Spikevax : Periodic safety update report assessment

18 June 2023 to 17 December 2023

This document consists of:

1. The PRAC assessment report of the Spikevax periodic safety update report (PSUR) covering the period 18 June 2023 to 17 December 2023, 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/295778/2024
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010897/202312

Active substance(s): elasomeran (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5)

Period covered by the PSUR: 18/06/2023 To: 17/12/2023

RMP version number: 8.3

Centrally authorised Medicinal product(s): 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:	14 March 2024	14 March 2024
☐	PRAC Rapporteur's preliminary assessment report (AR)	13 May 2024	13 May 2024
☐	MS/PRAC members and MAH comments	12 June 2024	12 June 2024
☐	PRAC Rapporteur's updated assessment report following comments	27 June 2024	21 June 2024
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	11 July 2024	11 July 2024

Procedure resources	
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1. Background information on the procedure

This is the assessment of PSUR(s) 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), andusomeran (Spikevax XBB.1.5).

2. Assessment conclusions and actions

This report assessed the 6th PSUR on elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran, summarising the safety information gathered during a 6-month reporting period covering the interval from 18 Jun 2023 to 17 Dec 2023.

Elasomeran was first authorised in the EU through the centralised procedure on 6 Jan 2021. The European Union reference date (EURD) is 18 Dec 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/imelasomeran 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.

Andusomeran (Spikevax XBB.1.5) was approved in the EU on 15 Sep 2023. Therefore, the current PSUR is the first that includes data on andusomeran.

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger ribonucleic acid (mRNA)-based vaccine against the 2019 coronavirus (CoV; Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2]). Elasomeran is authorised in the EU as a suspension for injection for active immunisation 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 immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older and 6 months of age and older respectively, who have previously received at least a primary vaccination course against COVID-19. Andusomeran is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

The estimated cumulative subject exposure in clinical trials is 59,907 subjects. Cumulatively, a total of 1,043,567,281 doses of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran are estimated to have been administered. The total interval exposure from marketing experience is estimated as 65,561,716 administered doses.

Changes to reference safety information

During the reporting period, the MAH updated its Company Core Data Sheet (CCDS) with safety information. The majority of these changes are either already reflected in the product information (PI) or were submitted via Type II variations and are currently under review. However, the MAH has also updated the frequency of anaphylaxis in section 4.8 of the CCDS to "rare". This update has not been implemented in the EU PI. However, this issue will be addressed in the procedure concerning the final study report of EU PASS P904.

Data in summary tabulations

The presentation of data in summary tabulations is incomplete, as the summary tabulations for clinical trials and for post-marketing data sources for andusomeran contain no data. Therefore, the MAH is

requested to make sure that all relevant data is included in the appended summary tabulations in future PSURs.

Literature

The MAH stated that it did not identify any articles with new relevant safety information. However, the assessors identified one noteworthy publication that was not presented or commented upon by the MAH. Marchand et al. found an increased risk of cardiac-related mortality after COVID-19 vaccination. In their response, the MAH highlighted critical methodological shortcomings of this publication as noted by Somovilla and Black et al. Consequently, the MAH considers that the study by Marchand et al., does not provide new and significant safety information. This is agreed by PRAC.

The MAH is requested in future PSURs to review its literature search process including search strategy and evaluation of retrieved publications to make sure that all relevant publications with new and significant safety findings are captured and considered for presentation.

Signals

Six signals were closed during the reporting period. Five of these were closed as refuted by the MAH ("IgA nephropathy flare-up", "Sensorineural Hearing Loss", "Breast swelling", "Mastitis" and "Postmenopausal Haemorrhage"). For these signals, the PRAC agrees that no further action is currently warranted. One signal was closed by the MAH as an important potential risk ("Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the US"). According to the MAH, this safety issue was restricted to the US. Based on the information presented by the MAH and the additional information retrieved by the assessors, PRAC agrees that the safety issue is restricted to the US and that regulatory action is not currently warranted in the EU.

In the presentation of the signal "IgA nephropathy flare-up", PRAC noted that the MAH used a several months old DLP without further justification. Therefore, the MAH is requested to use a DLP as recent as possible in future PSURs in signal evaluations, cumulative reviews, etc. to ensure that the evaluation is as complete and up to date as possible.

Safety concerns

No new and significant safety information was identified for any of the safety concerns. For the missing information topic "use while breastfeeding", PRAC noted that the MAH primarily focuses on lactation-specific adverse events. This approach is endorsed for cases concerning breastfeeding women, however, in cases concerning breastfed infants, any adverse event observed is deemed of interest. Therefore, in future PSURs, the MAH is requested to present the adverse events reported in children exposed via breastmilk and the MAH should provide a discussion of the reported cases including causality. Based on the current PI for elasomeran, vaccine reactogenicity is not considered a valid argument for dismissing cases of adverse events in infants exposed via breastmilk.

Furthermore, in future PSURs the MAH is requested to present new information evaluated during the reporting interval related to anaphylaxis, in PSUR section 16.3.1, in the same format and detail level as for the remaining safety concerns.

Requests from previous PSUSA

The MAH was requested to provide a cumulative review of autoimmune hepatitis (AIH) in the current PSUR. In the updated review, the MAH concluded that no new safety issue of concern was identified, and that available data does not warrant an update of the PI and/or the Risk Management Plan (RMP). The MAH will continue to monitor events of AIH using routine pharmacovigilance surveillance. This is agreed.

The MAH responded satisfactorily to the remaining requests from the previous PSUSA with no further action warranted.

Risk management plan

The MAH submitted an updated RMP version 8.3 to propose an update of the myocarditis/pericarditis follow-up questionnaire (FUQ) in Annex 4. In view of several Post-Authorisation Safety Studies (PASS) with the aim to further characterise the important identified risks myocarditis and pericarditis and the striking lack of effectiveness of these FUQs, as demonstrated by the MAH, the PRAC considers that there is no reasonable expectation that the FUQ will contribute to a better characterization of these risks. Upon response to an RSI raised during this procedure, the MAH proposed to delete the FUQ and updated the applicable sections of the RMP accordingly. These changes are acceptable and RMP version 8.3 with final sign off date of 11 June 2024 is endorsed.

Conclusion

No new and significant safety or efficacy information was identified for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran.

It was previously agreed that after the current 6-monthly PSUR, the PSUR frequency should change to annual. Therefore, the next PSUR will be the first yearly PSUR to be submitted.

The benefit-risk balance of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran remains unchanged.

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, elasomeran/davesomeran and andusomeran remains unchanged and therefore recommends the maintenance of the marketing authorisation.

4. Issues to be addressed in the next PSUR

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

- The presentation of data in summary of tabulations in appendices 3 and 4 is incomplete. For andusomeran, neither the summary tabulation for clinical trials (3f) nor for post-marketing data sources (4f) contain any data, which is obviously an error based on the andusomeran case reports presented elsewhere in the PSUR. In future PSURs, the MAH is requested to make sure that all relevant data is included in the appended summary tabulations.
- As the assessors identified a literature publication with potentially new safety information, that was not presented or commented upon by the MAH, the MAH is requested to review its literature search process including search strategy and evaluation of retrieved publications to make sure that all relevant publications with new and significant safety findings are captured and considered. In future PSURs, the MAH is expected to present literature published during the reporting interval with potentially new and significant safety findings. If the MAH identifies publications which include new significant safety information, these should be presented and commented upon even if the MAH disagrees with the conclusions of the authors.
- In future PSURs, the MAH is requested to use a Data Lock Point (DLP) as recent as possible in signal evaluations, cumulative reviews, etc. to ensure that the evaluation is as complete and up

to date as possible. DLPs that are several months old will not be accepted without a reasonable justification.

- In future PSURs, the MAH is requested to present new information evaluated during the reporting interval related to anaphylaxis, in PSUR section 16.3.1, in the same format and detail level as for the remaining safety concerns.
- In evaluations of the missing information topic "Use while breastfeeding" in future PSURs, the MAH is requested to present the adverse events reported in children exposed via breastmilk (as in the current PSUR). Furthermore, the MAH should provide an overall discussion of the reported cases, conclude on the causality between elasomeran exposure and the reported adverse events and provide specific arguments for this conclusion. Based on the current product information for elasomeran, vaccine reactogenicity is not considered a valid argument for dismissing cases of adverse events in infants exposed via breastmilk.

5. PSUR frequency

☒No changes to the PSUR frequency

The current **1**-year frequency for the submission of PSURs should remain unchanged.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is the PSUSA of the 6th PSUR on elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran, covering the interval from 18 Jun 2023 to 17 Dec 2023.

Currently, the elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran PSUR is on a 6-monthly submission schedule based on the European Union (EU) reference dates (EURD). In order to stay aligned with the EURD, this 6-monthly PSUR (with data lock point [DLP] 17 Dec 2023) will be the last 6-monthly PSUR to be submitted and then the PSUR frequency will change to annual. The first yearly PSUR to be submitted will be PSUR #7 (DLP of 17 Dec 2024). The first three PSURs (PSUR #1, PSUR #2 and PSUR #3) that were previously submitted included the single International Nonproprietary Name (INN) elasomeran. Beginning with PSUR#4, bivalent vaccines elasomeran/imelasomeran, and elasomeran/davesomeran were included; with the PSUR#6, andusomeran is also included.

The international birth date (IBD) of elasomeran is 18 Dec 2020, the date of the first marketing approval in any country. The product is currently authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome (SARS)-CoV-2. First authorization approval for elasomeran/imelasomeran was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom (UK) on 12 Aug 2022, elasomeran/davesomeran was granted Emergency Use Authorization (EUA) status by US Food and Drug Administration (US FDA) on 31 Aug 2022 and andusomeran was granted authorization for individuals >18 years of age and EUA status for individuals 6 months to 11 years of age by US FDA on 11 Sep 2023.

Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has Anatomical Therapeutic Chemical (ATC) code: J07BN01 (previously 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) (v18.0, dated 12 Oct 2023), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals six 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 6 years of age and older and 6 months of age and older respectively, who have previously received at least a primary vaccination course against COVID-19. Andusomeran is indicated for active immunization to prevent COVID-19 caused by SARS-CoV2 in individuals 6 months of age and older.

Elasomeran is Single-stranded, 5'-capped messenger Ribonucleic acid (RNA) (mRNA) produced using a cell-free in vitro transcription from the corresponding Deoxyribonucleic acid templates, encoding the full-length Spike protein of SARS-CoV-2, modified to introduce two proline residues to stabilize the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: heptadecane-9-yl-8-(2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and one mono-methoxy-polyethyleneglycol 2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG-2000DMG). 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 Deoxyribonucleic acid templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5).

The S-protein of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical. Andusomeran 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 XBB.1.5).

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 is formulated as a dispersion for injection to be supplied in single dose vial, multidose vial and single use pre-filled syringe.

Elasomeran/davesomeran is formulated as a dispersion for injection to be supplied in multidose vial.

Andusomeran is formulated as a dispersion for injection to be supplied in SDV, multidose vial and single use pre-filled syringe.

- Elasomeran 0.20 mg/mL dispersion for injection

Elasomeran is supplied as a multidose vial that contains ten 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

Elasomeran is supplied as a multidose vial that contains five doses of 0.5 mL each or a maximum of ten 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 LNPs).

- Elasomeran 50 ug dispersion for injection in pre-filled syringe

It has also been supplied as single use pre-filled syringe that contains one 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 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 in pre-filled syringe

Elasomeran/imelasomeran is supplied as a single-dose 0.5 mL vial (blue flip-off cap). One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of imelasomeran, 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, 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 or 10 doses of 0.25 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) or one dose (0.25 mL) contains 12.5 ug of elasomeran and 12.5 ug of davesomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Elasomeran/davesomeran 25 µg/25 µg dispersion for injection and in pre-filled syringe

Elasomeran/davesomeran is supplied as a single-dose 0.5 mL vial (blue flip-off cap). One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of davesomeran, 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, for single use only. One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of davesomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Andusomeran 0.1 mg/mL dispersion for injection

Andusomeran is supplied as a multi-dose 2.5 mL vial (blue flip-off cap). It contains 5 doses of 0.5 mL each or 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles) or one dose (0.25 mL) contains 25 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Andusomeran (50 µg/50 µg)/mL dispersion for injection and pre-filled syringe

Andusomeran is supplied as a single-dose 0.5 mL vial (blue flip-off cap) containing 1 dose of 0.5 mL for single use only. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). It is also supplied pre-filled syringe containing 1 dose of 0.5 mL for single use only. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Posology for primary series, a third dose in severely immunocompromised and booster doses for elasomeran and elasomeran/imelasomeran is provided in below Table 1, posology for primary series and for immunocompromised doses for elasomeran/davesomeran and andusomeran is provided in Table 2 and Table 3.

Table 1: Dosages and description for elasomeran and elasomeran/imelasomeran

Strength	Vaccination Type	Age and Dose	Recommendations
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 a 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. *Children 6 years through 11 years of age* One dose (0.25 mL each, containing 25 ug mRNA)*	Moderna COVID-19 Vaccine may be used to boost individuals 6 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 imelasomeran.	

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

Table 2: Elasomeran/davesomeran and Andusomeran posology

Age	Dose	Additional Recommendations
Children 6 months through 4 years of age, without prior vaccination	*Two doses of 0.25 mL each, given intramuscularly**	Administer the second dose, 28 days after the first dose. If a child has received one prior dose of elasomeran, one dose of elasomeran/davesomeran should be administered to complete the two-dose series. If a child has received one prior dose of any elasomeran vaccine, one dose of andusomeran should be administered to complete the two-dose series.
Children 6 months through 4 years of age, with prior vaccination	One dose of 0.25 mL, given intramuscularly*	Elasomeran/davesomeran or andusomeran should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.
Children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly*	
Individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	
Individuals 65 years of age and older	One dose of 0.5 mL, given intramuscularly	One additional dose may be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

*Do not use the SDV or pre-filled syringe to deliver a partial volume of 0.25 mL

Table 3: Elasomeran/davesomeran and Andusomeran posology for immunocompromised individuals

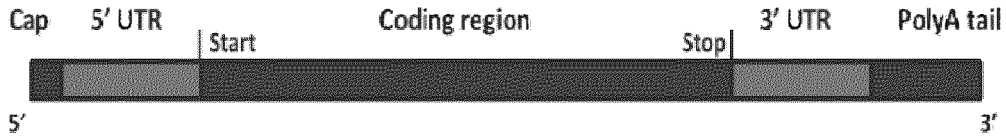
Age	Dose	Additional Recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	*Two doses of 0.25 mL, given intramuscularly**	An additional dose in severely immunocompromised may be given at least 28 days after the second dose.
Immunocompromised children 6 months through 4 years of age, with prior vaccination	*One dose of 0.25 mL, given intramuscularly**	Additional age-appropriate dose(s) may be administered in severely immunocompromised at least 2 months following the most recent dose of a COVID-19 vaccine at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances.
Immunocompromised children 5 years through 11 years of age, with or without prior vaccination	*One dose of 0.25 mL, given intramuscularly**	
Immunocompromised individuals 12 years of age and older, with or without prior vaccination	*One dose of 0.5 mL, given intramuscularly*	

*Do not use the SDV or pre-filled syringe to deliver a partial volume of 0.25 mL.

Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran 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 below.

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



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

Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran contain mRNA encapsulated in LNPs. The mRNA encodes for the full length SARS-CoV-2 spike protein modified with two proline substitutions within the heptad repeat one 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). Andusomeran contains nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5. 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.

Modified, variant-matched bivalent COVID-19 mRNA vaccine were developed containing 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 [BA.1], and elasomeran/davesomeran [BA.4-5]), each encapsulated into individual LNPs, and co-formulated into a single drug product (elasomeran 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. A modified variant-monovalent COVID-19 mRNA vaccine was developed encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5 (andusomeran). The nucleoside-modified mRNA in these vaccines, is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

Below are the target variants for the various mRNA-1273 vaccines used in the clinical development program (See Table 4).

