was 0.6% (95% CI: -2.8, 2.8). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

Immunogenicity in booster dose participants

mRNA-1273-P201 is an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series. In an open-label phase, 149 of those participants (Per Protocol Set) received a single booster dose (0.25 mL) at least 6 months after receiving the second dose in the primary series. A single booster dose (0.25 mL) was shown to be immunogenic at Day 29 post-booster dose and non-inferior to Day 57 immunogenicity of the primary series (two doses of 0.5 mL 1 month apart) in a subset of participants 18 years of age and older in mRNA-1273-P301.

Immunogenicity in participants 18 years of age and older–after elasomeran/imelasomeran booster dose (0.5 mL, 25 µg/25 µg)

The safety, reactogenicity, and immunogenicity of an elasomeran/imelasomeran booster dose are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the elasomeran/imelasomeran 50 µg booster dose, and 377 participants received the elasomeran (original) 50 µg booster dose.

Study P205 Part G evaluated the safety, reactogenicity and immunogenicity of elasomeran/imelasomeran when administered as a second booster dose to adults who previously received 2 doses of elasomeran (original) (100 µg) as a primary series and a booster dose of elasomeran (original) (50 µg) at least 3 months prior to enrolment. In P205 Part F, study participants received elasomeran/imelasomeran (50 µg) as a second booster dose and the Part F group serves as a within-study, non-contemporaneous comparator group to the elasomeran/imelasomeran group.

In this study, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). In the primary analysis, the original SARS-CoV-2 estimated neutralizing antibody geometric mean titre (GMT) and corresponding 95% CI was 6422.3 (5990.1, 6885.7) and 5286.6 (4887.1, 5718.9) 28 days after the elasomeran/imelasomeran and elasomeran (original) booster doses, respectively. This GMT represents the ratio between response of elasomeran/imelasomeran versus elasomeran against the ancestral SARS-CoV-2 (D614G) strain. The GMR (97.5% CI) was 1.22 (1.08, 1.37) meeting the pre-specified criterion for noninferiority (lower bound of 97.5% CI ≥0.67).

The estimated Day 29 neutralizing antibody GMTs against Omicron, BA.1 were 2479.9 (2264.5, 2715.8) and 1421.2 (1283.0, 1574.4) in the elasomeran/imelasomeran and elasomeran (original) booster groups, respectively, and the GMR (97.5% CI) was 1.75 (1.49, 2.04), which met the pre-specified superiority criterion (lower bound of CI >1).

In Study mRNA-1273-P205 Part G, all primary and key secondary immunogenicity objectives were met. mRNA 1273.214 50 µg elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2 (D614G) 28 days after booster dose administration as compared to a 50-µg booster dose of elasomeran [241]. The GMR (97.5% CI) for primary analysis population (participants with no prior infection) against the Omicron variant was 1.75 (1.49, 2.04) exceeding the recommended criteria [241]. Omicron neutralizing antibody responses were consistently higher in participants both with and without prior evidence of SARS-CoV-2 infection in the entire study population [GMR (97.5% CI) 1.79 (1.56, 2.04)]. The neutralizing antibody response against the ancestral SARS-CoV-2 (D614G) was also significantly higher with the 50-µg mRNA 1273.214, compared to 50 µg elasomeran, 28 days after the booster dose [GMR (97.5% CI): 1.22 (1.08, 1.37), primary analysis population], indicating that elasomeran/imelasomeran retained the neutralizing antibody response against the ancestral SARS-CoV-2. Additionally, 50 µg elasomeran/imelasomeran elicited potent neutralizing antibody against the Omicron BA.4 and BA.5 subvariants. Elasomeran/imelasomeran also elicited

significantly higher binding antibody responses against multiple variants not contained in the vaccine, including Alpha, Beta, Gamma, and Delta (nominal alpha of 0.05). Therefore, elasomeran/imelasomeran provides an enhanced immune response against multiple variants.

On the basis of these results, the elasomeran/imelasomeran 50 µg elicited superior nAb responses against the Omicron subvariants BA.4, BA.5 compared with elasomeran 50 µg (nominal alpha of 0.05) and the BA.4, BA.5 nAb response was consistently higher in the elasomeran/imelasomeran group compared to the elasomeran group in participants with and without prior SARS-CoV-2.

Immunogenicity of a booster dose following primary vaccination with another authorized or approved COVID-19 vaccine in adults 18 years of age and older

Effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series and from immunogenicity data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Moderna COVID-19 Vaccine (0.5 mL) was demonstrated regardless of primary vaccination.

Immunogenicity in adult participants against the B.1.617.2 (Delta) variant

Serum samples were obtained from participants in mRNA-1273-P201 (Part B) pre-booster and on Day 29 post-booster. Results of the pseudovirion neutralization assay (PsVNA) against the B.1.617.2 (Delta) variant showed that administration of the Moderna COVID-19 Vaccine booster (50 µg) induced an 18-fold rise in neutralizing titers against the Delta variant compared with pre-

booster levels (Geometric mean fold rise (GMFR) = 18.97; 95% CI, 16.72, 21.53; overall group, n = 295).

In the overall mRNA-1273-P201 (Part B) group (n = 293), the pre-booster neutralizing antibodies (nAb) Geometric mean titer (GMT) for the Delta variant was 42.27 (95% CI: 37.19, 48.04; n=293) and 28 days post-booster, the GMT was 803.51 (95% CI: 731.42, 882.70; n = 295). Over 90% of booster recipients in the overall group (92.2%; 95% CI: 88.5, 95.0%; n = 293) met the definition of a seroresponse for the Delta variant (using a 4-fold increase from pre-booster baseline).

Administration of the 50 μg elasomeran prototype booster resulted in robust increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 μg had a GMFR of 20.89 (95% CI: 17.54, 24.87); those primed with 100 μg had a GMFR of 17.28 (95% CI: 14.38, 20.77), showing the consistency in responses regardless of priming dose.

Additional analyzes of Delta variant nAb GMT by age group have been conducted. nAb responses in older adults are numerically similar to those observed in the younger groups (749.94 vs. 822.98).