Table 4: 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, BA.4/5

mRNA-1273.529	Omicron BA.1
mRNA-1273.815	Omicron XBB.1.5
mRNA-1273.231	Bivalent: 1:1 ratio of prototype and omicron XBB.1.5 (0.815)

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 Moderna vaccines targeting SARS-CoV-2 (current v18 dated 12 Oct 2023) in Appendix 1 [of the PSUR].

The MAH did not propose changes to the product information as part of the submission of this PSUR.

1.2. Worldwide marketing authorisation status

The IBD of elasomeran is 18 Dec 2020. Till DLP, elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran are authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2.

First marketing approval for elasomeran/imelasomeran was granted by the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by US FDA on 31 Aug 2022. Andusomeran was granted authorization for individuals >18 years of age and EUA status for individuals 6 months to 11 years of age by US FDA on 11 Sep 2023.

Marketed Moderna vaccines targeting SARS-CoV are 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 three bivalent vaccines (elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran) continue to expand.

Cumulative information on marketing authorizations in all countries and approval dates are provided in PSUR Appendix 2.

Rapporteur assessment comment:

The IBD of elasomeran is 18 Dec 2020. At DLP, elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran are authorised in 49 unique countries, regions, and unions/areas for active immunisation to prevent COVID-19 caused by SARS-CoV-2.

The date of marketing authorisation in the European Economic Area for the primary vaccination series in adults was 06 Jan 2021.

This section is acknowledged.

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:

- Since Oct 2023, reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age, were received from various sources, including spontaneous reports, quality complaints and HCP inquiries. This issue was restricted to the US and is limited to the US EUA of Moderna COVID-19 vaccine (andusomeran) for individuals 6 months through 11 years of age. The pediatric SDV contains notably more than 0.25 mL of vaccine, which has led to provider confusion or administration errors, including overdose. Several risk minimization activities were conducted, including the creation and distribution of a Dear Healthcare Provider Letter (DHCP) for clarification on the dosage and administration instructions for the US pediatric presentation of the Moderna COVID-19 vaccine (2023-2024 Formula)/andusomeran. The US Fact Sheet for Providers and for Consumers were updated providing correct dosage administration of the vaccine for the pediatric age group, specifically within the context of the US presentation. The US FDA and CDC distributed a notification to health care providers advising them to ensure appropriate dosing was provided to pediatric patients. No patient safety or quality issue were found to be associated with this incident. This medication error issue does not impact andusomeran approved in other countries.

Rapporteur assessment comment:

Since Oct 2023, reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age, were received from various sources. This issue was restricted to the US and is limited to the US EUA of Moderna COVID-19 vaccine (andusomeran) for individuals 6 months through 11 years of age.

According to the MAH, several risk minimisation activities were conducted, including the creation and distribution of a Dear Healthcare Provider Letter (DHCP). The US Fact Sheet for Providers and for Consumers were updated providing correct dosage administration of the vaccine for the pediatric age group, specifically within the context of the US presentation. The US FDA and CDC distributed a notification to health care providers advising them to ensure appropriate dosing was provided to pediatric patients.

The MAH states that no patient safety or quality issues were found to be associated with this incident and that this medication error issue does not impact andusomeran approved in other countries.

The signal "Overdose in children in the context of overfill of the SDV indicated for individuals 6 months through 11 years of age in the US" was closed during the reporting interval with substantiated outcome. Please refer to section 2.2 of this assessment report for more information.

This section is acknowledged.

1.3.2. Changes to reference safety information

The Reference Safety Information (RSI) for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran in effect at the end of the reporting period (DLP 17 Dec 2023) and used for this report is the CCDS v18.0 (dated 12 Oct 2023). 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 PSUR Appendix 1.

During this reporting period, the RSI (CCDS) was updated from v16.0 (dated 03 Jan 2023) to v17.0 (dated 11 Sep 2023) and further from v17.0 (dated 11 Sep 2023) to v18.0 (dated 12 Oct 2023). The safety-related changes are summarized below in Table 5.

Table 5: CCDS safety-related changes during the reporting period

Version	Date	Summary of changes
17.0	*11 Sep 2023*	**Section 4.1,** Updates to most recent age expansions for imelasomeran and davesomeran plus new andusomeran variant. **Section 4.2**: Updates to Posology per most recent approvals plus andusomeran variant, including simplified schedule and immunocompromised table. **Section 4.4**, Updated myocarditis, and immunocompromised text per Pharmacovigilance recommendations. **Section 4.8**, Updates to anaphylaxis and urticaria frequencies per latest data, Addition of andusomeran safety data per P205, Part J Addition of P203 Part 3 single dose data (12 to 17 years), Addition of solid organ transplant safety data per P304. **Section 5.1,** Updates to Mechanism of action for andusomeran, Addition of P901 RWE data, Addition of P203 Part 3 single dose data (12 to 17 years), Addition of andusomeran data per P205, Part J, Addition of GRADE Meta-analysis data.
18.0	*12 Oct 2023*	**Section 4.4**, Warnings and precautions, to update information related to myocarditis and pericarditis, as well as to update information related to immunocompromised. Addition of co-administration data for flu and herpes zoster (shingles) (**Sections 4.5, 4.8 and 5.1**). Clarification of text in **Section 6** per Tech Dev.

Rapporteur assessment comment:

The RSI used by the MAH for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran in effect at the end of the reporting period (DLP 17 Dec 2023) and used for this report is the CCDS v18.0 (dated 12 Oct 2023).

The MAH reports that the RSI (CCDS) was updated during the reporting period from v16.0 (dated 03 Jan 2023) to v17.0 (dated 11 Sep 2023) to include updates to anaphylaxis and urticaria frequencies per latest data, addition of andusomeran (mRNA-1273.815) safety data per P205, Part J addition of P203 Part 3 single dose data (12 to 17 years), and addition of solid organ transplant safety data per P304. Further CCDS v17.0 was updated to v18.0 (dated 12 Oct 2023) to add co-administration data for flu vaccine and herpes zoster (shingles) vaccine and Section 4.4 Warnings and precautions was updated to add information related to myocarditis and pericarditis, as well as to update information related to immunocompromised patients.

The Rapporteur notes that some of the CCDS safety-related changes mentioned above in table 5 do not appear in the currently available EU SmPC from EMA's website (last revision date: 11/04/2024). However, based on entries in the tracking table and the common repository, it appears that the majority of information recently added to the CCDS and not yet included in the SmPC has been submitted via Type II variations and is currently under review (e.g. information on immunocompromised individuals and information on coadministration with influenza and herpes zoster vaccines).

The MAH has also updated the frequency of anaphylaxis in section 4.8 of the CCDS to "rare". This update has not been implemented in the EU SmPC, where the frequency is currently "not known". It appears that

this update is based on the final results from a US PASS. In the procedure concerning the final study report of EU PASS P904, the MAH has been requested to propose a frequency of anaphylaxis based on EU data, US data or pooled data – whichever are considered of highest validity.

Anaphylaxis is a safety concern in the PSUR. The MAH did not identify any additional clinically relevant new safety information for this topic in PSUR section 16.3 or 16.4. Please refer to section 2.3.1.1.1. of this assessment report for more information on anaphylaxis.

1.3.3. Estimated exposure and use patterns

1.3.3.1. Cumulative exposure in clinical trials

Cumulatively, 59,907 subjects have been exposed in CTs 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, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 (including its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administered with mRNA-1010 or co-administered with mRNA-1345, or co-administered active licensed sFLU vaccines (Fluzone HD or Fluarix) in the mRNA-1083 clinical development program sponsored by ModernaTx, Inc. The total count of 59,907 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 clinical trials (CTs) and the enrolment/randomization schemes for ongoing and blinded trials is provided in Table 6 below. Further details on cumulative subject exposure categorized by age, gender, racial group and ethnicity are provided in Table 7, Table 5-3 [please see PSUR], Table 5-4 [please see PSUR] and Table 5-5 [please see PSUR], respectively.

Table 6: 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[a]
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	20[a]
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	mRNA-1273.222 50 ug	388[a]
mRNA-1273-P203	mRNA-1273 Booster	155[a]
mRNA-1273-P203	Primary series+mRNA-1273 Booster	1,427
mRNA-1273-P204	Placebo	883[a]
mRNA-1273-P204	mRNA-1273	11,032[a]
mRNA-1273-P204	mRNA-1273 10 ug Booster	212
mRNA-1273-P204	mRNA-1273 25 ug Booster	2,925
mRNA-1273-P204	mRNA-1273.214 10 ug Booster	2,768
mRNA-1273-P204	mRNA-1273.214 25 ug Booster	209
mRNA-1273-P204	mRNA-1273.214 5 ug Booster	6
mRNA-1273-P205	mRNA-1273 Booster	681[a]
mRNA-1273-P205	mRNA-1273.211 Booster	758[a]
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	135[a]
mRNA-1273-P205	mRNA-1273.213 Booster	951[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	424[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.231 Booster	45[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.815 Booster	42[a]
mRNA-1273-P205	mRNA-1273.529 Booster	508[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	1,167[a]
mRNA-1273-P205	mRNA-1273.815 Booster	8[a]
mRNA-1273-P205	mRNA-1273.231 Booster	6[a]
mRNA-1273-P206	mRNA-1273.214	68[a]
mRNA-1273-P301	Placebo	2,503[a]
mRNA-1273-P301	mRNA-1273	27,833[a]
mRNA-1273-P301	Primary series+mRNA-1273 Booster	19,609
mRNA-1273-P301	Placebo+mRNA-1273 Booster	10[a]
mRNA-1273-P304	mRNA-1273	81[a]
mRNA-1273-P304	mRNA-1273	71[a]
mRNA-1273-P304	mRNA-1273 Booster	82[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	87
mRNA-1273-P305	mRNA-1273 Booster	1,759[a]
mRNA-1273-P305	mRNA-1273.214 Booster	1,422[a]
mRNA-1273-P305	mRNA-1273.529 Booster	367[a]
mRNA-1273-P306	mRNA-1273.214	391[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	5[a]
mRNA-1283-P101	mRNA-1273	22[a]
mRNA-1283-P201	mRNA-1273 Booster	57[a]
mRNA-1283-P301	mRNA-1273.222	5,716[a,b]
mRNA-CRID-001	mRNA-1273	60[a]
mRNA-1073-P101	mRNA-1010+mRNA-1273 co-administration	101[a]
mRNA-1073-P101	mRNA-1273+Placebo	49[a]
mRNA-1083-P101	mRNA-1273.222	102[a,b]
mRNA-1083-P301	mRNA-1273.815	4,013[a,b]
mRNA-1230-P101	mRNA-1273.214	44[a,b]
mRNA-1345-P302	Overall (mRNA-1273.214, or mRNA-1345 + mRNA-1273.214 co-administration)	1,690[a,b]

[a]=These numbers were counted to get the total for each study.
[b]=Estimated numbers per randomization scheme as the study is currently blinded.

Table 7: Cumulative Subject Exposure to Investigational Drug from Completed and Ongoing Unblined/Open-label Clinical Trials by Age[a]

	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	P101	
<2 years	0	0	2,601	0	68	0	0	0	244	0	0	0	0	2,799
2 to <6 years	0	0	3,882	0	0	0	0	0	686	0	0	0	0	4,142
6 to <12 years	0	0	4,549	0	0	0	0	0	0	0	0	0	0	4,549
12 to <16 years	0	2,397	0	0	0	0	0	0	0	0	0	0	0	2,397
16 to <18 years	0	780	0	0	0	0	0	1	0	0	0	0	0	781
18 to <65 years	475	0	0	3,869	0	20,679	184	2,349	0	27	51	56	127	24,819
65 to <75 years	120	0	0	1,035	0	5,825	43	1,118	0	0	5	4	22	7,342
75 to <85 years	20	0	0	236	0	1,256	7	75	0	0	1	0	1	1,415
>=85 years	3	0	0	22	0	83	0	5	0	0	0	0	0	98
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	618	3,177	11,032	5,162	68	27,843	234	3,548	930	27	57	60	150	48,342[b]

[a]=Data from completed and ongoing unblinded/open-label till 17 Dec 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 of mRNA-1273 studies is only counted once in total number.

1.3.3.2. Cumulative and interval exposure from marketing experience

Cumulatively, a total of 1,776,284,733 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered to 92 countries. North America, Europe, and Asia accounted for approximately 91% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed (Table 8). Cumulatively, 130,546,560 (7.3%) doses had been distributed in lower- and middle-income countries.

In this PBRER reporting period (18 Jun 2023 to 17 Dec 2023), a total of 111,594,410 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered and an estimated total of 65,561,716 doses had been administered. North America, Europe, and Asia accounted for approximately 91% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed (Table 8).

Given that elasomeran distribution was discontinued worldwide after Jun 2023, no new doses were distributed during this PBRER reporting period.

A total of 129,007,543 booster doses of elasomeran/imelasomeran had been delivered to 42 countries and an estimated total of 70,954,149 doses had been administered. North America, Europe, and Asia accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 245,792,144 booster doses of elasomeran/davesomeran had been delivered to 43 countries and an estimated total of 135,185,679 doses had been administered. North America, Europe, and Asia accounted for approximately 93% of all doses delivered and administered (Table 9 and 10).

Andusomeran was introduced as a new marketed Moderna vaccine targeting SARS-CoV-2 in Sep 2023. As of 17 Dec 2023, 83,301,090 doses of andusomeran had been delivered to 19 countries and an estimated total of 45,815,600 doses were administered. North America, Europe, and Asia accounted for approximately >95% of all doses delivered and administered (Table 11).

Table 8: Total Doses Distributed and Administered for All Marketed Moderna Vaccines Targeting SARS-CoV-2

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	1,776,284,733	100.0	1,043,567,281	100.0	111,594,410	100.0	65,561,716	100.0
North America	673,022,534	37.9	370,162,394	35.5	39,298,840	35.2	21,614,362	33.0
US	604,271,844	34.0	332,349,514	31.8	31,050,290	27.8	17,077,660	26.0
All Europe	508,715,193	28.6	279,793,356	26.8	18,621,070	16.7	10,241,589	15.6
European Economic Area	421,024,343	23.7	231,563,389	22.2	1,573,750	1.4	865,563	1.3
Asia	427,640,616	24.1	235,202,339	22.5	43,822,380	39.3	24,102,309	36.8
Latin America	77,124,950	4.3	42,418,723	4.1	6,654,950	6.0	3,660,223	5.6
Africa	32,474,530	1.8	17,860,992	1.7	5,250	0.0	2,888	0.0
Oceania	29,068,080	1.6	15,987,444	1.5	1,336,880	1.2	735,284	1.1
Middle East	28,238,830	1.6	15,531,357	1.5	1,855,040	1.7	1,020,272	1.6
International donations	-	-	66,610,677	6.4	-	-	4,184,790	6.4

Table 9: Doses Distributed and Administered for Elasomeran/Imelasomeran

Elasomeran/Imelasomeran								
Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	129,007,543	100.0	70,954,149	100.0	10,250	100.0	5,638	100.0
North America	10,521,450	8.2	5,786,798	8.2	0	0.0	0	0.0
US	21,600	0.0	11,880	0.0	0	0.0	0	0.0
All Europe	83,496,993	64.7	45,923,346	64.7	0	0.0	0	0.0
European Economic Area	58,739,963	45.5	32,306,980	45.5	0	0.0	0	0.0
Asia	29,554,550	22.9	16,255,003	22.9	0	0.0	0	0.0
Latin America	1,100,150	0.9	605,083	0.9	0	0.0	0	0.0
Africa	104,850	0.1	57,668	0.1	5,250	51.2	2,888	51.2
Oceania	2,891,400	2.2	1,590,270	2.2	0	0.0	0	0.0
Middle East	1,338,150	1.0	735,983	1.0	5,000	48.8	0	0.0

Table 10: Doses Distributed and Administered for Elasomeran/Davesomeran

Elasomeran/Davesomeran								
	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	245,792,144	100.0	135,185,679	100.0	28,283,070	100.0	15,555,689	100.0
North America	69,347,234	28.2	38,140,979	28.2	0	0.0	0	0.0
US	67,846,884	27.6	37,315,786	27.6	0	0.0	0	0.0
All Europe	65,556,530	26.7	36,056,092	26.7	0	0.0	0	0.0
European Economic Area	59,256,930	24.1	32,591,312	24.1	0	0.0	0	0.0
Asia	93,671,610	38.1	51,519,386	38.1	21,801,750	77.1	11,990,963	77.1
Latin America	12,826,800	5.2	7,054,740	5.2	5,644,550	20.0	3,104,503	20.0
Africa	0	0	0	0	0	0.0	0	0.0
Oceania	1,999,970	0.8	1,099,984	0.8	836,770	3.0	460,224	3.0
Middle East	2,390,000	1.0	1,314,500	1.0	0	0.0	0	0.0

Table 11: Doses Distributed and Administered for Andusomeran

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	83,301,090	100.0	45,815,600	100.0	83,301,090	100.0	45,815,600	100.0
North America	39,298,840	47.2	21,614,362	47.2	39,298,840	47.2	21,614,362	47.2
US	31,050,290	37.3	17,077,660	37.3	31,050,290	37.3	17,077,660	37.3
All Europe	18,621,070	22.4	10,241,589	22.4	18,621,070	22.4	10,241,589	22.4
European Economic Area	1,573,750	1.9	865,563	1.9	1,573,750	1.9	865,563	1.9
Asia	22,020,630	26.4	12,111,347	26.4	22,020,630	26.4	12,111,347	26.4
Latin America	1,010,400	1.2	555,720	1.2	1,010,400	1.2	555,720	1.2
Africa	0	.	0	.	0	0.0	0	0.0
Oceania	500,110	0.6	275,061	0.6	500,110	0.6	275,061	0.6

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, United Kingdom

Asia: Bangladesh, Bhutan, Cambodia, Hong Kong, 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.

Summaries of ModernaTx, Inc. distribution administered by country and distribution by lots/batches are included in PSUR Appendix 12.1.

Rapporteur assessment comment:

Exposure from Clinical trials

The estimated cumulative subject exposure in clinical trials is estimated to 59,907 subjects.

Exposure from Post-marketing

Cumulative exposure

Cumulatively, a total of 1,043,567,281 doses of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and andusomeran are estimated to have been administered.

For elasomeran/imelasomeran the estimated cumulative exposure is 70,954,149 administered doses.

For elasomeran/davesomeran the estimated cumulative exposure is 135,185,679 administered doses.

Andusomeran was introduced as a new marketed Moderna vaccine targeting SARS-CoV-2 in Sep 2023. As of 17 Dec 2023, an estimated total of 45,815,600 doses were administered.

Interval exposure

The total interval exposure from marketing experience is estimated as 65,561,716 administered doses.

Given that elasomeran distribution was discontinued worldwide after Jun 2023, no new doses were distributed during this reporting period.

For elasomeran/imelasomeran the estimated interval exposure is 5,638 administered doses.

For elasomeran/davesomeran the estimated interval exposure is 15,555,689 administered doses.

For andusomeran the estimated interval exposure is 45,815,600 administered doses.

This section is acknowledged.

1.3.3.2.1. 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.

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.

1.3.3.2.2. Post authorisation in Special Populations

Use in elderly

Evaluation of information received during the PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in the elderly population has not identified any additional clinically relevant new safety information for this subpopulation. Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

The number of cases received during this reporting period and the associated MAH comment are presented by product in Table 12. Most of the cases with fatal outcome (48, 80.0%), irrespective of product type, were assessed as unlikely related to the products due to concurrent comorbidities that provided alternate etiologies. Review of the data did not reveal any differences from the general population. Refer to PSUR Appendix 12.3 for more information.

Table 12: Case Reports and MAH Comment by Product

Source of New Information	• ModernaTx, Inc. Global Safety Database (GSDB) • Literature Sources: o Search Criteria Applied: See Appendix 13.4 o New and Significant Safety Information: None (0)		
Product	**Exposed Population by Age groups**	**Number of Case Reports Received**	**Comment on Benefit and/or Risk (any observed differences from overall population)**
Elasomeran	>65 years of age	1,648	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/imelasomeran	>65 years of age	177	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/davesomeran	>65 years of age	491	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Andusomeran	>65 years of age	1,051	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
SPIKEVAX (NOS)	>65 years of age	64	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.

Andusomeran

During this reporting period, the MAH received 1,051 cases (210 serious, 717 medically confirmed, 11 fatal) with 3,182 events (511 serious) in the elderly population (>65+ years of age) who received andusomeran. When gender was known, most cases were reported in females (604, 57.5%) compared to males (336, 32.0%), with small proportion of cases (111, 10.6%) having no gender reported. The mean patient age was 75.6 years (SD: 7.8) and median age of 74.0 years (range: 65.0 to 106.0 years). Almost half of the cases were reported in United States (487, 46.3%) followed by UK (313, 29.8%) and Canada (176, 16.7%).

During the reporting period, when dose number and time to onset (TTO) could be determined, events were most often reported after Dose 5 (238, 7.5%) followed by Dose 6 (232, 7.3%) and Dose 4 (221, 6.9%), typically within 14-30 days of vaccination. When outcome was recorded, 17.6% of events had resolved (561 events), 11.0% were resolving (350 events) and 26.0% of events had not resolved (828 events), at the time of report. Most of the cases with fatal outcome (7, 63.6%) were evaluated as

unlikely related to the use of the product. Concurrent polymorbid conditions provided alternate etiologies for the occurrence of the event.

SPIKEVAX (NOS)

During this reporting period, the MAH received 64 cases (17 serious, 45 medically confirmed, 3 fatal) with 141 events (21 serious) in the elderly population (>65+ years of age) who received a marketed Moderna vaccine targeting SARS-CoV-2 but for which there was insufficient information to attribute the relationship of the case and events to a specific vaccine (SPIKEVAX [NOS]). When gender was known, there were more cases reported in females (38, 59.4%) compared to males (23, 35.9%), with 3 cases (3, 4.7%) having no gender reported. The mean patient age was 74.0 years (SD: 6.7) and median age was 73.5 years (range: 65.0 to 94.0 years). The majority of the cases were reported in United States (51, 77.3%) followed by the EEA (5, 7.6%) and Asia/ UK (3, 4.5%).

Overall, the events reflected reactogenicity or those known to occur following vaccination with Moderna vaccine targeting SARS-CoV-2. Other reported events did not reveal any new or unusual patterns.

No new safety concerns were identified in these reports.

Use in children

Evaluation of information received during the PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in children has not identified any additional clinically relevant new safety information for this subpopulation. The number of cases received during this reporting period and associated MAH comment are presented by age group in Table 13. Refer to PSUR Appendix 12.4 for additional information.

During the reporting period, the MAH received 1,315 cases (26 serious, 1,263 medically confirmed, 1 fatal) with 2,575 events (40 serious) reported for children <18 years of age who received any marketed Moderna vaccine targeting SARS-CoV-2. When gender was known, no significant difference was noted in cases involving males (655; 49.8%) and females (596; 45.3%), with small proportion of cases (64; 4.9%) having no gender reported. The mean patient age was 4.0 years (standard deviation: 4.2) and median age of 3.0 (range: 0.0 to 17.0 years). Most of these reports were from regulatory authorities (873; 66.4%), of which 783 (59.5%) reports were received in batch from Peru health authority following a new paediatric vaccination campaign initiated in Peru in Jun 2023. The highest number of cases were reported in Latin America (801; 60.9%), followed by The United States (419; 31.9%) and European Economic Area (51; 3.9%).

During the reporting period, the majority of events (1,678; 65.2%) did not provide information on dose number and TTO (1,266, 49.2%). When dose number and TTO could be determined, events were most often reported after Dose 1 (484, 18.8%) followed by Dose 2 (298, 11.6%) and Dose 3 (79, 3.1%), typically within 7 days of vaccination.

The most frequently reported events in children were "Vaccination site pain" (466; 18.1%), "Pyrexia" (447; 17.4%) and "No adverse event (395; 15.3%)".

Table 13: Case Reports and MAH comment by Age Group

Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources: ○ Search Criteria Applied: Refer to Appendix 13.4 ○ New and Significant Safety Information: None (0)	
Exposed Population by Age groups	**Number of Case Reports Received**	**MAH Comment on Benefit and/or Risk (any observed differences from overall population)**
<6 months of age	Total cases • Andusomeran: 2 non-serious cases • Elasomeran: 9 cases (3 serious, 0 fatal) • Elasomeran/imelasomeran: 1 serious case • Elasomeran/davesomeran: 4 non-serious cases • SPIKEVAX NOS: No cases were reported during this reporting period.	[redacted] describes occurrence of neonatal brady arrhythmia in a 1-month-old male. Please refer to Section 16.3.5.1 for further details. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children (6 months to 5 years)	• Andusomeran: 88 cases (1 serious, 0 fatal) • Elasomeran: 775 cases (6 serious, 0 fatal) • Elasomeran/imelasomeran: No cases were reporting during this reporting period. • Elasomeran/davesomeran: 179 non-serious cases • SPIKEVAX NOS: 4 non-serious cases	One case [redacted]) described occurrence of foetal growth restriction in 1-year-old female. Please refer to Section 16.3.5.1 for further details. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children 6-11 years	• Andusomeran: 84 non-serious cases • Elasomeran: 30 non-serious cases • Elasomeran/imelasomeran: No cases reported during this reporting period. • Elasomeran/davesomeran: 19 cases (1 serious, 0 fatal) • SPIKEVAX NOS: No cases reported during this reporting period.	The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Adolescents (12 to 17 years)	• Andusomeran: 55 cases (2 serious, 0 fatal) • Elasomeran: 52 cases (10 serious, 1 fatal) • Elasomeran/imelasomeran: No cases were reported during this reporting period. • Elasomeran/davesomeran: 12 cases (1 serious, 0 fatal). • SPIKEVAX NOS: 1 serious case (0 fatal).	There were 6 cases reported concerning myocarditis /pericarditis. Please refer to Section 16.3.1.2 for further details. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Elderly population

According to the MAH, no new clinically relevant safety information was identified for the elderly population in the reporting period.

64 fatal cases were reported in the elderly population for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, or Spikevax NOS (see PSUR appendix 12.3). Most of the cases with fatal outcome (48, 80.0%), irrespective of product type, were assessed by the MAH as unlikely related to the products due to concurrent comorbidities that provided alternate etiologies. 7 of the fatal cases were deemed WHO possible. Overall, the events reflected reactogenicity or those known to occur following vaccination with Moderna vaccine targeting SARS-CoV-2. No new safety concerns were identified by the MAH in these reports.

Paediatric population

During the reporting period, the MAH received 1,315 cases (26 serious). Fatal outcome was reported in 1 case, concerning a 17-years-old patient of unknown gender. No medical history or concomitant medication was reported. The patient died an unknown time after a dose of mRNA-1273.

According to the MAH, no additional new clinically relevant safety information was identified for the paediatric population in the reporting period.

This section is acknowledged.

1.3.3.3. Other clinical topics

Overdose

Table 14: Overdose

Source of New Information	• ModernaTx, Inc. GSDB
	• Literature Sources:
	  ○ Search Criteria Applied: See Appendix 13.4
	  ○ New and Significant Safety Information: None (0)

Background	Assessing harm due to administration of an extra dose of a vaccine is not well understood. Among reports where an AE could be included, most of the common events refers to expected conditions such as pyrexia, injection site erythema, pain, and headache. Since Oct 2023, reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age were received by the MAH. This issue was restricted to the United States and was limited to US EUA of ModernaTx, Inc COVID-19 Vaccine (andusomeran). The paediatric SDV contains notably more than 0.25 mL of vaccine, which had led to provider confusion or administration errors, including overdose.
Methods	The MAH queried the GSDB for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for Marketed Moderna vaccines targeting SARS-CoV-2. The search criteria applied for identification of Overdose cases included the following terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.
Results	*Overdose Cases Involving use of elasomeran* During the review period, the MAH received 3 cases (3 events) of overdose with 2 serious cases (1 serious event), and no cases with a fatal outcome. Two cases (66.7%) were medically confirmed, and the reported events were "Overdose" (3; 100.0%). Of the three events reported, two events occurred prior to the

	discontinuation of elasomeran in Jun 2023. However, these events were not reported till after the discontinuation of elasomeran. *Overdose Cases Involving use of elasomeran/imelasomeran* During this review period, there were no cases of overdose reported involving elasomeran/imelasomeran. *Overdose Cases Involving use of elasomeran/davesomeran* During the review period, the MAH received 4 medically confirmed cases (4 events) of overdose with no serious cases and no cases with a fatal outcome. The reported events were "Overdose" and "Accidental Overdose" (2 events; 50% each). *Overdose Cases Involving use of andusomeran* It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new Omicron variant XXB 1.5. Since its approval, the MAH has received 204 cases (204 events) of and no cases with a fatal outcome. A total of 202 cases (99.0%) were medically confirmed. The reported events were "Accidental overdose" (128; 62.7%) and "Overdose" (76; 37.3%). Most of these reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age have been received. This issue was mostly restricted to the United States and was limited to US EUA of ModernaTx, Inc COVID-19 Vaccine (andusomeran). The paediatric SDV contains notably more than 0.25 mL of vaccine, which had led to provider confusion or administration errors, including overdose. The MAH considered Overdose in children aged 6 months to 11 years in the context of overfill of SDV in the US as an important potential risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified is it considered a potential risk. Additional risk minimization measure in place. Refer Section 16.2.5. *Overdose Cases Involving use of Unspecified SPIKEVAX COVID-19 Vaccine-SPIKEVAX (NOS)* During the review period, the MAH received 2 medically confirmed cases (2 events) no cases with a fatal outcome. The reported events were "Accidental overdose" and "Overdose" (1 event; 50.0% each).
Discussion	A review of the data received during the reporting period of this PBRER, showed that among reports of overdose where an AE was reported, no harm was caused to any vaccinee, with most of the events reported included reactogenicity events. The reports of accidental overdose in the paediatric population were not associated with adverse events. These reports concerned medication use error where the entire volume of the SDV (0.5 mL) of andusomeran was administered to children 6 months through 11 years of age rather than the indicated 0.25 mL dose for this age group as described in the EUA Fact Sheet. The MAH decided on the following risk minimization actions:

	• Update of the current Fact Sheet, to clarify the dosage and administration instructions to providers. • Update of corresponding websites to clarify dosage and administration information. • Communication of the findings to the appropriate health authorities, including CDC. • Distribution of a DHCP letter in the US only and in addition, the MAH is closely monitoring overdose in children in the context of overfill of SDV and associated harms as a part of routine pharmacovigilance activities. Overall, the events reflected reactogenicity or those known to occur following vaccination with marketed Moderna vaccines targeting SARS-CoV-2. Other reported events did not show any new or unusual patterns. The Benefit-risk evaluation remains positive. No new safety concerns were identified in these reports.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Overdose reported in temporal association with the administration of marketed Moderna vaccines Targeting SARS-CoV-2 did not raise any safety issue of concern. The MAH will continue to monitor events of overdose using routine surveillance. The benefit-risk evaluation remains positive.

Refer to PSUR Appendix 12.5 for more detailed information.