The GMFR (Day 29 post-booster: pre-booster) achieved by Moderna COVID-19 Vaccine booster, measured by the Delta pseudovirus assay (18.97; 95% CI: 16.72, 21.53), points to the ability of the prototype vaccine booster to enhance a breadth of nAb responses, including against the highly transmissible Delta variant. Just as the Moderna COVID-19 Vaccine booster generated enhanced nAb levels against the original strain (GMFR 15.06 [95% CI: 13.43, 16,89]), it also was able to broaden, and increase nAb levels against Delta variant.

Immunogenicity in children against the B.1.617.2 (Delta) variant

Additional data on the immunogenicity of the Moderna COVID-19 Vaccine against the Delta variant comes from the pediatric study. Serum samples were obtained at baseline and on Day 57 from participants 6 to <12 years of age.

In the per protocol immunogenicity subset (n=134), the baseline nAb GMT against Delta (measured by PsVNA ID50) in children 6 years to < 12 years old was below the LLOQ; 28 days after 2 doses of 50 μg of the Moderna COVID-19 Vaccine, serum nAb GMT was 756.46 (95% CI: 650.99, 878.77). Furthermore, 99.3% of children met the definition of seroresponse against the Delta variant. The GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant.

Important endpoints that support the benefit

Primary Efficacy Endpoints: efficacy of the mRNA-1273 vaccine in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second injection in the per protocol population, among participants who were seronegative at baseline.

Secondary Efficacy Endpoints: efficacy of mRNA-1273 in the prevention of severe COVID-19 as defined by one of the following criteria: respiratory rate of 30 or more breaths per minute; heart rate at or exceeding 125 beats per minute; oxygen saturation at 93% or less while the participant was breathing ambient air at sea level or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg; respiratory failure; ARDS; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or a need for vasopressors); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; or death.

Primary Immunogenicity endpoints:

From mRNA-1273-201:

1. Immunogenicity of elasomeran by measure of specific binding antibody levels
2. Immunogenicity of elasomeran by measure of specific neutralizing antibody levels

From Study mRNA-1273-P101/20-0003:

- Immunogenicity of elasomeran measured by IgG ELISA to SARS-CoV-2 spike protein

From Study mRNA-1273-P204:

- Immunogenicity of elasomeran 3 by measure of specific neutralizing antibody levels and the seroconversion rate

Evidence of Efficacy and Effectiveness in authorized indications:

The primary analysis of efficacy (data cut 25 Nov 2020) included a total of 196 adjudicated COVID-19 cases in the per protocol population, which exceeded the target total number of cases (151) specified in the protocol. This was an increase from the 95 cases observed at the first interim analysis data cut-off on 11 Nov 2020. After Day 1 and through 25 Nov 2020, a total of 269 COVID-19 cases were identified, with an incidence of 79.7 cases per 1,000 person-years (95% CI, 70.5 to 89.9) among participants in the placebo group with no evidence of previous SARS-CoV-2 infection. For the primary analysis, 196 cases of COVID-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1,000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1,000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of

the elasomeran vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo.

17.2 Newly Identified Information on Efficacy and Effectiveness

Study mRNA-1273-P204 is an ongoing Phase 2/3 study conducted to evaluate the safety, tolerability, reactogenicity, and effectiveness of elasomeran in healthy children 6 months through 11 years of age. The study enrolled children in 3 age groups: 6 years through 11 years; 2 years through 5 years; and 6 months through 23 months.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cut-off date of 21 Feb 2022 was performed in 5,476 participants 6 months through 5 years of age who received two doses (at 0 and 1 month) of either elasomeran (n=4,105) or placebo (n=1,371) and had a negative baseline SARS-CoV-2 status (referred to as the Per Protocol Set for Efficacy). Between participants who received elasomeran and those who received placebo, there were no notable differences in demographics.

The median length of follow-up for efficacy post Dose 2 was 71 days for participants 2 through 5 years of age and 68 days for participants 6 months through 23 months of age.

Vaccine efficacy in this study was observed during the period when the B.1.1.529 (Omicron) variant was the predominant variant in circulation.

For children aged 2 years through 5 years of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n = 264; 25 micrograms) to those of young adults (n=295; 100 μg) demonstrated a GMR of 1.014 (95% CI: 0.881, 1.167), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The geometric mean fold rise (GMFR) from baseline to Day 57 for these children was 183.3 (95% CI: 164.03, 204.91). The difference in SRR between the children and young adults was -0.4% (95% CI: -2.7%, 1.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the SRR difference > -10%).

For infants and toddlers from 6 months through 23 months of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n=230; 25 μg) to those 24 of young adults (n=295; 100 μg) demonstrated a GMR of 1.280 (95% CI: 1.115, 1.470), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The difference in SRR rates between the infants/toddlers and young adults was 0.7% (95%

CI: -1.0%, 2.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the seroresponse rate difference > -10%).

Accordingly, the pre-specified success criteria for the primary immunogenicity objective were met for both age groups, allowing efficacy of 25 µg to be inferred in both children 2 years through 5 years and infants and toddlers aged 6 months through 23 months (Table 17.6 and Table 17.7).

Table 17.6 Summary of geometric mean concentration ratio and seroresponse rate–comparison of individuals 6 months through 23 months of age to participants 18 years through 25 years of age–per protocol immunogenicity set

		6 months through 23 months n=230	18 years through 25 years n=291	6 months through 23 months/18 years through 25 years	
Assay	**Time point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralization assay[c]	28 days after Dose 2	1 780.7 (1 606.4, 1 973.8)	1 390.8 (1 269.1, 1 524.2)	1.3 (1.1, 1.5)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		100 (98.4, 100)	99.3 (97.5, 99.9)	0.7 (-1.0, 2.5)	

GMC = Geometric mean concentration

n = number of participants with non-missing data at baseline and at Day 57

* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.

[a] The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[b] Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%.

[c] Final geometric mean antibody concentrations (GMC) in AU/mL were determined using SARS-CoV-2 microneutralization assay.

[d] Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralizing antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.