Off-label

Table 15: Off-Label use

Source of New Information	• ModernaTx, Inc, GSDB
	• Literature Sources:
	  ○ Search Criteria Applied: See Appendix 13.4
	  ○ New and Significant Safety Information: None (0)

Background	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 Good Pharmacovigilance Practices Annex 1 – Definitions [Rev 4]) [6].
Methods	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, and Intentional product use issue. If warranted, the Company causality assessment is provided utilizing the World Health Organization-Uppsala Monitoring Center (WHO-UMC) standardized case causality assessment for serious cases classified as meeting the definition of Off-label use.
Results	*Off-label Use Cases involving use of elasomeran* During the review period, the MAH received 20 cases (21 events) of Off-label use with 16 serious cases (15 serious events), and no cases with a fatal outcome. In one case the event off label use was reported non serious but based on other reported events the case was serious (at case level). There were 12 medically confirmed cases involving elasomeran. These cases were reported mostly in females (13 cases, 65.0%) and in males (7 cases, 35.0%). The mean age was 54.1 years (Standard deviation: 12.2) and median age was 55 years (range: 32.0 to 73.0 years). The country with the most frequent cases of Off-label use was Canada (12; 60.0%) followed by Germany (6; 30.0%). The events reported were "Off-label use" (20; 95.2%) and "Intentional product misuse" (1; 4.8%). *Off-label Cases involving use of elasomeran/imelasomeran* During this review period, there were no cases of Off-label use reported involving elasomeran/imelasomeran. *Off-label Cases Involving use of elasomeran/davesomeran* During the review period, the MAH received 45 cases (45 events) of Off-label use with 2 serious cases (2 serious event) and no case with a fatal outcome. There were 44 medically confirmed cases involving elasomeran/davesomeran. There were 2 cases reported in females (4.4%), and 1 case reported in males (2.2%). Gender information was missing in 42 cases (93.3%) The mean age was 77.7 years (SD: 10.7) and median age was 72.0 years (range: 71.0 to 90.0 years). The country with the most cases of Off-label use reported was the United States (42; 93.3%). The events reported were "Off-label use" (45; 100%). *Off-label Cases involving use of andusomeran* It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new Omicron variant XXB 1.5. Since its approval, the MAH has received 1 non serious, medically confirmed case (1 event) of Off-label use and no cases with a fatal outcome. The case involved a 77-year-old female from the United States. *Off-label Cases involving Use of Unspecified SPIKEVAX COVID-19 Vaccine-SPIKEVAX (NOS)* During this review period, there were no cases of Off-label use reported involving SPIKEVAX (NOS).
Discussion	The total number of cases of off-label use was lower during the current reporting period compared to the prior reporting period (47 vs 67 cases) as were the number of medically

	confirmed cases (25 vs 56 cases). During this reporting period, majority of the off-label use cases had limited information, missing ages and no associated AEs reported. Consistent with the prior reporting period, "off-label use" was the most frequently reported Preferred Term (PT) during the current reporting period. Off-label use observed during the review period did not change the safety profile of Moderna vaccines Targeting SARS-CoV-2.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases of off-label use reported in temporal association with the administration of Moderna vaccines Targeting SARS-CoV-2 did not raise any safety issue of concern. The information provided does not support evidence of causality between Moderna vaccines Targeting SARS-CoV-2 exposure. The MAH will continue to monitor events for off-label use using routine surveillance. The benefit-risk evaluation remains positive.

Refer to PSUR Appendix 12.6 for more detailed information.

Rapporteur assessment comment:

Overdose

During the reporting period, 3 cases with overdose were identified for elasomeran, 0 cases for elasomeran/imelasomeran, 4 cases for elasomeran/davesomeran, 204 cases for andusomeran, and 2 cases for unspecified Spikevax (NOS). No cases were reported with fatal outcome. According to the MAH, overall, the events reported in received overdose cases reflected reactogenicity or reactions known to occur following vaccination.

Since Oct 2023, reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age were received by the MAH, where the entire volume of the SDV (0.5 mL) of andusomeran was administered, rather than the indicated 0.25 mL dose as described in the EUA Fact Sheet. The MAH states that this issue was restricted to the United States and was limited to US EUA of ModernaTx, Inc COVID-19 Vaccine (andusomeran).

The reports of accidental overdose in the paediatric population were not associated with adverse events.

The signal "Overdose in children in the context of overfill of the SDV indicated for individuals 6 months through 11 years of age in the US" was closed during the reporting interval with substantiated outcome. Please refer to section 2.2 of this assessment report for more information.

Off-label use

During the reporting period, 20 cases of Off-label use were identified for elasomeran, 0 cases for elasomeran/imelasomeran, 45 cases for elasomeran/davesomeran, 1 case for andusomeran, and 0 cases for unspecified Spikevax (NOS). No cases were reported with fatal outcome. The MAH states that the majority of the off-label cases had limited information, missing ages and no associated AEs reported. Please note that the MAH presents that the total number of off-label cases was lower during the current reporting period compared to the prior reporting period (47 vs 67 cases), however, based on the numbers presented in the results section of table 15 above, the true number for this reporting period is 66 cases.

No new significant safety information was identified from overdose or off-label use.

The section is acknowledged.

1.3.4. Data in summary tabulations

Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 was used for the coding of 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 PT.

Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative (18 Dec 2020 to 17 Dec 2023) summary tabulation of Serious Adverse Events (SAEs) from Company-sponsored CTs is provided in PSUR Appendix 3. 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, mRNA-1273.214, mRNA-1273.222, mRNA-1273.815 and mRNA-1273.231, 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 2023) and interval (18 Jun 2023 to 17 Dec 2023) summary tabulation of ADRs (serious and non-serious) is provided in PSUR Appendix 4. 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 in the reporting period. However, the Rapporteur notes that the presentation of data in summary tabulations in appendices 3 and 4 is incomplete. For andusomeran, neither the summary tabulation for clinical trials (3f) nor for post-marketing data sources (4f) contain any data, which is obviously an error based on the andusomeran case reports presented elsewhere in the PSUR. In future PSURs, the MAH is requested to make sure that all relevant data is included in the appended summary tabulations.

Otherwise, this section is acknowledged.

1.3.5. Findings from clinical trials and other sources

Clinical trials	Non-interventional studies	Other clinical trials and sources	Medication errors	Non-clinical data	Literature	Other periodic reports
Completed: 1 Ongoing: 16	Completed: 9 Ongoing: 13	Investigator-sponsored studies Completed: 1 Ongoing: 7 License partner studies Completed: 1 Ongoing: 12	Elasomeran 447 cases (1,831 events) Elasomeran/imelasomeran 162 cases (471 events) Elasomeran/davsesomeran 1,366 cases (3,390 events) Andusomeran 2,038 cases (4,765 events)	None	None	None

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

Completed clinical trials

During the reporting period, ModernaTx, Inc sponsored clinical trial of mRNA-1273-P301 was completed.

mRNA-1273-P301: A 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**.**

Country: USA

Final Summary: This study aimed at long-term immunogenicity, safety follow-up and effectiveness (COVID-19 incidence rates) data following the 2-dose primary series (Part A and Part B) and booster dose, with a median follow-up of 415 days following Dose 1 and a median of 385 days following Dose 2. As of the end of study, the overall median duration of follow-up after the booster dose was 330 days (range: 1 to 478 days).

Efficacy

Long-term COVID-19 incidence rates for the mRNA-1273 and placebo-mRNA-1273 groups in Part A and Part B showed the rates during both the Delta and the Omicron variant waves were similar between the mRNA-1273 (earlier vaccinated) and the placebo-mRNA-1273 (later vaccinated) groups, suggesting durability of protection after the primary series in the mRNA-1273 group despite the longer interval. However, the higher incidence in both groups during the Omicron wave demonstrates the need to boost immune responses to enhance protection.

Analysis of incidence rates in Part C booster participants showed the majority of COVID-19 cases were detected during the Omicron variant waves. Incidence rates coinciding with Omicron BA.1 predominance (01 Dec 2021 to 31 Mar 2022), Omicron BA.2 predominance (01 Apr 2022 to 30 Jun 2022), and Omicron BA.4/5 predominance (01 Jul 2022 to 30 Nov 2022) were 25.845 (95% CI: 24.542, 27.199), 33.151 (95% CI: 31.252, 35.136), and 36.469 (95% CI 34.148, 38.906) cases per 1,000 person-months, respectively.

Safety

Long-term follow-up data for participants who received the mRNA-1273 primary series vaccination in Part A do not suggest any safety concerns based on events occurring beyond 6 months after vaccination. Safety findings for participants who received the primary series during the Open-Label Observational Phase (Part B) of the study were consistent with those for the double-blind period in Part A. Based on post-authorization data (subsequent to reporting of the double-blind period), myocarditis and pericarditis are included in the CCDS and labels as an important identified risk. No new safety concerns were identified based upon review of the data for this final study report, including long-term safety follow-up.

The mRNA-1273 50 µg booster dose was well-tolerated and no new safety concerns were identified. The incidence of all TEAEs, including those considered by the investigator to be related to study vaccine, as well as the types and frequencies of events by SOC and PT, were similar among participants with positive

SARS-CoV-2 status at pre-booster baseline compared with participants with negative status at pre-booster baseline. In the overall population of participants who received a booster dose, the types and incidence of reported events were generally consistent with observations for the primary series and with known risks, including very rare events of myocarditis and pericarditis.

Immunogenicity

Overall, following Dose 2 of the primary series, nAb levels were increased by 119-fold (Geometric Mean Fold Rise [GMFR {95% CI} = 119.058 [110.663, 128.089]) at Day 57 (28 days after Dose 2). A reduction in nAbs was apparent at Day 209 (GMFR [95% CI] = 25.744 [23.754, 27.900]) and at pre-booster BD-Day 1 (GMFR [95% CI] = 17.965 [16.146, 19.988]).

The VAC62 neutralizing antibody in PPIS was significantly higher post-booster (BD-Day 29) nAb GMCs (GMC [95% CI] = 8122.189 [7603.021, 8676.808]) compared to pre-booster BD-Day 1 participants (GMC [95% CI] = 163.848 [147.977, 181.421]). The booster dose induced a significant rise in nAb GMC (GMFR [95% CI] = 50.157 [45.642, 55.120]) by BD-Day 29, with SRR = 94.5 % [92.5, 96.1]. Levels decreased at BD-Day 181 but were still markedly elevated (GMC [95% CI] = 2951.123 [2701.648, 3223.636]).

Superiority of the booster as compared with the 100 µg mRNA-1273 primary series (Part C BD-Day 29 / Part A Day 57) was demonstrated based on nAb (6.996 [95% CI: 6.509, 7.520]) and SRR difference (0.9% [95% CI: 0.1, 1.8]) in the PPIS-Neg. Results of bAb S-protein were consistent with nAb.

Rapporteur assessment comment:

One clinical trial (mRNA-1273-P301) evaluating efficacy, safety, and long-term immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older was completed during the reporting interval.

According to the MAH, the Phase 3 study mRNA-1273-P301 includes a total of 24 months follow-up; no long-term safety concerns have been identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants.

Endorsed.

Ongoing clinical trials

There was a total of 16 ModernaTx, Inc. sponsored CTs with mRNA-1273 ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P206, mRNA-1273-P304, mRNA-1273-P305, mRNA-1273-P306, mRNA-1283-P101, mRNA-1283-P201, mRNA-1283-P301, mRNA-CRID-001, mRNA-1083-P101, mRNA-1083-P301, mRNA-1273-1073-P101, mRNA-1230-P101, and mRNA-1345-P302), during the current reporting period. Of these 16 ongoing CTs, nine trials (mRNA-1283-P101, mRNA-1283-P201, mRNA-1283-P301, mRNA-1083-P101, mRNA-CRID-001, mRNA-1083-P301, mRNA-1273-1073-P101, mRNA-1230-P101, and mRNA-1345-P302) included mRNA-1273 treatment arms as active controls. Cumulative exposure by study has been presented in Table 16.

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

Table 16: Summary of Estimated Cumulative Subject Exposure to mRNA-1273 and its variants by Study[a]

Study ID	Total subjects exposed
mRNA-1273-P203	3,177
mRNA-1273-P204	11,032
mRNA-1273-P205	5,162
mRNA-1273-P206	68
mRNA-1273-P304	234
mRNA-1273-P305	3,548
mRNA-1273-P306	930
mRNA-1283-P101	27
mRNA-1283-P201	57
mRNA-1283-P301	5,716
mRNA-CRID-001	60
mRNA-1083-P101	102
mRNA-1083-P301[b]	4,013
mRNA-1073-P101[b]	150
mRNA-1230-P101[b]	44
mRNA-1345-P302[b]	1,690

a=Data from ongoing trials till 17 Dec 2023.

b=Estimated numbers per randomization scheme as the study is currently blinded.

Refer to PSUR Appendix 6 [Please see the PSUR] for further details of all the ongoing and completed studies during the reporting period.

Rapporteur assessment comment:

The MAH reports that no clinically important safety information that arose from the 16 ongoing CTs during the reporting period.

Endorsed.

Long-term Follow-up

The Phase 3 study mRNA-1273-P301 includes a total of 24 months follow-up; no long-term safety concerns have been identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days).

In the adolescent Phase 3 Study mRNA-1273-P203, participants from the age of 12 through 17 years had a median follow-up of 342 days after Dose 1, 312 days after Dose 2 and 204 days after a booster dose. In the paediatric Phase 3 Study mRNA-1273-P204, participants 6 months through 11 years had a median follow-up ranging between 183 and 363 days across age groups from Dose 1 and 183 to 266 days from Dose 2. In the paediatric Phase 3 Study mRNA-1273-P306, participants 6 months through 5 years had a

median follow-up of 187 (1,386) days from Dose 1 and 168.5 (9,355) days from Dose 2. These studies are ongoing, and no findings related to long-term safety have yet been identified.

Post-authorization safety studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911 are ongoing, and no findings related to long-term safety have yet been identified.

As of the DLP of this PBRER, no clinically important safety concerns have been identified upon review of long-term follow-up data in CTs.

Other Therapeutic Use of Medicinal Product

Marketed Moderna vaccines targeting SARS-CoV-2 have not been investigated for any other therapeutic use during the reporting period.

New Safety Data Related to Fixed Combination Therapies

For Moderna vaccines Targeting SARS-CoV-2 there were two combination therapies in which marketed Moderna vaccines Targeting SARS-CoV-2 are part of the fixed combinations: mRNA-1073, and mRNA-1230. There are separate Development Safety Update Reports (DSURs) for each of these fixed combination therapies. No new safety information has been identified from the fixed combination therapies that are in development.

Rapporteur assessment comment:

The MAH reports that, as of the DLP, no clinically important safety concerns have been identified upon review of long-term follow-up data in CTs.

There were two combination therapies in which marketed Moderna vaccines Targeting SARS-CoV-2 are part of the fixed combinations: mRNA-1073, and mRNA-1230. There are separate Development Safety Update Reports (DSURs) for each of these fixed combination therapies. According to the MAH, no new safety information has been identified from the fixed combination therapies that are in development.

Endorsed.

1.3.5.2. Findings from Non-Interventional Studies (NIS)

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

Study ID	Country	Study Title	Study results
mRNA-1273-P903	United States	Post-marketing safety of SARS-CoV-2 SPIKEVAX vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity.	The final report for this study was submitted 30 Jun 2023, however final analyses were reported in PBRER 5.
mRNA-1273-P915	Japan	Survey on Shock and Anaphylaxis for Persons with Underlying Diseases with High Risk of Severe COVID-19 Using Vaccination Information.	The overarching goal of this post-marketing surveillance (PMS) activity was 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 provisional report for this database survey was submitted to Pharmaceuticals and Medical Devices Agency (PMDA) on 17 May 2023. Based on the analysis of 13,309 individuals, the occurrence of hypersensitivity in individuals at high risk for COVID-19 infection was consistent with the known safety profile of elasomeran.
mRNA-1273-P916	Japan	Survey on acute phase safety for persons with underlying diseases with high risk of worsening of COVID-19 using vaccination information.	The overarching goal of this PMS activity was 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 provisional report for this database survey was submitted to PMDA on 17 May 2023. Based on the analysis of 8,844 individuals, the occurrence of solicited AEs, particularly, reactogenicity had an occurrence of > 1% within 8-days of vaccination in individuals at high risk for COVID-19 infection.
mRNA-1273-P928	United States	Relative effectiveness of the BNT162b2 (Pfizer–BioNTech), mRNA-1273 (ModernaTx, Inc), and Ad26.COV2.S (Johnson &	This observational cohort study consistent of two pats. Part I: To determine the rVE of 2 doses of the mRNA-1273 vaccine vs. 2 doses of the BNT162b2 vaccine and 2 doses of the Mrna-1273 vaccine vs. 1 dose

Study ID	Country	Study Title	Study results
		Johnson–Janssen) COVID-19 Vaccine in adults with COVID-19 related at-risk conditions.	of the Ad26.COV2.S vaccine in individuals aged 18 years and older who have at least one underlying medical condition (endpoints: medically-attended COVID-19 illness/COVID-19 illness in outpatients/ COVID-19 illness requiring hospitalization). Part II: To determine the Rve of a single homologous booster dose of the Mrna-1273 vaccine vs. a single homologous booster dose of the BNT162b2 vaccine in adults aged 18 years and older who have at least one underlying medical condition associated with higher risk for severe COVID-19 (endpoints: medically-attended COVID-19 illness/ COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization). Protocol was approved on 02 Mar 2023 and interim updates were done on 12 May 2023. At this time, no safety findings have been identified. Results were presented at ID Week 2023. No safety outcomes were assessed.
Mrna-1273-P930	United States	Relative effectiveness of BNT162b2, Mrna-1273, and Ad26.COV2.S vaccines and homologous boosting in preventing COVID-19 in adults in the US.	This study evaluated the relative effectiveness (Rve) of a primary series of Mrna-1273 vs BNT162b2 and Ad26.COV2.S and a homologous Mrna booster against any medically attended, outpatient, and hospitalized COVID-19. Following adjustment, Part 1 Rve for Mrna-1273 vs BNT162b2 was 23% (95% Confidence Interval [CI], 22%–25%), 23% (95% CI, 22%–25%), and 19% (95% CI, 14%–24%), while the rVE for mRNA-1273 vs Ad26.COV2.S was 50% (95% CI, 48%–51%), 50% (95% CI, 48%–52%), and 57% (95% CI, 53%–61%) against any medically attended, outpatient, and hospitalized COVID-19, respectively. The adjusted rVE in Part 2 for mRNA-1273 vs BNT162b2 was 14% (95% CI, 10%-18%), 13% (95% CI, 8%–17%), and 19% (95% CI, 1%–34%) against any medically attended, outpatient, and hospitalized COVID-19, respectively. rVE against medically attended COVID-19 was higher in adults age ≥65 years (35%; 95% CI, 24%–47%) than in those age

Study ID	Country	Study Title	Study results
			18-64 years (13%; 95% CI, 9%–17%) after the booster. No safety outcomes were assessed.
mRNA-1273-P931	United States	Relative effectiveness of the Bivalent COVID-19 mRNA Vaccines (ORIGINAL AND OMICRON BA.4/BA.5) in adults in the US.	This study estimated the rVE against COVID-19-related hospitalizations (primary outcome) and outpatient visits (secondary) for 1,034,538 mRNA-1273.222 and 1,670,666 BNT162b2 Bivalent vaccine recipients, with an adjusted rVE of 9.8% (95% CI: 2.6-16.4%) and 5.1% (95% CI: 3.2-6.9%), respectively, for mRNA-1273.222 versus BNT162b2 Bivalent. The incremental relative effectiveness was greater among adults ≥ 65; the rVE against COVID-19-related hospitalizations and outpatient visits in these patients was 13.5% (95% CI: 5.5-20.8%) and 10.7% (8.2-13.1%), respectively. Overall, we found greater effectiveness of mRNA-1273.222 compared with the BNT162b2 Bivalent vaccine in preventing COVID-19-related hospitalizations and outpatient visits, with increased benefits in older adults. No safety outcomes were assessed.
mRNA-1273-P932	United States	Real-world comparative effectiveness of a third dose of mRNA-1273 versus BNT162b2 among immunocompromised adults in the US.	The main objective of this retrospective cohort study was to compare real-world effectiveness of third doses of mRNA-1273 versus BNT162b2 at multiple time points on occurrence of COVID-19 hospitalization and medically-attended COVID-19 among IC adults in the US. In propensity score-adjusted analyses, receiving mRNA-1273 vs BNT162b2 as third dose was associated with 32% (relative risk [RR] 0.68; 95% CI 0.51-0.89), 29% (0.71; 0.57-0.86), and 23% (0.77; 0.62-0.93) lower risk of COVID-19 hospitalization after 90, 180, and 270 days, respectively. Corresponding reductions in medically-attended COVID-19 were 8% (0.92; 0.86-0.98), 6% (0.94; 0.90-0.98), and 2% (0.98; 0.94-1.02), respectively. No safety outcomes were assessed.
mRNA-1273-P933	United States	Real world comparative effectiveness of a booster dose of SPIKEVAX versus Comirnaty among adults age 65+ in the US.	In this study, 94,587 and 92,377 individuals received a third dose of mRNA-1273 and BNT162b2, respectively. Among the weighted population, the median age was 69 years (interquartile range, 66-74), 53%

Study ID	Country	Study Title	Study results
			were female, and 46% were commercially insured. COVID-19 hospitalization rates per 1000 person-years (PYs) were 5.61 (95% CI, 5.13-6.09) for mRNA-1273 and 7.06 (95% CI, 6.54-7.57) for BNT162b2 (Hazard ratio [HR], 0.82; 0.69-0.98). Medically attended COVID-19 rates per 1000 PYs (95% CI) were 95.05 (95% CI, 93.03-97.06) for mRNA-1273 and 106.55 (95% CI, 104.53-108.57) for BNT162b2 (HR, 0.93; 0.89-0.98). No safety outcomes were assessed.
mRNA-1273-P936	United States	Comparative Effectiveness of the Bivalent (Original / Omicron BA.4/BA.5) COVID-19 mRNA Vaccines, mRNA1273-222 and BNT162b2 Bivalent in Adults at Higher Risk for Severe COVID-19 Outcomes in the US.	In this study, mRNA-1273 prevented more medically-attended COVID-19 cases than BNT162b2 and Ad26.COV2.S, with rVEs of 24% (95% CI: 22-25%) and 51% (49–52%), respectively. Similarly, mRNA-1273 also prevented more outpatient and hospitalized COVID-19 cases than the two comparator vaccines. Findings were consistent across age groups. In Part 2, rVE of mRNA-1273 vs. BNT162b2 against medically attended COVID-19 cases was 14% (95% CI: 9 19%). Following a booster dose, mRNA-1273 prevented more hospitalizations than BNT162b2 with an rVE of 22% (95% CI: 3–37%) in the overall study population and increased with age, with estimates of 32% (13–47%) and 46% (19–65%) in adults ≥ 50 years and ≥ 65 years, respectively. No safety outcomes were assessed.

Rapporteur assessment comment:

9 Non-Interventional Studies were completed during the reporting period.

mRNA-1273-P916: The MAH reported that in an analysis of 8,844 individuals, the occurrence of solicited AEs, particularly, reactogenicity had an occurrence of > 1% within 8-days of vaccination in individuals at high risk for COVID-19 infection. The Rapporteur considers this finding expected and in accordance with the safety profile described in the SmPC, as adverse reactions related to reactogenicity such as e.g. pyrexia and injection site pain are listed in SmPC section 4.8 with the frequency "very common".

For the remaining studies, no new safety information that has not been assessed in other procedures has been presented.

The provided information is acknowledged.

Ongoing studies

A summary of safety findings from non-interventional studies that were ongoing during the report follows. Additional details for ongoing studies with the Primary Aim of Identifying, Characterizing, or Quantifying a Safety Hazard; Confirming the Safety Profile of the Medicinal Product; or Measuring the Effectiveness of

Risk Management Measures, including those with no safety findings due to study stage, is shown in Appendix 7 [Please see the PSUR].

mRNA-1273-P901

Title: Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the US. Summary: Secondary database study using electronic healthcare data from an integrated healthcare system in the US (Kaiser Permanente Southern California). Vaccination information and SARS-CoV-2 related outcomes (symptomatic illness, hospitalization, and death) will be identified using electronic healthcare data. Both matched cohort and test-negative study designs will be used to estimate relative and absolute vaccine effectiveness of mRNA-1273. The study population includes individuals ≥ six months of age. Start date for this study was 18 Dec 2020 and anticipated study completion date is 30 Apr 2024. The final clinical study report (CSR) date for this study is currently anticipated to be submitted by 14 Apr 2025.

Real-world effectiveness data of authorized COVID-19 mRNA vaccines have become available from study P901, a cohort study utilizing electronic healthcare data collected in the Kaiser Permanente Southern California integrated healthcare system. As of the latest interim report dated Jun 2023, Study P901 estimated the relative vaccine effectiveness and absolute vaccine effectiveness among individuals who received mRNA-1273.222 (following receipt of 2 or more doses of monovalent mRNA COVID vaccine) against COVID-19 hospitalization, SARS-CoV-2 infection requiring emergency department/urgent care, and in-hospital death between 31 Aug 2022 and 31 Jan 2023, a time when the omicron variants (e.g., BA.5) were circulating. The analysis population was composed of 290,292 individuals who received mRNA-1273.222 and 580,584 comparators who received 2 or more doses of monovalent mRNA COVID vaccine only (for relative vaccine effectiveness analyses), and 204, 655 who were unvaccinated for any COVID-19 vaccines (for absolutely vaccine effectiveness analyses). Comparators were matched to bivalent vaccinees on age, sex, race/ethnicity, and date receipt of bivalent vaccination. Compared to individuals who did not receive any bivalent mRNA vaccine but received ≥2 doses of any monovalent mRNA vaccine, the relative vaccine effectiveness (rVE) against hospitalization for COVID-19 disease was 70.3% (95% CI). Relative vaccine effectiveness against SARS-CoV- 2 infection requiring emergency department/urgent care and against COVID-19 hospital death was 55.0% (50.8%-58.8%) and 82.7% (63.7%-91.7%), respectively. Compared to individuals who were unvaccinated for any COVID-19 vaccine, the absolute Vaccine effectiveness against hospitalization for COVID-19 disease was 82.8% (78.8%-86.0%). Absolute vaccine effectiveness against SARS-CoV-2 infection requiring emergency department/urgent care and against COVID-19 in-hospital death was 55.4% (50.3%-60.1%) and 89.7% (77.7%-95.2%), respectively.

Since the last interim report dated Jun 2023, Study P901 also estimated the relative and absolute vaccine effectiveness among individuals who received mRNA-1273.222 (following receipt of 2 or more doses of monovalent mRNA COVID vaccine) against SARS-CoV-2 infection overall, SARS-CoV-2 infection requiring emergency department/urgent care, COVID-19 hospitalization, and COVID-19 in-hospital death by Omicron sub-variant BA.4/BA.5 and XBB-sub-lineages between 01 Sep 2022 and 30 Jun 2023. Utilizing a test-negative case control design, the relative vaccine effectiveness analysis included 20, 966 cases and 62, 898 controls. Relative vaccine effectiveness against BA.4/BA.5 was 46.8% (41.5%-51.6%) for infection, 58.3% (50.0%-65.1%) for ED/UC encounters, 67.2% (43.9%-80.8%) for hospitalization, and 53.1% (-84.2%-96.5%) for death. Relative vaccine effectiveness against XBB was 9.3% (-0.6%-18.2%) for infection, 25.9% (13.2%-36.7%) for ED/UC encounters, 59.9% (37.0%-74.5%) for hospitalization, and 31.8% (-83.7%-92.4%) for death. The absolute vaccine effectiveness analysis included 10, 366 cases and 31, 008 controls. Absolute vaccine effectiveness against BA.4/BA.5 was 18.6% (8.1%-27.9%) for infection, 51.9% (40.3%-61.3%) for ED/UC encounters, 78.4% (58.3%-88.8%) for hospitalization, and 45.9% (-66.1%-90.1%) for death. Absolute vaccine effectiveness against XBB was -25.0% (-35.0-[-

]13.5%) for infection, 8.2% (-12.2%-26.1%) for ED/UC encounters, 73.3% (51.2%-85.4%) for hospitalization, and 31.0% (-92.6%-96.5%) for death.

Prior analyses conducted from the P901 study assessing relative vaccine effectiveness of receipt of a single booster dose of the monovalent mRNA-1273 (following receipt of 2 doses of monovalent mRNA COVID vaccine) between 20 Oct 2021 and 31 Dec 2021 demonstrated rVE against hospitalization, SARS-CoV-2 infection and death to be 89.0% (95% CI: 86.2%-91.2%), 61.3% (95% CI: 60.5% – 62.2%), and 96% (95% CI: 68.0%-99.5%), respectively among 431,328 immunocompetent adults receiving a single booster dose of mRNA-1273 (and a similar number of matched comparators who received a 2 dose mRNA monovalent COVID vaccine only) [7]. In addition, an analysis conducted between 01 Jan 2022 and 30 Jun 2022 among 30,809 SARS-CoV-2 cases and 92,427 matched controls looking at Omicron variant specific relative vaccine effectiveness of a booster dose of mRNA-1273 against hospitalization for COVID-19 demonstrated the rVE against BA.1, BA.2, and BA.4/5 Omicron sub-variants to be 88.8% (95% CI: 83.3-92.5); 75.0% (95% CI: 47.6-88.1); and 87.5% (95% CI: 51.8%-96.8%) [8].

mRNA-1273-P904

Title: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of SPIKEVAX in the EU.

Summary: A preliminary screening stage analyzes for selected databases in this observational study using large administrative databases in Denmark, Norway, Spain, and the UK was presented in Interim Report 4 on 31 Mar 2023.

During the study period covered by Interim Report 4, the number of eligible elasomeran recipients with at least one dose of elasomeran and no previous record of a COVID-19 vaccine was 564,137 in Denmark, 543,429 in Norway, 621,240 in Spain, and 228,889 in the UK. Rates of the AESI varied widely across the databases. The variation is attributable both to the database characteristics, to algorithm refinement activities that are in progress within the VAC4EU network, and to data limitations (specifically, in Norway, inflation of some rates was due to lack of specific diagnosis subcodes in the current data extraction, which will be corrected for the final report).

The MAH identified more than 50 strata with standardized mortality ratio ≥2.0 based on ≥5 elasomeran exposed cases in at least one country for the AESIs diabetes type 1, idiopathic thrombocytopenia, heart failure, myocarditis, pericarditis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalized convulsions, acute respiratory distress syndrome, anosmia/ageusia, multisystem inflammatory syndrome, and death of any cause. There was a maximum of 11 to 50 signals in at least one country for the AESIs microangiopathy, coronary artery disease, arrhythmia, cerebrovascular disease, SOCV, encephalitis/meningoencephalitis, Bell's palsy, erythema multiforme, and anaphylaxis. The MAH did not identify any signals for narcolepsy, cerebral venous sinus thrombosis, Kawasaki disease, transverse myelitis, and sudden death. For the remaining AESIs, there was a maximum of 10 signals for each country. Most signals were detected in Spain (Information System for Research in Primary Care).