[e] Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Table 17.7 Summary of geometric mean concentration ratio and seroresponse rate– comparison of individuals 2 years through 5 years of age to participants 18 years through 25 years of age – per protocol immunogenicity set

		2 years through 5 years n=264	18 years through 25 years n=291	2 years through 5 years/ 18 years through 25 years	
Assay	**Time point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralization assay[c]	28 days after Dose 2	1 410.0 (1 273.8, 1 560.8)	1 390.8 (1 262.5, 1 532.1)	1.0 (0.9, 1.2)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		98.9 (96.7, 99.8)	99.3 (97.5, 99.9)	-0.4 (-2.7, 1.5)	

GMC = Geometric mean concentration
n = number of participants with non-missing data at baseline and at Day 57
* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
[a] The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
[b] Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%.
[c] Final geometric mean antibody concentrations (GMC) in AU/mL were determined using SARS-CoV-2 microneutralization assay.
[d] Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralizing antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.
[e] Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

17.3 Characterization of Benefits

From the study mRNA-1273-P204, Vaccine efficacy (VE) in Part 2 for the Per Protocol Set for Efficacy for COVID-19 cases 14 days or more after dose 2 using the "COVID-19 P301 case definition" (i.e., the definition employed in the pivotal adult efficacy study) was 36.8% (95% CI: 12.5, 54.0) for children 2 through 5 years of age and 50.6% (95% CI: 21.4, 68.6) for children 6 months through 23 months of age.

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR AUTHORIZED INDICATIONS

18.1 Benefit-Risk Context – Medical Need and Important Alternatives

The WHO declared COVID-19 a pandemic on 11 Mar 2020 [242]. As of 17 Dec 2022, over 649 million confirmed cases and over 6.6 million deaths have been reported globally [243]. Primary prevention of COVID-19 through vaccination has been a crucial factor in controlling the SARS-CoV-2 pandemic and mitigating its impact on public and individual health. At the end of Dec 2022, hospitalizations due to confirmed COVID-19 among unvaccinated adults during the period of Omicron dominance reached approximately 1,289.8 per 100,000 population [244]. Prevention through vaccination is important because of the ease of transmission from asymptomatic or pre-symptomatic individuals [227] and because COVID-19, particularly when severe, may result in critical illness and/or long-term sequalae [229,230,245] [245] [246].

As of 17 Dec 2022, an estimated 1,315,589,716 doses of elasomeran (Original) had been delivered to 91 countries and an estimated total of 772,908,958 doses had been administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. A total of 127,413,973 booster doses of elasomeran/imelasomeran (Original/BA.1) had been delivered to 41 countries and an estimated total of 70,077,685 doses had been administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 110,745,780 booster doses of elasomeran/davesomeran (Original/BA.4/5) had been delivered to 25 countries and an estimated total of 60,910,179 doses had been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses delivered and administered. Low- and middle-income countries [247] are estimated to account for approximately 13% of the doses distributed globally and approximately 13% of doses administered.

Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations (e.g., immunocompromised) and/or as a booster dose, including authorization for two bivalent vaccines (elasomeran/imelasomeran, and elasomeran/davesomeran) continue to expand.

Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 408,226,293 individuals received a first dose, 275,197,667 received a second dose,

166,419,347 received a third dose, and 62,984,506 received a fourth dose, with third and fourth doses including both original elasomeran (Original) andelasomeran/imelasomeran and elasomeran/davesomeran booster dose formulations.

The SARS-CoV-2 virus has continued to evolve globally, and 5 VOCs have been identified to date: namely Alpha, Beta, Gamma, Delta, and Omicron. The Omicron variant has become the epidemiologically dominant variant in multiple countries in 2022 and Omicron subvariants with additional spike protein mutations (BA.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, BN.1 and XBB.1) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). According to the NOWCAST report from the Center of Disease Control and Prevention in the US (12 Nov 2022–17 Dec 2022) the BQ.1.1, BQ.1, BA.5, and XBB.1.5 subvariants comprised approximately 35.3%, 23.3%, 16.1%, and 7.2%, respectively, of the SARS-CoV-2 sequences analyzed.

On 17 Jun 2022, the World Health Organization (WHO) issued an interim statement on the composition of current COVID-19 vaccines. Due to the continued evolution of SARS-CoV-2 viruses and the associated increasing potential for immune escape from currently authorized COVID-19 vaccines based on the ancestral (Wuhan-Hu-1) strain, WHO recommended that inclusion of Omicron variant of concern (VOC) in an updated vaccine composition may be considered to achieve "broader immunity against circulating and emerging variants, while retaining protection against severe disease and death."

Subsequently on 28 Jun 2022, the FDA convened the VRBPAC to discuss the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines to be used in the United States, followed by a worldwide convention of the International Coalition of Medicines Regulatory Authorities in a workshop co-chaired by FDA and EMA to discuss adapted vaccines to address emerging VOCs.

The general consensus reached amongst the regulators was aligned with WHO recommendation that an inclusion of an antigenically distinct variant, primarily Omicron (but to a lesser extent, Beta) should be considered as an additional component for a modified variant vaccine to be used going forward. The bivalent approach was favored over the monovalent approach however, a monovalent Omicron could also be considered.

The MAH developed a portfolio of modified, bivalent booster vaccines, which contain equal amounts of the mRNA sequence for the spike protein of ancestral SARS-CoV-2 and of a VOC. The first developed bivalent booster was mRNA-1273.211 (also referred to as ".211"), which

contains 25 µg of elasomeran and 25 µg of the Beta spike mRNA sequence, and was evaluated in Study P205 Part A. Elasomeran/imelasomeran 50 µg (also referred to as ".214"), which contains 25 µg of elasomeran and 25 µg of the Omicron BA.1 spike mRNA sequence was evaluated in Study P205 Part G. Data from study P205 Part G showed that mRNA 1273.214 50 µg elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2 (D614G) 28 days after booster dose administration as compared to a 50-µg booster dose of elasomeran [241]. Elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. Supportive data from the first bivalent vaccine (mRNA-1273.211) demonstrate a durable neutralizing antibody response to multiple variants, suggesting improved antibody persistence with bivalent vaccines.