In the squamous cell carcinoma of the skin signal evaluation analyses, IRR with point estimates exceeding 1.5 were observed in at least one of the three countries for the AESIs (idiopathic) thrombocytopenia, stress-induced cardiomyopathy, myocarditis, pericarditis, splanchnic vein thrombosis, Acute liver injury, generalized convulsions, anaphylaxis, and Vaccine-induced immune thrombotic thrombocytopenia. The largest effect sizes were observed for myocarditis and pericarditis.

No indication of VAED was identified in Norway, the only country for which these analyses were performed in the Interim Report. Concerning cohort analyses of myocarditis and pericarditis, the majority of myocarditis and pericarditis cases was male; among those exposed to elasomeran, exposed the

majority had received the second dose of elasomeran before diagnosis of myocarditis in Norway and Denmark or before the diagnosis of pericarditis in Denmark.

Discussion

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-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. This retrospective observational cohort study used secondary, de-identified individual level medical and pharmacy claims data provided by HealthVerity. The interim report was submitted 15 Sep 2023. The incidence of AESI among patients who receive at least one dose of Elasomeran bivalent to two concurrent comparator groups (influenza vaccine and medically-attended COVID-19, analyzed separately). Where a potential increase in the rate of an AESI following elasomeran vaccination was identified, SCRI analyses for signal refinement is planned.

Statistical analysis:

For the primary analyses, propensity scores (PS) were calculated to estimate the probability of receiving a dose of elasomeran bivalent conditional on measured covariates. The PS was calculated via multivariable logistic regression model using inverse probability treatment weights (IPTW) method. Cox proportional hazards regression was used to evaluate the relationship between vaccine group and AESI. The Cox proportional hazard regression models estimated HR with 95% CI and cumulative incidence curves for the time-to-AESI stratified by exposure status, plotted for the PS-weighted populations. If the proportional hazard assumptions were not met an alternative outcome model for restricted mean survival time (RMST) was used. Weighted rates of endpoints were reported as the number of patients with the event of interest per 100,000 person-years. Analyses of the medically-attended COVID-19 concurrent comparator was limited to weighted estimates of the incidence rates; HRs were not estimated.

As a secondary analysis for influenza vaccine cohort, eligible vaccine episodes with Elasomeran bivalent and influenza vaccine administration on the same day or within 14 days of each other were included as eligible elasomeran bivalent vaccine episodes into the exposed group. As a subgroup analysis, a separate exposure cohort consisting of only eligible, concurrent Elasomeran bivalent and influenza vaccine episodes occurring on the same day or within 14 days was identified; the date of the elasomeran bivalent administration was considered the index date for this subgroup. These concurrent vaccine episodes were compared to eligible influenza vaccine episodes that do not overlap with an elasomeran bivalent vaccine episode. PS-weighted incidence rates and weighted HRs were estimated with 95% CIs within this secondary analysis.

In the final report, self-controlled risk interval analysis will be conducted for myocarditis, pericarditis, and AESI with increased lower bound of HR >1.

Results:

There were 519,838 and 5,332,765 episodes of elasomeran bivalent and influenza vaccinations among adults at least 18 years of age, respectively, that met inclusion criteria in comparator 1 analyses. In contrast, there were 1,061,073 and 1,051,868 episodes of elasomeran bivalent and medically-attended COVID-19 episodes among adults, respectively, that met inclusion criteria in comparator 2 analyses.

Among children less than 18 years of age, 10,500 and 2,646,986 episodes of elasomeran bivalent and influenza vaccinations were included in comparator 1 analyses, while 26,489 and 247,538 episodes of elasomeran bivalent and medically-attended COVID-19 episodes met inclusion criteria for the comparator cohort 2 without excluding any prevalent AESI.

Myocarditis:

Among the 519,390 and 5,327,428 elasomeran bivalent and influenza vaccine administrations included in the comparator 1 analyses, there were only 2 and 17 myocarditis cases observed in the 1-7 days following each type of vaccination episodes, respectively. The weighted incidence rate (IR) among the elasomeran bivalent episodes was 27.10 (95% CI: 16.55 - 41.85) per 100,000 person-years (PY) compared to a weighted IR of 19.81 (95% CI: 12.03 - 29.91) per 100,000 PY following influenza vaccination. The estimated HR from the weighted Cox model indicated no increased risk of myocarditis in the 1-7 days following elasomeran bivalent compared to influenza vaccination (weighted HR= 1.54, 95% CI: 0.32 - 7.34). However, the proportional hazards assumption was not met in this model, though estimation of the RMST was consistent with the observed weighted HR indicating no increased risk of myocarditis following Elasomeran bivalent (RMST = 1.000001, 95% CI 0.999999 - 1.000002).

There were 1,060,257 and 1,050,345 elasomeran bivalent and medically-attended COVID-19 episodes included in the comparator 2 analyses, for which 8 and 51 myocarditis cases were observed, respectively. The weighted IR in the 1-7 days following elasomeran bivalent administration was 57.30 (95% CI 36.56 - 88.80) per 100,000 PYs compared to a weighted IR of 281.70 (95% CI 229.89 - 341.92) per 100,000 PYs following medically-attended COVID-19.

Among children less than 18 years of age, there were no cases of myocarditis observed in the 1-7 days following elasomeran bivalent administration.

Pericarditis:

Among the 518,842 and 5,320,809 elasomeran bivalent and influenza vaccine administrations included in the comparator 1 analyses, there were only 1 and 29 pericarditis cases observed in the 1-7 days following vaccination, respectively. The weighted IR among the elasomeran bivalent episodes was 13.57 (95% CI: 6.50 - 24.95) per 100,000 PYs compared to a weighted IR of 32.97 (95% CI: 23.04 - 46.32) per 100,000 PYs following influenza vaccination. The estimated HR from the weighted Cox model indicated no increased risk of pericarditis in the 1-7 days following elasomeran bivalent compared to influenza vaccination (weighted HR= 0.44, 95% CI: 0.06 - 3.33).

There were 1,059,209 and 1,048,589 elasomeran bivalent and medically-attended COVID-19 episodes included in the comparator 2 analyses, for which 7 and 38 pericarditis cases were observed, respectively. The weighted IR in the 1-7 days following elasomeran bivalent administration was 47.30 (95% CI 27.40 - 74.13) per 100,000 PYs compared to a weighted IR of 159.03 (95% CI: 119.88 - 203.86) per 100,000 PYs following medically-attended COVID-19.

Among children less than 18 years of age, there were no cases of pericarditis observed in the 1-7 days following elasomeran bivalent administration for comparator 1 analyses and 1 case for comparator 2 analyses.

Other AESIs:

There were no observed increased risks or elevated incidence rates of any AESI following SPIKEVAX bivalent compared to either comparator 1 or 2 in pre-weighted and propensity score weighted estimates of incidence rates or HR among elasomeran bivalent episodes unique to adults or children.

Discussion:

This interim analysis supports the known safety profile of elasomeran bivalent, and new associations with AESI have not been observed. The final report will also include additional sensitivity and exploratory analyses, as well as signal evaluation for myocarditis and pericarditis through self-controlled risk interval analyzes, and any other AESI that meets the specified threshold.

Rapporteur assessment comment:

13 Non-Interventional Studies were ongoing as of DLP [see PSUR appendix 7].

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

The provided information is acknowledged.

Other studies describing risks or benefits of Moderna vaccines targeting SARS-CoV-2 are described here:

Study ID	Country	Study Title	Status
mRNA-1273-P905	Denmark, Norway, Italy, Spain, United Kingdom	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries.	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 Mar 2023 interim study update
mRNA-1273-P910	Denmark, Norway, Italy, Spain, United Kingdom	Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARSCoV-2.	The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and elasomeran bivalent vaccination. Startup activities including creation of the case adjudication system and preliminary analyses of structured data are currently in progress
mRNA-1273-P911	United States	Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA).	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. An interim feasibility report was completed 31 Oct 2023. Cases of myocarditis identified in routine clinical practice meeting the CDC case definition, including those occurring following administration of elasomeran as well as cases not secondary to vaccines targeting SARS-CoV-2 were described.
mRNA-1273-P917	Japan	Survey on non-acute phase safety for persons with underlying diseases who are considered to be at high risk of aggravation of COVID-19 using vaccination information.	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 provisional report for this database

Study ID	Country	Study Title	Status
			survey was submitted to PMDA on 20 Dec 2023. The final report will be submitted on 17 Mar 2024.
mRNA-1273-P918	Japan	General use-results survey (follow-up of participants in the priority survey at the early stage of inoculation with COVID-19 vaccine [SPIKEVAX {monovalent: original strain}]).	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. Enrolment for this survey ended in Dec 2022. There were 8,637 individuals in the safety and efficacy analysis set. At this time, no safety findings have yet been identified. The observation of the final subject was completed in Apr 2023, and final analyses are ongoing. A provisional report for this database survey was submitted to PMDA on 20 Dec 2023. The final report will be submitted on 17 Mar 2024.
mRNA-1273-P919	United States	An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to SPIKEVAX During Pregnancy.	This observational study will evaluate the risk of adverse pregnancy and infant outcomes following maternal exposure to elasomeran during pregnancy. Analyses are currently in progress. At this time, no safety findings have yet been identified given the early stage of the study.
mRNA-1273-P922	United States	DisCOVEries 2 - An Observational Study to Evaluate the Immunogenicity of mRNA COVID-19 Bivalent Vaccines (Original and Omicron BA.4/BA.5) and 2023 Updated mRNA COVID-19 Vaccines	The study was amended and includes two parts: Part A: 2022-2023 mRNA COVID-19 Bivalent Vaccine (Original and Omicron BA.4/BA.5) A six-month observational prospective study (with an optional long-term follow-up of up to 12 months), to investigate antibody levels with respect to time since receiving a bivalent

Study ID	Country	Study Title	Status
		(XBB.1.5).	COVID-19 booster dose. The protocol was approved on 06 Dec 2022. At this time, no safety findings have been identified. Part B: 2023 mRNA COVID-19 Updated Vaccine (XBB.1.5) A six-month observational prospective study (with an optional long-term follow-up of up to 12 months), to investigate antibody levels with respect to time since receiving an updated monovalent COVID-19 vaccine (XBB.1.5). The protocol was amended and approved on 25 Jul 2023.
mRNA-1273-P924	South Korea	A Multi-Centre, Prospective, Observational Post-marketing Surveillance to Investigate the Long-term Safety of SPIKEVAX BIVALENT Under Routine Clinical Care in Korea.	This PMS activity aims to evaluate safety of elasomeran elasomeran/imelasomeran (SARS-CoV-2 mRNA vaccine)] and elasomeran/davesomeran in Korea. Enrollment for this study is ongoing. No safety findings have been identified given the early stage of the study.
mRNA-1273-P934	United States	Effectiveness Comparison Between the Two mRNA Monovalent COVID-19 Vaccine Boosters in Medicare Fee-For-Service.	The objective of this study was to compare the real-world effectiveness of a first original booster dose (1 BD) of mRNA-1273 versus BNT162b2. Analyses are ongoing.
mRNA-1273-P935	Australia	Vaccine effectiveness against COVID-19 variants in Victoria, Australia.	The objectives of this study are to assess (i) the VE of several COVID-19 vaccinations (Vaxzevria, elasomeran, Comirnaty and Nuvaxovid, including various combinations of primary course and booster vaccines) in Victorian adults and children using two alternative study designs (a cohort study and a test-negative case-control study) and (ii) how this VE wanes over time in adults and children. Analyses are ongoing.
mRNA-1273-P937	Denmark	Real-world comparative effectiveness of 3rd dose of mRNA-1273 and BNT162b2 vaccines in Denmark	The primary aim of this study is to compare the real-world effectiveness of the third monovalent dose of mRNA-1273 versus the third monovalent dose of BNT162b2 on medically attended COVID-19 infection among populations who have

Study ID	Country	Study Title	Status
			completed the primary series of mRNA-based COVID-19 vaccines. Analyses are ongoing.
mRNA-1273-P940	United States	Effectiveness of mRNA-1273 original booster vaccination against medically attended post-acute sequelae of SARS-CoV-2 infection (PASC) in a cohort of primary series recipients of mRNA vaccines in the United States.	The aim of this study is to assess effectiveness of mRNA-1273 booster vaccination against PASC. Analyses are ongoing with study results anticipated in 2024 Q2.

In addition, the following studies are planned as of the DLP of this PBRER:

Study ID	Country	Study Title	Status
mRNA-1273-P921	Saudi Arabia	Evaluation of Post-marketing safety of elasomeran in the Kingdom of Saudi Arabia (KSA).	The overarching aim of this study is to characterize the safety of Moderna vaccines targeting SARS-CoV-2 in Saudi Arabia. A feasibility assessment in development.
mRNA-1273-P923	South Korea	Post-marketing safety of SPIKEVAX vaccine in South Korea.	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 in development for a retrospective database study supporting this aim.
mRNA-1273-P929	Japan	Special Use-Results Survey: Assess the safety of marketed Moderna vaccines targeting SARS-CoV-2 in the Japanese pediatric population.	The overarching aim of the study is to characterize the safety of Moderna vaccines targeting SARS-CoV-2 in the pediatric population in Japan. A protocol is under review.

Rapporteur assessment comment:

The MAH presents other studies which describe risks or benefits of Moderna vaccines targeting SARS-CoV-2. No new and significant safety information is identified from the information presented by the MAH.

Endorsed.

1.3.5.3. Information from other clinical trials and sources

1.3.5.3.1. Other clinical trials

Investigator sponsored studies

The following Investigator-sponsored Studies were completed during the reporting period:

Short Title: SCQM

Title: Real-world dynamics of anti-S1-binding antibodies after COVID-19 vaccination in patients with inflammatory rheumatic diseases

Summary: For this study enrolment is complete, first patient first visit was 03 Apr 2021 and final report date was 28 Feb 2023. The total number of subjects enrolled was 912. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

The following Investigator-sponsored Studies were ongoing during the reporting period:

Short Title: T-Cell immunity

Title: T-Cell immunity

Description for T-Cell immunity: Recently, two mRNA vaccines for 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. The MAH found that vaccinated individuals had robust T-cell responses to the wild type of spike and nucleocapsid proteins, even more so than convalescent patients. The MAH 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: Enrolment is complete, first patient first visit dated in 2022 and projected end date is 31 Mar 2024. The total number of subjects enrolled was 62. No AEs have been reported and no significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: COVERALL Extension

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 is complete, first patient first visit was 26 Oct 2022 and planned final report date is 31 Mar 2024. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: CoviBoost 2

Title: AP-HA (ARNCOMBI). Multicenter, Randomized, Open-label Trial Comparing the Immunological Efficacy of a Vaccine Regimen Combining Two COVID-19 mRNA Vaccines

(Pfizer-BioNTech and ModernaTx, Inc) With That of a Homologous Vaccination of Each COVID-19 mRNA Vaccine: Non-inferiority Trial.

Summary: For this study enrolment was complete, first patient first visit was 22 Aug 2022 and planned final report date is 01 Jun 2024. The total number of subjects enrolled was 414. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: SCQM Extension

Title: Real-world dynamics of anti-S1-binding antibodies after COVID-19 vaccination in patients with inflammatory rheumatic diseases.

Summary: For this study enrolment was complete, first patient first visit was 03 Apr 2021 and planned final report date is 01 Jun 2024. The total number of subjects enrolled was 917. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: MIViral

Title: Mucosal Immunity Influence on Infectious Viral Load prospective observational study.

Summary: For this study enrolment was complete, first patient first visit was in Oct 2022 and planned final report date is 01 May 2024. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: Fukushima Community Vaccine Study.

Title: A cohort study of antibody titer and cellular immunity assessment after bivalent vaccination among medical personnel and elderly people in the affected area of Fukushima Prefecture, Japan.