At the request of FDA, based on the outcome of the 28 Jun 2022 VRBPAC, the MAH developed a modified, bivalent booster; elasomeran/davesomeran (also referred to as ".222") vaccine, based on the addition of Omicron BA.4/BA.5 sublineage in combination with the prototype ancestral strain, 25 µg each, 50 µg total. Data from Study P205 Part H, assessing safety and immunogenicity of elasomeran/davesomeran as a fourth dose (second booster following primary series and booster with elasomeran) using a historical mRNA-1273 fourth dose comparator (P205 Part F, Cohort 2) was initiated on 11 Aug 2022, after FDA review and feedback, and enrolment of Part H was completed on 23 Aug 2022. The bivalent elasomeran/davesomeran (Original/ Omicron BA.4/BA.5) produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine. Although randomized comparative clinical trial data comparing the VE of an original monovalent booster versus a bivalent booster (Original plus Omicron BA.4/BA.5) are not available at this time, effectiveness of the bivalent mRNA boosters against both symptomatic disease, hospitalization, and death have been observed to be improved following a bivalent mRNA booster compared to those who did not receive a bivalent mRNA booster [248].

Since Jul 2021, myocarditis and pericarditis have been considered an important identified risk that may occur following vaccination with a COVID-19 vaccine, especially in young men. Available data suggest that the course of myocarditis and pericarditis following vaccination is typically

milder than viral myocarditis or pericarditis and is self-limited. The clinical course of vaccine-associated cases of myocarditis and pericarditis appears generally favorable; those individuals who are hospitalized have lengths of stay of around 2 to 4 days on average. Analysis of post-authorization safety data has shown that this identified risk of myocarditis and pericarditis is generally within 7 days following vaccination against COVID-19 in people aged 12 to 40 years, particularly young people under 30 years old.

Cases involving myocarditis/pericarditis received during this reporting period were consistent with the known safety profile of elasomeran. A review of the data received cumulatively and during this reporting period showed a continuous decreasing trend in the number of reported cases, with events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second of the vaccine, with a TTO less than 7 days. The same pattern was observed for cases reported after receiving a 3rd or more doses of elasomeran (Original). Overall, evaluation of data received during this reporting period of those patients receiving a 3rd dose or a booster dose (Original) shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series, as it had been described in the literature.

There is also evidence of chronic sequelae known as "long COVID-19" in children and adults even after mild infection; this includes fatigue, muscle and joint pain, insomnia, concentration difficulties, respiratory problems, persistence anosmia and ageusia, and cardiac palpitations that may persist 6 months or more after infection [249].

As the pandemic continues, it is evident that the vaccination coverage in pediatric and adolescent populations has not reached the level in adults, leaving a group of individuals vulnerable to both COVID-19 as well as severe COVID-19 and sequelae.

18.2 Benefit-Risk Analysis Evaluation

There is an established safety profile of 3 or more doses of elasomeran, from data in clinical studies and post licensure data with more than 132 billion doses of elasomeran distributed, and more than 770 million doses estimated to have been administered globally as of 17 Dec 2022. Further, bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran) safety has been demonstrated in adults including young adults (18 to < 25 years) in clinical studies and post-authorization settings, where approximately more than 13 million doses have been administered.

In the adult clinical development program for elasomeran, two doses of 100 µg elasomeran demonstrated 93.2% efficacy against COVID-19 in more than 30,000 participants over a median observation period of over 5.3 months [250]. The safety profile of the adult primary series of elasomeran has been well characterized in clinical studies, including 15,184 adults exposed to mRNA-1273 in Study 301.

Across the full pediatric program, encompassing 3 age groups, 12 to 17 years, 6 to 11 years, and 6 months to 6 years, the effectiveness of the elasomeran primary series has been successfully demonstrated in infants and young children (2 doses of 25 µg each), older children (2 doses of 50 µg each) and adolescents (2 doses of 100 µg each). Primary immunobridging criteria were met in all pediatric age groups and across elasomeran doses by meeting the pre-specified NI success criteria comparing nAb responses in the pediatric/adolescent group to those of young adults in the pivotal P301 efficacy trial.

The administration of a 50 µg booster dose (BD) to adults and adolescents restored waning serum nAb levels and enhanced clinical effectiveness against COVID-19, hospitalization, and COVID-19–associated deaths [251] [25].

As the pandemic continues, an increasing proportion of individuals have hybrid immunity (following both vaccination and SARS-CoV-2 infection). While participants with evidence of prior SARS-CoV-2 infection had higher nAb levels pre-booster, administration of a BD nonetheless enhanced serum nAb levels in this group. Results confirm that regardless of baseline status, administration of a BD increases nAb levels relative to pre-booster levels.

The two dose primary series of elasomeran has been shown to be effective against infection and hospitalization related to SARS-CoV-2 variants, including Alpha, Beta, Delta, Gamma, and Omicron [252] [25].

Vaccine effectiveness data show that despite the epitope divergence from the original strain, elasomeran continues to protect adults against severe outcomes associated with Omicron, including hospitalization and death (VE ~ 80%) [25]. Although severe COVID-19-related outcomes are rare in children, one case of MIS-C and one case of long COVID were observed in placebo recipients in the 2 to 5 and 6-to-11-year age groups, respectively. Data from the Omicron wave continue to show that the vast majority of hospitalizations are occurring in unvaccinated individuals [253] [254] [255] [256].

The tolerability and safety of elasomeran in the pediatric age groups was evaluated across each age group in a total of > 10,800 adolescents, children, toddlers, and infants who received at least 1 dose of elasomeran. Elasomeran in these age groups was generally safe, well tolerated, and no new safety signals were identified. The overall safety profile of two doses of elasomeran observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as PMS. The profile of elasomeran in children is also consistent with other routinely administered pediatric vaccines for the respective age groups. Across all pediatric age groups, the AE profile of elasomeran in the pediatric populations is characterized primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration. Across all 4 age groups fever ≥ 40°C was the only Grade 4 solicited systemic AR reported in more than 1 participant. Febrile seizure was reported in 1 participant proximal to vaccination, but the event, along with a number of the Grade 4 fevers were associated with evidence of co-existing viral infections.

A review of the post-authorization data received during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. A large proportion of the myocarditis and pericarditis events received were reported as either resolved or resolving. Overall, evaluation of data received during this reporting period of those patients receiving a 3rd dose or a BD shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series, as it had been described in the literature.

Evaluation of the cumulative information for reports of myocarditis and/or pericarditis following exposure to elasomeran and/orelasomeran/imelasomeran and elasomeran/davesomeran during pregnancy does not indicate a safety issue and cases of myocarditis and pericarditis in this subpopulation are consistent with the known safety profile of elasomeran. Similar to myocarditis and pericarditis events, overall, most of the myocarditis and pericarditis events reported in pregnancy were resolved or resolving at the time the report was received.