Summary: Planned enrolment for this study is about 1,500-2,000. No subjects have been enrolled till DLP. This study started on 31 Aug 2023 and the projected end date for this study is 31 Mar 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: PARACOV Study in Japan.

Title: Prophylactic Antipyretics to Reduce Adverse Reactions after COVID-19 Vaccination in Japan.

Summary: Planned enrolment for this study is about 80. No subjects have been enrolled till DLP. This study started on 01 Nov 2023 and the projected end date for this study is 01 Dec 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

License partner studies

Completed trials

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 140 subjects and actual subjects exposed to mRNA-1273 was 120. Start date for this study was 16 Mar 2020 and end date was 26 Apr 2023. The estimated completion date for the CSR is Oct 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. 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. Clinical Safety report preparation been completed.

Ongoing trials

Sponsored by DMID of National Institute of Allergy and Infectious Diseases (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 two different arms and further 2nd arm was divided into eight 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 210 subjects and actual subjects exposed to mRNA-1273 was 135. Start date for this study was 29 Mar 2020 and end date was in Apr 2023. The estimated completion date for the CSR is Jan 2024. 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. CSR review and finalization for Cohorts 1/2 is underway.

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 433 subjects and actual subjects exposed to mRNA-1273 were 423. Start date for this study was 28 May 2021 and final database lock was 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. Final CSR is estimated Apr 2024.

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 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.

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 is administered in 2 doses, 28 days apart. Participants 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 tumour 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 leukaemia, lymphoma, multiple myeloma and participants post-allogeneic stem cell transplant will be enrolled based on their perceived risk of immunosuppression. As of 17 Dec 2023, 19 subjects were exposed to mRNA-1273. Start date for this study was 30 Apr 2021 and estimated study completion date is 01 Jun 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 Adult Lung Transplant Recipients.

Country: US

Dosing details: 50 ug (n=20), 100 ug (n=20), and 200 ug (n=20).

Summary: Planned enrolment was 60 subjects and number of subjects enrolled and exposed to mRNA-1273 were 19. Enrolment was terminated due to the availability of the bivalent mRNA-1273.222 vaccine. Start date for this study was on 10 Mar 2022, enrolment stopped by 27 Feb 2023. Data analysis is completed, and final study report was submitted after the DLP of this PBRER, in Feb 2024. 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.

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 15,000 subjects and number of subjects enrolled and exposed to mRNA-1273 was 12,340 subjects. Actual recruitment end date was 12 Nov 2022 and last subject visit was on 09 May 2023. One hundred and fifteen adverse events have been reported. Seventeen SAEs were reported, all of which were assessed as not related to the study product. Eight adverse Events of Special Interest have been reported, 4 of which were related to study product. Five hundred and seventy-five cases of Reactogenicity have been reported, none of which were Grade 3 or higher. Three hundred and ninety-eight Breakthrough infections have been reported, 1 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 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 23-Valent Pneumococcal Polysaccharide Vaccine (V110) or 15-Valent Pneumococcal Conjugate Vaccine (V114) (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive placebo (blinded) in the left arm 30 days later at Visit 3 (Day 30). Participants enrolled in the non-concomitant groups will receive placebo (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive V110 or V114 (blinded) in the left arm 30 days later at Visit 3 (Day 30).

Summary: Planned enrolment was 1,300 subjects and total subjects enrolled were 850 subjects and 843 subjects enrolled were exposed to mRNA-1273. The early closure of enrolment was due to the rescinding of the monovalent mRNA-1273 booster EUA. Start date for this study was 12 Jan 2022 and last participant last visit was on 21 Feb 2023. Database lock was Oct 2023. The CSR is targeted for finalization in Feb 2024. 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 was 400 subjects and total number of subjects enrolled were 165 and out of which 162 subjects were exposed to mRNA-1273. Start date for this study was 28 Mar 2022 and projected end date is 14 Jun 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 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 and mRNA-1273.214 50 µg

Summary: For mRNA-1273.529 50 µg, planned enrolment is 205 subjects and the number of subjects enrolled and exposed to mRNA-1273 were 209. Start date for this study was 18 Feb 2022 and projected end date is 31 Mar 2024. Last patient last visit was conducted on 05 Dec 2022. Study analysis was ongoing with joint paper on mRNA-1273.529 and mRNA-1273.214 planned. No SAEs have been 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 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 Mar 2024. Last patient last visit was conducted on 02 May 2023. Study analysis was ongoing with joint paper on mRNA-1273.529 and mRNA-1273.214 planned. 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.

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.

1.3.5.3.2. Medication errors

Table 17: Medication errors

Source of New Information	• ModernaTx, Inc. GSDB
	• Literature Sources
	  o Search Criteria Applied: Appendix 13.4
	  o New and Significant Safety Information: None (0)

Background	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. EU legislation requires information on medication errors to be collected and reported through national pharmacovigilance systems.
Methods	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.
Results	Refer to Appendix 9.g [Please see the PSUR] for additional information. **Medication Errors Involving Use of elasomeran** During this review period, the MAH received 447 cases (1,831 events) of Medication errors with 192 serious cases (558 serious events), and 3 cases with a fatal outcome. There were 317 medically confirmed cases involving elasomeran. The most frequently reported PTs were "Interchange of vaccine product" (149; 8.1%), followed by "No adverse event" (148; 8.1%) and "Expired product administered" (95; 5.2%). During the review period, there were 261 cases (1,088 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (81; 7.4%), followed by "Fatigue" (29; 2.7%) and "Pyrexia" (20; 1.8%). **Medication Errors Involving Use of elasomeran/imelasomeran** During the review period, the MAH received 162 cases (471 events) of Medication errors with 5 serious cases (12 serious events), and no cases with a fatal outcome. There were 145 medically confirmed cases involving elasomeran/imelasomeran. The most frequently reported PTs were Expired product administered" and "No adverse event" (152 events; 32.2% each), followed by "Product storage error" (72; 15.3%), and "Product temperature excursion issue" (54; 11.5%). During the review period, there were 7 cases (12 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" and "Drug ineffective" (2 events; 16.7% each). **Medication Errors Involving Use of elasomeran/davesomeran**

	During the review period, the MAH received 1,366 cases (3,390 events) of Medication errors with 13 serious cases (36 serious events), and 1 case with a fatal outcome. There were 1,309 medically confirmed cases involving elasomeran/davesomeran. The most frequently reported PTs were "No adverse event" (1,234; 36.4%) followed by "Expired product administered" (889; 26.2%) and "Product storage error" (404, 11.9%). During the review period, there were 34 cases (98 events) of medication error reported with an associated AE. The most frequent AE reported were "Pyrexia" (14; 14.3%), followed by "Chills" and "COVID-19" (7 events; 7.1% each). **Medication Errors involving use of andusomeran** It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new Omicron variant XXB 1.5. Since its approval, the MAH received 2,038 cases (4,765 events) of Medication errors with 4 serious cases (13 serious events), and no cases with a fatal outcome. There were 1,947 medically confirmed cases involving andusomeran. The most frequently reported PTs were "No adverse event" (1,988; 41.7%) followed by "Expired product administered" (1,100; 23.1%) and "Poor quality product administered" (181; 3.8%). During the review period, there were 99 cases (228 events) of medication error reported with an associated AE. The most frequent AE reported were "Product packaging quantity issue" (37; 16.2%) followed by "Pyrexia" (12; 5.3%), and "fatigue" (10; 4.4%). The reports coded as "Product packaging quantity issue" concerned medication use error where the entire volume of the SDV (0.5 mL) of andusomeran was administered to children 6 months through 11 years of age rather than the indicated 0.25 mL dose for this age group as described in the EUA Fact Sheet. Please refer to Section 5.2.2.2 [Please see the PSUR] (Use in children) for further details. **Medication Errors involving use of unspecified SPIKEVAX COVID-19** **Vaccine-SPIKEVAX (NOS)** During the review period, the MAH received 24 cases (75 events) of Medication errors with 4 serious cases (8 serious events), and no cases with a fatal outcome. There were 22 medically confirmed cases involving SPIKEVAX (NOS). The most frequently reported PTs were "COVID-19 Immunisation" and "Interchange of vaccine products" (11 events; 14.7% each). During the review period, there were 17 cases (31 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (7; 22.6%) and "Illness" (3; 9.7%).
Discussion	A review of the data received during the reporting period of this PBRER, showed that events of medication errors do 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 Marketed Moderna vaccines targeting SARS-CoV-2 vaccine beyond the primary series or any interchange of other COVID-19 vaccine products. There seemed no difference for the nature of reported medication errors

	and importantly associated AEs among the Marketed Moderna vaccines targeting SARS-CoV-2 in general. AEs associated with reported medication errors were usually known to the elasomeran, Marketed Moderna vaccines targeting SARS-CoV-2 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	Evaluation of the data during this reporting period did not provide any new safety information that would suggest medication errors associated with administrations of Marketed Moderna vaccines targeting SARS-CoV-2 impact the benefit-risk profile for Marketed Moderna vaccines targeting SARS-CoV-2. The benefit-risk evaluation remains positive. Medication errors reported to ModernaTx, Inc. will continue to be monitored using the routine pharmacovigilance measures implemented for Marketed Moderna vaccines targeting SARS-CoV-2.

Rapporteur assessment comment:

No new and significant safety information was identified from the review of medication error cases presented by the MAH. The pattern of medication errors reported in the current interval is similar to the pattern observed previously.

With regards to Andusomeran, reports coded as "Product packaging quantity issue" concerned medication use error where the entire volume of the SDV (0.5 mL) of andusomeran was administered to children 6 months through 11 years of age rather than the indicated 0.25 mL dose for this age group as described in the EUA Fact Sheet. Please refer to section 2.2 of this assessment report for more information on the signal "Overdose in children in the context of overfill of the SDV indicated for individuals 6 months through 11 years of age in the US."

The information provided is acknowledged.

1.3.5.3.3. Medical device incidents

A review of reports of device related issues from elasomeran or andusomeran containing vaccines did not reveal any patterns or other safety information relevant to the benefit-risk assessment for marketed Moderna vaccines targeting SARS-CoV-2.

Rapporteur assessment comment:

No device related issues in relation to safety were reported by the MAH in association with the elasomeran containing vaccines.

Endorsed.

1.3.5.3.4. Non-clinical data

No relevant new safety finding was identified in non-clinical *in vivo* and *in vitro* studies during the period of this PBRER.

Rapporteur assessment comment:

Endorsed.

1.3.5.4. Literature

A global literature search and analysis were performed utilizing Embase, Medline and PubMed databases for the reporting period 18 Jun 2023 to 17 Dec 2023. 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, Modernatx 1273, elasomeran/davesomeran, mRNA-1273.214 (BA.1), mRNA-1273.222 (BA.4/BA.5), SPIKEVAX XBB1.5, andusomeran, elasomeran/imelasomeran, SPIKEVAX X injection, SPIKEVAX XBB1.5 PFS, SPIKEVAX XBB.1.5, SPIKEVAX intramuscular injection (Monovalent: Omicron XBB.1.5), SPIKEVAX XBB.1.5 Prefilled Syringe, SPIKEVAX (COVID-19 Vaccine, mRNA) 2023-2024 Formula (Pre-filled Syringe). Find the complete global literature search strategy used for Medline and Embase search under Appendix 13.1 and search strategy used for PubMed under Appendix 13.2.

A local literature search was performed for the journals which were not indexed in Medline or Embase using product names as key search terms for the review period 18 Jun 2023 to 17 Dec 2023. Please find the journal list under Appendix 13.3.

During the reporting period, there were a total of 30,182 abstracts retrieved and upon removal of duplicates, 11,532 abstracts reviewed from the global searches. There were 9,793 local journal searches performed and 321 abstracts were reviewed. From all the searches performed, there were no articles identified with any new relevant safety information.

Rapporteur assessment comment:

From its review of 11,853 abstracts published during the reporting interval, the MAH did not identify any articles with new relevant safety information.

On the 9th of April 2024, the assessors conducted their own risk-based literature review using the following simplified search string on PubMed:

(("2023/06/18"[PDAT] : "2023/12/17"[PDAT]) AND (elasomeran OR (COVID-19 Vaccines[MeSH Terms]) OR (2019-nCoV Vaccine mRNA-1273[MeSH Terms])) OR mRNA-1273 OR mRNA 1273 OR mRNA1273 OR Moderna Covid19 Vaccine or Moderna Covid-19 Vaccine OR Moderna Covid 19 Vaccine or Spikevax) AND (("safety"[MeSH Terms] OR "safety"[All Fields]) OR adverse reaction OR adverse event)

As this search string yielded 2,013 hits, the assessors used PubMed's filters and only focused on studies categorised as systematic reviews (n=94) or meta-analyses (n=34). Please note that some of these publications were captured by both filters meaning that the number of unique articles screened was less than the sum (128).

The assessors identified one publication which warrants presentation here. Marchand et al. found an increased risk of cardiac-related mortality after COVID-19 vaccination (HR = 1.06, 95% CI [1.02, 1.11], p = .007). In relation to this, it is noted that myocarditis and pericarditis are very rare adverse reactions listed in section 4.8 of the SmPC and that SmPC section 4.4 informs that fatal cases of myocarditis/pericarditis have been observed. **As this publication has not been mentioned by the MAH and as it potentially includes new and significant safety information, the MAH is requested to comment upon it within this procedure**.

As the assessors identified a publication with potentially new safety information, that was not presented or commented upon by the MAH, the MAH is requested to review its literature search process including search strategy and evaluation of retrieved publications to make sure that all relevant publications with new and significant safety findings are captured and considered. **In future PSURs, the MAH is expected to present literature published during the reporting interval with potentially new and**

significant safety findings. If the MAH identifies publications which include new significant safety information, these should be presented and commented upon even if the MAH disagrees with the conclusions of the authors.

References

Marchand G, Masoud AT, Medi S. Risk of all-cause and cardiac-related mortality after vaccination against COVID-19: A meta-analysis of self-controlled case series studies. Hum Vaccin Immunother. 2023 Aug 1;19(2):2230828. doi: 10.1080/21645515.2023.2230828. PMID: 37534766; PMCID: PMC10402862.

Additional assessor comment of literature published after the reporting interval

Acute disseminated encephalomyelitis (ADEM)

The MAH has previously provided cumulative data for *acute disseminated encephalomyelitis (ADEM)* with data from the global safety database and observed/expected analysis; the data covered a complete 2-year-period (from 18 Dec 2020 to 17 Dec 2022, addressed in the 4th PSUR) and did not give rise to concern about a causal association between ADEM and Spikevax. The observed cases equalled a cumulative reporting rate of 0.20 cases per 100,000 person-years, which was clearly lower than the expected incidence estimates (Spanish estimate from 2019 was 0.50, RR = 0.41 [0.33, 0.51]; US estimate from 2018 was 0.49, RR = 0.42 [0.33, 0.52]; US estimate from 2021 was 0.40, RR = 0.51 [0.40, 0.64]). In conclusion, the issue about ADEM was considered resolved, and continued monitoring through routine pharmacovigilance supported.

However, the assessors note that ADEM is brought up again as an AESI in a recently published paper (post PSUR DLP) presenting big data comprising 99 million individuals vaccinated against COVID-19. The cited paper is: ***Faksova, K et al. "COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals." Vaccine vol. 42,9 (2024): 2200-2211. doi:10.1016/j.vaccine.2024.01.100.*** This paper presented a retrospective observational study designed to estimate the O/E ratios of selected AESIs after COVID-19 vaccination in a multicountry population cohort, ADEM being one of them. This study found that with 7 observed events compared to 2 expected, the O/E ratio for ADEM within 42 days after 1st dose of mRNA-1273 statistically met the prioritised safety signal (OE ratio: 3.78 [95% CI: 1.52-7.78]).