Based on the data presented in this PBRER, elasomeran administered as two 100 µg doses (for individuals >12 years of age), two 50 µg doses (for individuals 6 to 11 years of age), or two 25 µg doses (for individuals 6 months to 5 years of age) given 28 days apart or as a third 100 µg/ 50 µg/25 µg dose for immunocompromised individuals, respectively, including a 50 µg BD at least 6 months after primary vaccination against SARS-CoV-2 for individuals >12 years of age, is a highly effective vaccine and capable of restoring nAbs to levels observed following receipt of the primary series. This is true as well against emerging VOCs, with the use of the bivalent vaccines

elasomeran/ imelasomeran or elasomeran/davesomeran, providing an attribute that can be used to help contain the pandemic, along with an acceptable safety profile for the prevention of COVID-19.

Considering the ongoing public health emergency due to SARS-CoV-2, the available safety and efficacy data from the 11 clinical studies presented herein, and the ongoing post-authorization surveillance, the MAH considers that the known and potential benefits outweigh the known and potential risks for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Risks associated with elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran are considered adequately managed with the product labels. An RMP is in place with ongoing studies including the continuation of the ongoing pivotal trial, Study mRNA-1273-P301, and other observational studies to further characterize important risks. Routine pharmacovigilance will monitor for potential new ARs.

Because the purpose of vaccination is different from that of treatment of infection, the focus of this section is on vaccines only. In addition to many vaccines that remain under development, several vaccines against COVID-19 are currently available for use under various regulatory provisions in countries around the world, as follows:

- mRNA-based vaccines: Pfizer-BioNTech Comirnaty (BNT162b2); Comirnaty Original/ Omicron BA.1® from Pfizer, Comirnaty Original/Omicron BA.4-5® from Pfizer; Moderna COVID-19 Vaccine SPIKEVAX (elasomeran; the subject of this application) SPIKEVAX bivalent Original/Omicron BA.1®, and SPIKEVAX bivalent Original/ Omicron BA.4-5® both from ModernaTx, Inc.
- Viral vector, nonreplicating: Adenovirus vaccine: AstraZeneca (Vaxzevria/Covishield); Janssen Vaccines (Johnson & Johnson) (JNJ-78436735; Ad26.COV2.S)
- Recombinant adenovirus vaccines: VidPrevtyn Beta from Sanofi Pasteur, Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik V (rAd26 and rAd5); Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik Light (rAd26); CanSino Biologics Convidicea (PakVac, Ad5-nCov)
- Inactivated vaccines: Sinovac (CoronaVac); Beijing Institute of Biological Products (BBIBP-CorV); Bharat Biotech Indian Council of Medical Research (ICMR), Ocugen, ViroVax (Covaxin); Wuhan Institute of Biological Products, China National Pharmaceutical Group (WIBP-CorV); Chumakov Federal Scientific Center for Research

and Development of Immune and Biological Products (CoviVac); Research Institute for Biological Safety Problems (QazVac); Minhai Biotechnology Co, Kangtai Biological Products Co. Ltd. (Unnamed vaccine candidate); Shifa Pharmed Industrial Group (CovIran Barekat); Chinese Academy of Medical Sciences, Institute of Medical Biology (Unnamed vaccine candidate)

- Peptide vaccine: Federal Budgetary Research Institution State Research Center of Virology and Biotechnology (EpiVacCorona)
- Recombinant vaccine: Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences (ZF2001)
- Protein subunit vaccine: Center for Genetic and Engineering Biotechnology (Abdala); Medigen Vaccine Biologics, Dynavax (MVC-COV1901)
- Conjugate vaccine: Finlay Institute of Vaccines, Pasteur Institute (Soberana 02).

Table 18 1. Benefit-Risk Evaluation Table

Decision Factors	Evidence/ Uncertainties	Conclusions
Analysis of Condition/ Disease	An outbreak of COVID-19 caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in Dec 2019, and the disease quickly spread globally. The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 Jan 2020 and declared COVID-19 a pandemic on 11 Mar 2020. Of major public health concern is whether immunity to early pandemic strains, developed via vaccination (or natural infection), confers protection against newly circulating variants. Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults but develop symptomatic COVID-19 primary infection at significantly lesser rates and rarely develop severe disease. It also became clear that a fraction of children develops a life-threatening hyperinflammatory state 4–6 weeks after infection with primary COVID-19 termed Multisystem Inflammatory Syndrome in Children (MIS-C). In Nov of 2021, the Omicron variant (B.1.1.529; BA.1) emerged as the most antigenically divergent variant to date with > 30 mutations in the spike protein [20]. Omicron shares antibody escape site mutations with the	COVID-19 disease is a pandemic and a public health emergency. Evidence suggests that immunity against COVID-19 is waning worldwide and may contribute to reinfection or breakthrough infections from the original virus strain or escape variants. Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults but develop symptomatic COVID-19 primary infection at significantly lesser rates. Complications are rare but may be severe (e.g., MIS-C). The Omicron variant has become the epidemiologically dominant variant in multiple countries in 2022 Omicron subvariants with additional spike protein mutations (BA.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, BN.1 and XBB.1) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). Evaluation of COVID-19 incidence

Decision Factors	Evidence/ Uncertainties	Conclusions
	Beta variant and it also exhibits transmissibility advantages [257] [258] [259]. As of 17 Dec 2022, over 649 million confirmed cases and over 6.6 million deaths have been reported globally. At the end of Dec 2022, hospitalizations due to confirmed COVID-19 among unvaccinated adults during the period of Omicron dominance reached approximately 1,289.8 per 100,000 population. The Omicron variant has become the epidemiologically dominant variant in multiple countries in 2022 and Omicron subvariants with additional spike protein mutations (BA.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, BN.1 and XBB.1) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). According to the NOWCAST report from the Center of Disease Control and Prevention in the US (12 November 2022 – 17 December 2022) the BQ.1.1, BQ.1, BA.5, and XBB.1.5 subvariants comprised approximately 35.3%, 23.3%, 16.1%, and 7.2%, respectively, of the SARS-CoV-2 sequences analyzed.	over time indicates marked increases in children ages 0 to 4 years old during the Delta and Omicron variant waves. After the onset of the Omicron wave, the demographics of hospitalized patients with COVID-19 shifted to younger age groups.
Medical Need for Treatment of Condition/ Disease	As of 17 Dec 2022, over 649 million confirmed cases and over 6.6 million deaths have been reported globally. At the end of Dec 2022, hospitalizations due to confirmed COVID-19 among unvaccinated adults during the period of Omicron dominance reached approximately 1,289.8 per 100,000 population. [218]. Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [22] [23]. Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults [260] [261] [262]. However, COVID-19 can also lead to severe outcomes in children and adolescents [263,264]. As of 14 Dec 2022, confirmed COVID-19 mortality has surpassed 1 million deaths in the US with more than 2,000 deaths reported in children 0–17 years of age. As of 14 Dec 2022, there have been more than 99 million COVID-19 cases in the US with more than 16 million cases reported in children 0 to 17 years (CDC). In the US, due to COVID-19, an	Since Dec 2020, elasomeran and other COVID-19 vaccines have been available under EUA and conditional approvals worldwide. As of 17 Dec 2022, an estimated 1.3 billion doses of elasomeran, 127 million doses of elasomeran/imelasomeran, and 110,745,780 dose of elasomeran/ davesomeran have been distributed; more than 772 million doses of elasomeran, more than 70 million doses of elasomeran/ imelasomeran, and more than 60 million doses of elasomeran/ davesomeran are estimated to have been administered. Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations

Decision Factors	Evidence/ Uncertainties	Conclusions
	excess of around 12,000 hospitalizations among children 0 years to 17 years of age have been observed through 17 Dec 2022 with 74.8% requiring intensive care unit interventions [262]. Comparison of apparent case fatality rates from early in the pandemic (acknowledging the limitations of such data) showed that the risk of death from COVID-19 was higher among the elderly and among individuals with certain pre-existing health conditions. Among all fatal cases, 75% had one of the listed pre-existing conditions. The most common was cardiac disorder, diabetes, and cancer malignancy. Two thirds (67.8%) of all severe hospitalizations were in patients with one of the listed pre-existing conditions. Elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. The bivalent elasomeran/davesomeran (Original/ Omicron BA.4/BA.5) produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine.	(e.g., immunocompromised) and/or as a BD, including authorization for two bivalent vaccines (elasomeran/imelasomeran, and elasomeran/davesomeran) continue to expand.
Key Benefits	The efficacy of elasomeran to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273-P301. Analysis of the 04 May 2021 dataset showed that elasomeran 100 µg was 98.2% effective in preventing severe COVID-19. Subgroup analyzes of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection.	The efficacy of elasomeran to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273 P301. Demonstration of elasomeran capacity to greatly enhanced immune responses compared to pre-boost levels after the administration of a BD of 50 µg at least 6 months after administration of the second of 2 doses of the elasomeran primary series has been confirmed in Study mRNA-1273-P201 Part A, Part B,

Decision Factors	Evidence/ Uncertainties	Conclusions
	Elasomeran was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of elasomeran (VE of 92.8% based on HR). Multiple studies from the US and other countries have demonstrated high effectiveness of a 2 dose COVID-19 mRNA vaccination series against SARS-CoV-2 infection (including both symptomatic and asymptomatic infections) caused by the original and variant strains and sequelae including severe disease, hospitalization, and death. Real-world effectiveness studies report COVID-19 mRNA vaccine effectiveness ranging from 86-89% for SARS-CoV-2 infection, 65-92% for asymptomatic infections, 85 to 97% for symptomatic disease, 87 to 98% for hospitalization or severe disease, and 97% effectiveness against death depending on the population studied and geographic region. Data from both P201 Part A and P301 Part A studies support persistence of immunogenicity and effectiveness through at least 6 months. Results from the P301 final blinded analysis were consistent with results of the interim and primary analyzes, confirming persistence of high rates of efficacy over a median of 5.3-month blinded observation period. Administration of a BD of elasomeran of 50 µg at least 6 months after administration of the second of 2 doses of the primary series greatly enhanced immune responses compared to pre-boost levels showing within 2 weeks nAb responses against these variants a 32- to 44-fold rise compared to the pre-booster titers. Across the full pediatric program, the effectiveness of elasomeran was demonstrated from 6 months to 17 years. In Studies 203 and 204 the pre-specified co-primary immunogenicity objectives were met in all age groups, demonstrating noninferiority to young adults (18 to 25 years of age) in the pivotal efficacy trial, Study 301. The GMT ratio of nAb titers as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a two dose primary	and P301, as well as Study DMID 21-0012. In Studies 203 and 204 the co-primary immunogenicity objectives were met in all age groups, demonstrating noninferiority to young adults (18 to 25 years of age) in the pivotal efficacy trial, Study 301. The GMT ratio of nAb titers as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a two dose primary series (two doses of 100 µg in adolescents, two doses of 50 µg elasomeran in older children and two doses of 25 µg of elasomeran in younger children and infants/toddlers). Vaccine effectiveness data show that despite the epitope divergence from the original strain, elasomeran continues to protect adults against severe outcomes associated with Omicron, including hospitalization and death (VE ~ 80%) [25]. Elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. Supportive data from the first bivalent vaccine (mRNA-1273.211) demonstrate a durable neutralizing antibody response to multiple variants, suggesting improved antibody persistence with bivalent vaccines. The bivalent elasomeran/davesomeran (Original/ Omicron BA.4/BA.5) produce immune responses not only to the

Decision Factors	Evidence/ Uncertainties	Conclusions
	series (two doses of 100 µg in adolescents, two doses of 50 µg elasomeran in older children and two doses of 25 µg of elasomeran in younger children and infants/toddlers). mRNA 1273.214 50 µg elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2 (D614G) 28 days after BD administration as compared to a 50-µg BD of elasomeran [241]. elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. The bivalent elasomeran/davesomeran (Original/ Omicron BA.4/BA.5) produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine.	Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine.
Key Risks	The safety of elasomeran in controlled clinical studies is based largely on data from Study mRNA-1273-P301, which was a 2-part Phase 3 study: Part A, the blinded Phase was a randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS-CoV-2 infection. Part B, the open-label observational Phase was designed to offer participants who received placebo in Part A of this study and who met EUA eligibility an option to request 2 doses of mRNA-1273 vaccine and remain on study. Cumulatively, 52,530 subjects have been exposed to either mRNA-1273, or its variants (mRNA 1273.351, mRNA-1273.211, mRNA-	In the ongoing CTs for elasomeran the most common solicited local AR was pain, and the most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. The majority of the solicited local and systemic ARs occurred within the first 2 days after administration of mRNA 1273 and generally persisted for 1 to 3 days. Overall, in the Phase 1/2/3 ongoing CTs no new clinically significant abnormalities or new safety risks were identified beyond those already included in the CCDS/ IB. Tolerability and safety of elasomeran evaluated across each age group in a total of > 10,800 adolescents, children, toddlers, and infants who

Decision Factors	Evidence/ Uncertainties	Conclusions
	1273.213, mRNA-1273.214, mRNA-1273.222, mRNA 1273.617.2, mRNA-1273.529), and participants exposed to mRNA-1273 in conjunction to mRNA-1283(including its variants mRNA-1283.211), in the mRNA clinical development program sponsored by ModernaTx, Inc. Out of the 52,530 subjects, 42,434 subjects were exposed to mRNA-1273 primary series. The total count of 52,530 represents unique subjects (Subjects enrolled in both trials P301 and P201 (part (Part C)/P205 or in both P204 and P306 and are only counted once in total). Cumulatively, 1,280 subjects were exposed to mRNA 1273 in CTs sponsored by DMID, 1,534 subjects from a clinical trial sponsored by GSK, 204 subjects from a clinical trial sponsored by Sanofi, 17 subjects from a clinical trial sponsored by NCI, 19 subjects from a clinical trial sponsored by UCLA, 12,340 subjects from a clinical trial sponsored by SAMRC, 931 subjects from CTs sponsored by MSD, 209 subjects from a clinical trial sponsored by University of Southampton, 336 subjects from a clinical trial sponsored by Moffitt Cancer Center, and 150 subjects were exposed to mRNA-1273 from a clinical trial sponsored by Takeda. Cumulatively, 1,566 subjects were enrolled in investigator-initiated trials. The type, incidence, and severity of ARs and TEAEs reported with elasomeran in CTs were consistent with the clinical trial data previously submitted in support of authorization. No unexpected safety findings were identified. Solicited local and systemic ARs were more common in participants who received mRNA 1273 compared with those who received placebo after both the first and second doses. While the severity of solicited symptoms increased after the second mRNA-1273 dose, relative to the first dose, the majority of ARs were mild-to-moderate in severity. The most common solicited local AR was pain, and the most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. The majority of the	received at least 1 dose of mRNA-1273 was generally safe, well tolerated, and no new safety signals were identified. The overall safety profile of two doses of elasomeran observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as PMS. The profile of elasomeran in children is also consistent with other routinely administered pediatric vaccines for the respective age groups. Across all pediatric age groups, the AE profile of elasomeran in the pediatric populations is characterized primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration. Across all 4 age groups fever ≥ 40°C was the only Grade 4 solicited systemic AR reported in more than 1 participant. Febrile seizure was reported in 1 participant proximal to vaccination, but the event, along with a number of the Grade 4 fevers were associated with evidence of co-existing viral infections Anaphylaxis has been reported in individuals who have received the Moderna COVID-19 Vaccine. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Since Jul 2021, myocarditis and pericarditis have been considered as an important identified risks that may occur following vaccination against COVID-19 with a messenger RNA vaccine, especially in young men. Available data suggest that the course of myocarditis and pericarditis following vaccination is typically milder than viral myocarditis or

Decision Factors	Evidence/ Uncertainties	Conclusions
	solicited local and systemic ARs occurred within the first 2 days after administration of mRNA 1273 and generally persisted for 1 to 3 days. In the mRNA-1273 group, pain was the most common grade 3 solicited local AR, and grade 3 pain was more common after the second injection than after the first. Fatigue and headache were the most commonly reported grade 3 systemic ARs in the elasomeran group after the first injection and second injection. The local and systemic ARs are considered risks with minimal and temporary clinical impact. Hypersensitivity events were more common among elasomeran participants than placebo participants, however, most imbalance was due to injection site urticaria and rashes. In Study mRNA-1273 P301, anaphylaxis, a potentially life-threatening hypersensitivity reaction that can occur after any vaccination was not reported within 30 minutes after injection with elasomeran. No confirmed cases of myocarditis have been reported in any of the ongoing studies for elasomeran. Pericarditis was reported in 5 participants, 2 each in the elasomeran and placebo groups during Part A, with 1 female and 1 male participant in each group having an SAE of pericarditis reported, and 1 male participant in Part B. There was no evidence of an increased risk of pericarditis in the elasomeran group. In addition, the careful review of symptoms suggestive of myocarditis did not identify a concern. The tolerability and safety of mRNA-1273 was evaluated across each age group in a total of > 10,800 adolescents, children, toddlers, and infants who received at least 1 dose of mRNA-1273. mRNA-1273 in these age groups was generally safe, well tolerated, and no new safety signals were identified. The overall safety profile of two doses of mRNA-1273 observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as PMS. The profile of mRNA-1273 in children is also consistent with other routinely	pericarditis and is self-limited. The clinical course of cases of myocarditis and pericarditis appears generally favorable; those individuals who are hospitalized have lengths of stay of around 2 to 4 days on average. A review of the post-authorization data received during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. Evaluation of data received during this reporting period of those patients receiving a 3rd dose or a BD, shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series To date, based on the data from ongoing trials, and post-authorization safety information, the general safety profile of elasomeran continues to appear well tolerated and with an acceptable safety profile.

Decision Factors	Evidence/ Uncertainties	Conclusions
	administered pediatric vaccines for the respective age groups. Across all pediatric age groups, the AE profile of mRNA-1273 in the pediatric populations is characterized primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration. Across all 4 age groups fever ≥ 40°C was the only Grade 4 solicited systemic AR reported in more than 1 participant. Febrile seizure was reported in 1 participant proximal to vaccination, but the event, along with a number of the Grade 4 fevers were associated with evidence of co-existing viral infections. No confirmed cases of myocarditis or pericarditis were reported in Studies 203 and 204. Cases involving myocarditis/pericarditis received during this reporting period were consistent with the known safety profile of elasomeran. A review of the data received cumulatively and during this reporting period showed a continuous decreasing trend in the number of reported cases, with events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second of the vaccine, with a TTO less than 7 days. The same pattern was observed for cases reported after receiving a 3rd or more doses of Elasomeran (Original). Overall, evaluation of data received during this reporting period of those patients receiving a 3rd dose or a BD shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series, as it had been described in the literature. Evaluation of the cumulative information for reports of myocarditis and/or pericarditis following exposure to elasomeran orelasomeran/imelasomeran and elasomeran/davesomeran during pregnancy does not indicate a safety issue and cases of myocarditis and pericarditis in this subpopulation are consistent with the known safety profile of elasomeran. Similar to myocarditis and pericarditis events, overall, most of the myocarditis and pericarditis events	

Decision Factors	Evidence/ Uncertainties	Conclusions
	reported in pregnancy were resolved or resolving at the time the report was received. Passive and observational surveillance information shows that the clinical profile of patients experiencing myocarditis/ pericarditis following exposure to a COVID-19 mRNA vaccine result in events with a relatively short period of hospitalization, most cases follow an uncomplicated clinical course and complete resolution of symptoms is rapidly achieved, and can be effectively treated with a standard medication treatment with ibuprofen and colchicine, without any CMR-detectable consequence [45].	

19 CONCLUSIONS AND ACTIONS

Overall, the cumulative evidence on the safety and efficacy for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran, fully supports the indications as described in the RSI, authorized as a suspension for injection for active immunizations to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older, or a BD in individuals 6 years of age and older, and individuals 12 years of age and older, respectively.

Clinical trial data and the results of the post-authorization Non-interventional study (NIS) conducted to date support the positive safety and efficacy profile of mRNA-1273, mRNA-1273.214, and mRNA-1273.222.

During the reporting period, the MAH conducted a signal evaluation of the potential signal of medication errors due to product confusion and/or product underdosing. The signal evaluation included a cumulative review of the MAH safety database with a (DLP of 04 Oct 2022. Analysis of the data showed that medications error reports have been received at a higher proportion for individuals vaccinated with one of the authorized Spikevax bivalent vaccines (relative to elasomeran Original). Based on the findings of the safety assessment evaluation regarding possible medication errors due to product confusion and/or product underdose, the MAH considered that this was a Potential Risk (Not Important) and was classified as a Priority 1 (Urgent (emerging) Safety Issue. A communication letter was distributed to those countries where Spikevax bivalents was authorized, and additional informational material regarding dosing information was posted on the ModernaTx, Inc. website for easy access by providers and consumers. The MAH will continue

to monitor events for potential medication errors related to product confusion and/or product underdose using routine pharmacovigilance surveillance.

In addition, during the reporting period, requests related to the topics IgA Nephropathy, HMB (re-evaluation), Myocarditis/Pericarditis (re-evaluation), Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran), CLS (Re-evaluation), Amenorrhea (re-evaluation) and Pemphigus and pemphigoid were received from Health Authorities (HAs) or regulatory bodies; as such, these were all considered as validated signals. Of these 7 signals, 2 signals Amenorrhea (re-evaluation) and Pemphigus and pemphigoid, were ongoing at the DLP of the reporting period, 3 signals IgA Nephropathy, HMB (re-evaluation), Myocarditis/Pericarditis (re-evaluation) were closed and refuted and one (1) signal [Product label confusion leading to underdosing of Bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran)] was categorized as a Potential Risk (not important) during the reporting period. Lastly the signal of CLS (Re-evaluation), which was closed as a refuted Signal before the reporting period of this PBRER, but not presented in PBRER#3, is presented here for completeness.

During the reporting period, elasomeran RMP v4.0 was approved on 23 Jun 2022. This RMP version was updated to remove 'anaphylaxis' as an important identified risk and reclassify it as an identified risk (not important); while anaphylaxis, remains as an identified risk for the product, as with any other biologicals, it does not have a considerable impact on the benefit-risk balance of the vaccine.

At the time of the DLP of this PBRER, the following important identified and important potential risks were closely monitored as per the elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran RMP v6.3 (approved on 15 Dec 2022):

Important identified risks

- Myocarditis
- Pericarditis

Important potential risks

- Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

Missing information

- Use in pregnancy and while breastfeeding
- Long-term safety
- Use in immunocompromised subjects
- Interaction with other vaccines
- Use in frail subjects with unstable health conditions and comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in subjects with autoimmune or inflammatory disorders

The MAH has been evaluating all available safety information regarding VAED, and as the data presented as of DLP (17 Dec 2022) indicate, there is no evidence to support the hypothesis that this phenomenon exists. The MAH is proposing the removal of VAED as an Important Potential risk from the EU-RMP, and to continue monitoring VAED through routine surveillance.

The MAH has been evaluating all available safety information regarding the missing information for "Use in pregnancy and while breastfeeding", "Use in immunocompromised subjects", "Interaction with other vaccines", "Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders)", and "Use in subjects with autoimmune or inflammatory disorders", and as the data presented in this PBRER (please refer to each topic for additional information) use of elasomeran (including bivalents elasomeran/imelasomeran and elasomeran/davesomeran) in any of these missing information topics, has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines and no longer constitutes missing information in the safety profile of elasomeran. The extensive use of the elasomeran vaccines (>800 million individuals vaccinated with at least one dose), has provided extensive safety information for all these subpopulation group to support their removal as missing information. The MAH will continue to evaluate all these topics in reports of elasomeran (original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorization safety studies.

The data included in this PBRER does not indicate any changes in the benefit-risk profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. The safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran is closely monitored on a continuous basis and the analysis of the data contained within this report supports the current RSI (CCDS v15.0, dated 15 Sep 2022) for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Examination of the data contained within this report further supports

the conclusion that the overall benefit-risk balance for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran continues to be positive and remains unchanged.

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Approval	Marie Caby-Tosi Pharmacovigilance 22-Feb-2023 21:50:22 GMT+0000

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