Nevertheless, it must be emphasized that the numbers of both observed and expected cases are very small, and therefore even coincidental variations in disease occurrence can give rise to statistical significance. Furthermore, there is no indication of a tendency of ADEM occurring following mRNA vaccination against COVID-19, this accounts for the vaccine from MODERNA (mRNA-1273) as well as the vaccine from Pfizer-BioNTech (BT162b2). The statistical finding on ADEM in relation to Spikevax was based on only 7 cases (versus 2 expected), while there were no increased findings for neither the 2nd, 3rd or 4th dose, just as there was no increased finding for ADEM in relation to any dose number of the other mRNA vaccine (BT162b2).

The potential safety signal found for ADEM after an mRNA vaccine was only seen after 1st dose of mRNA-1273 vaccine, and was based on only 5 more observed events than expected in a calculation comprising 1,035,871 person-years and 10.5 million doses. With the small number of cases and the wide confidence interval and no other indication of ADEM as an adverse event following any other shot of an mRNA vaccine against COVID-19, the conclusion is - as previously - that the assessed information does not give rise to concern about a causal association between ADEM and Spikevax.

In conclusion, the issue is considered resolved, and continued monitoring of ADEM through routine pharmacovigilance is supported.

1.3.5.5. Other periodic reports

No other PBRERs have been written for Marketed Moderna vaccines targeting SARS-CoV-2.

Rapporteur assessment comment: This section is acknowledged.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 17 provides the Summary of Safety Concerns as per RMP v6.5 approved on 26 May 2023 in place at the beginning of the reporting period.

Table 17: Summary of Safety Concerns valid at the beginning of the reporting period (as per RMP v6.5 approved on 26 May 2023)

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., COPD, diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders.

During the reporting period, the following changes were made to the RMP:

- SPIKEVAX RMP v6.5 was updated to v6.6 and v6.7 (endorsed on 20 Jul 2023) with no additional changes to the list of safety concerns.
- Additionally, v6.3 was updated to v7.0 (endorsed by PRAC on 06 Jul 2023 in procedure EMEA/H/C/PSUSA/00010897/202212) to update the list of safety concerns by removing "VAED including VAERD" as an important potential risk, and "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.

- Also, v7.0 was updated to include mRNA-1273-P910 for pericarditis and study details for mRNA-1273-P901, mRNA-1273-P910 and mRNA-1273-P919 in Part II.C.2 as per Part III update. Of note, a consolidated SPIKEVAX EU RMP v7.1 including all versions endorsed/approved by PRAC/CHMP (v6.5, 6.7 and 7.0) received positive opinion by CHMP on 21 Jul 2023 and the opinion was adopted within procedure EMEA/H/C/005791/II/0104/G by European Commission on 11 Aug 2023.
- Further, RMP v7.0 was updated to v8.0 (endorsed on 16 Aug 2023) to add the INN SPIKEVAX XBB.1.5 (andusomeran) and indication for andusomeran with no further updates on safety concerns.
- Lastly, RMP v8.0 was updated to RMP V8.1 (CHMP favourable opinion received on 23 Oct 2023) to remove the Summary Safety Reports (SSRs) as a requirement for COVID-19 vaccine, core RMP19 guidance EMA/PRAC/709308/2022 and no further changes to list of safety concerns were made in this version.

Table 18 provides the Summary of Safety Concerns as per RMP v8.1 approved on 25 Sep 2023 valid at the end of the reporting period.

Table 18: Summary of Safety Concerns valid at the end of the reporting period (as per RMP v8.1 CHMP favorable opinion received on 23 Oct 2023)

Important identified risks	• Myocarditis • Pericarditis
Important potential risks	• None
Missing information	• Use in pregnancy and while breastfeeding • Long-term safety

Table 19 provides the Summary of the PSUR/PBRER list of Safety Concerns valid at the end of the reporting period.

Table 19: Summary of Safety Concerns for the PSUR/PBRER valid at the end of the reporting period

Important identified risks	• Anaphylaxis • Myocarditis • Pericarditis
Important potential risks	• IgA Nephropathy
Missing information	• Use in pregnancy and while breastfeeding • Long-term safety • Use in immunocompromised subjects • Use in frail subjects with unstable health conditions and comorbidities (e.g. COPD,

	diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders.

Rapporteur assessment comment:

The MAH presented the RMP Summary of safety concerns at baseline and at the end of the reporting period, and the PSUR summary of safety concerns valid at the end of the reporting period. Furthermore, the MAH reported on changes to the RMP during the reporting interval.

This section is acknowledged.

2.2. Signal evaluation

- Tabular overview of signals: new, ongoing or closed during the reporting interval 18 June 2023 to 17 December 2023.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
IgA nephropathy flare-up	21 Apr 2023	Closed	22 Jun 2023	Health Authority Request, Literature Article	MAH considered IgA nephropathy flare-ups as a validated signal following receipt of a signal letter from Swissmedic, triggered by the publication Canney et al. MAH has performed several evaluations regarding IgAN with the latest analysis provided in PSUR#4 (Reporting period: 19 Jun 2022 to 17 Dec 2022). Also, as part of PSUSA procedure EMEA/H/C/PSUSA/00010897/202112, IgA nephropathy is considered as an important potential risk in PSURs for further risk characterization. In summary, no cases of IgAN were reported in MAH's clinical trials. Cumulatively through 17 Dec 2022, a total of 68 reports of IgAN were reported from MAH's Global Safety Database in association with elasomeran with an estimated reporting rate of < 1 case of IgAN/10 million elasomeran vaccinees, constituting an extremely rare	Signal Evaluation Report, RTQ	Close Monitoring via Signal Detection, Updates in PBRER/PSUR, Routine Pharmacovigilance Refuted Signal

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					occurrence. Of the 68 reports of IgAN following elasomeran, 43 cases were DeNovo and 25 cases were flares. From the scientific literature, no high-quality studies showed a causal link between IgAN and elasomeran. No pathophysiologic process has been shown to explain a causal association between Elasomeran and IgAN, and no pathognomonic sign of such an association was found. The study by Canney et al had some important limitations and did not provide a sufficient basis for new recommendations with regard to IgAN in association with COVID-19 vaccine administration. In conclusion, MAH considered IgAN flare-ups in association with elasomeran as a refuted signal. MAH did not plan to update the PI and/or RMP, including relevant risk minimization measures. IgA nephropathy will continue to be closely monitored within signal detection activities and regular updates of IgAN will be presented in PSUR. Response was submitted to Swissmedic, which acknowledged MAH conclusions.		
Sensorineural Hearing Loss (SNHL)	15 Jun 2023	Closed	09 Aug 2023	Health Authority Request, Spontaneous Reports	MAH considered Sensorineural hearing loss (SNHL) as a validated signal following receipt of a request from TGA, triggered by disproportionate reporting of hearing loss with elasomeran in TGA's Adverse Event Management System (AEMS). Following MAH assessment based on the review of all available sources, no imbalance for SNHL was observed between	Signal Evaluation Report, PBRER/PSUR	PASS, Routine Pharmacovigilance Refuted Signal

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					mRNA-1273 vaccination and placebo arms from clinical trial data. In the postmarketing setting, SNHL cases with elasomeran were identified from the Company global safety database (GSDB) in a stepwise approach (1.MedDRA HLT Hearing losses, further characterization of SNHL cases using an algorithm, categorization of SNHL cases using BC case definition for SNHL, and WHO causality assessment). Out of 1,076 SNHL cases, 227 cases included sufficient diagnostic information, and were categorized as 0 Definite cases (Level 1), 7 Probable cases (Level 2), 136 Possible cases (Level 3), 62 Level 4 cases (insufficient information to assess), 22 Level 5 cases (Not a case). WHO causality assessment distribution was Certain (0), Probable (1), Possible (72), Unassessable (99) and Unlikely (55). Overall, most cases were unassessable but when information was provided, SNHL was confounded by medical history and/or concomitant medications. In majority of cases TTO of SNHL following vaccination with Elasomeran was less than 3 days. The observed reporting (O/E) rate of SNHL with elasomeran (1.92 cases per 100,000 persons), was below the expected estimated reference rate (27.00 per 100,000 persons) and all age/gender stratified O/E analyzes did not show any atypical ratios. Review of the literature retrieved a very limited number of articles describing SNHL after mRNA vaccination;		

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					published results were consistent with the Company GSDB data (e.g., median age 50 years, more females than males, treatment with steroids and a temporal association within 10 days of vaccination). In conclusion MAH considered SNHL in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the PI and/or RMP, including relevant risk minimization measures. SNHL will however be included as an ad hoc outcome in mRNA-1273-P920 PASS for further characterization. Conclusions from other health authorities on same topic: On 06 Jul 2023, as part of PSUSA procedure EMEA/H/C/PSUSA/00010897/20221 PRAC concluded "Following review of additional data submitted by the MAH in response to RSI, the PRAC Rapporteur considers that a causal association between hearing loss and Elasomeran cannot currently be established. No further actions beyond routine PV pharmacovigilance are required".		
Breast swelling	05 Jul 2023	Closed	22 Aug 2023	Health Authority Request	MAH considered Mastitis and Breast swelling as validated signals following receipt of a request from TGA, triggered by disproportionate reporting of mastitis and breast swelling with elasomeran in TGA's AEMS. Mastitis is a common breast condition that predominately affects nursing women. Breast edema (swelling) is fluid accumulation within the breast tissue due	Signal Evaluation Report, RTQ	Routine Pharmacovigilance Refuted Signal

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					to obstruction/disruption of the lymphatic vessels that drain the breast. The lymphatic system is a critical part of the immune system and lymph nodes play a major role in triggering the body's immune response to vaccines. Given the clinical similarities between mastitis and breast swelling, MAH analyzed the two signals together. Following MAH assessment based on the review of all available sources, nonclinical studies showed that there were no vaccine-related adverse effects on females, fetal development, or postnatal development. In rats, high levels of mRNA were detected in lymph nodes and pathologic findings revealed enlarged lymph nodes. Across mRNA-1273 clinical trials, 4 cases of mastitis (2)/breast swelling (2) were observed with mRNA-1273 vaccination, all were assessed as not related to mRNA-1273 vaccination. A total of 117 cases of mastitis and 616 cases of breast swelling were retrieved from the Company GSDB. Respective median TTO following mRNA-1273 vaccination was 2.5 days for mastitis and 2.0 days for breast swelling. Majority of the cases had multiple risk factors and/or confounding factors for mastitis / breast swelling (e.g., breastfeeding, lymphadenopathy/ lymphoedema/ lymphadenitis, concomitant medications for gynecomastia/ breast swelling, menstrual disorders, diabetes mellitus, breast cancer, thyroid disease). Overall, postmarketing		

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					data suggested that mastitis /breast swelling were most likely secondary to postvaccinal lymphadenopathy triggered by the immune response to the vaccine. The observed reporting rate of mastitis (lactational and nonlactational) with elasomeran (0.39 cases per 100,000 persons), was below the expected estimated reference rate (15.06 per 100,000 persons). For breast swelling no relevant published incidence estimates were found, hence no O/E analysis was conducted. Review of the literature retrieved a small number of articles describing mastitis and/or breast swelling as mostly transient events occurring within 14 days following administration of mRNA vaccine against COVID-19. The articles suggested, however, the presence of axillary lymphadenopathy following mRNA COVID-19 vaccine administration (which is a listed adverse reaction for elasomeran) as a potential contributing precursor to the events of mastitis and/or breast swelling. In conclusion MAH considered mastitis and Breast swelling in association with elasomeran as refuted signals, due to the lack of evidence across data sources reviewed. MAH did not plan to update the PI and/or RMP, including relevant risk minimization measures.		
Mastitis	05 Jul 2023	Closed	22 Aug 2023	Health Authority	MAH considered Mastitis and Breast swelling as validated signals following	Signal Evaluation	Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
				Request	receipt of a request from TGA, triggered by disproportionate reporting of mastitis and breast swelling with elasomeran in TGA's AEMS. Mastitis is a common breast condition that predominately affects nursing women. Breast edema (swelling) is fluid accumulation within the breast tissue due to obstruction/disruption of the lymphatic vessels that drain the breast. The lymphatic system is a critical part of the immune system and lymph nodes play a major role in triggering the body's immune response to vaccines. Given the clinical similarities between mastitis and breast swelling, MAH analyzed the two signals together. Following MAH assessment based on the review of all available sources, nonclinical studies showed that there were no vaccine-related adverse effects on females, fetal development, or postnatal development. In rats, high levels of mRNA were detected in lymph nodes and pathologic findings revealed enlarged lymph nodes. Across mRNA-1273 clinical trials, 4 cases of mastitis (2)/breast swelling (2) were observed with mRNA-1273 vaccination, all were assessed as not related to mRNA-1273 vaccination. A total of 117 cases of mastitis and 616 cases of breast swelling were retrieved from the Company global safety database. Respective median TTO following mRNA-1273 vaccination was 2.5 days for mastitis and 2.0 days for breast swelling. Majority of the cases had multiple risk factors and/or	Report, RTQ	Refuted Signal

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					confounding factors for mastitis / breast swelling (e.g., breastfeeding, lymphadenopathy/lymphoedema/lymphadenitis, concomitant medications for gynecomastia/ breast swelling, menstrual disorders, diabetes mellitus, breast cancer, thyroid disease). Overall, post-marketing data suggested that mastitis /breast swelling were most likely secondary to post-vaccinal lymphadenopathy triggered by the immune response to the vaccine. The observed reporting rate of mastitis (lactational and non-lactational) with elasomeran (0.39 cases per 100,000 persons), was below the expected estimated reference rate (15.06 per 100,000 persons). For breast swelling no relevant published incidence estimates were found, hence no O/E analysis was conducted. Review of the literature retrieved a small number of articles describing mastitis and/or breast swelling as mostly transient events occurring within 14 days following administration of mRNA vaccine against COVID-19. The articles suggested, however, the presence of axillary lymphadenopathy following mRNA COVID-19 vaccine administration (which is a listed adverse reaction for elasomeran) as a potential contributing precursor to the events of mastitis and/or breast swelling. In conclusion MAH considered mastitis and breast swelling in association with elasomeran as refuted signals, due to the		

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					lack of evidence across data sources reviewed. MAH did not plan to update the PI and/or RMP, including relevant risk minimization measures.		
Postmeno-pausal haemorrhage	20 Oct 2023	Closed	13 Dec 2023	Health Authority Request	The signal of postmenopausal haemorrhage (PMH) was triggered by PRAC (EPITT No. 20015) having considered the available evidence from literature and post-marketing data, including EVDAS and Vigilyze. Following evaluation based on the review of all available sources, non-clinical studies showed no changes to ovary or uterus. In the clinical trial setting, no imbalance between mRNA-1273 and placebo was observed (3 PMH with placebo, 3 with mRNA-1273). All were non-serious, and all had medical history that provided an alternate etiology. In the postmarketing setting, a total of 978 cases of HMB (113 medically confirmed [MC] cases, and 24 non-medical confirmed cases with a positive rechallenge [nMC+]) were retrieved from the Company global safety database. Postmenopausal haemorrhage is defined as any vaginal hemorrhage/bleeding that occurs 12 months or more after the final menstrual period, in the absence of HRT use or pelvic surgery (WHO, FIGO, International Menopause Society). Only 22% (25/113) of the MC cases and 25% (6/24) of nMC+ cases met Level 1 case definition for PMH. Majority of cases had missing relevant information (74.3% [84/113]). WHO-UMC causality was assessed as follows: definite /probable (no	Signal Evaluation Report	Routine Pharmacovigilance Refuted Signal

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					cases), possible (5 MC cases), unlikely (4 MC, 1 nMC+), unassessable (16 MC, 5 nMC+). Most of the cases (when data was available) reported final menstrual period < 5 years and had alternate etiologies (e.g., medical history of/ concomitant medications for thyroid disorders, breast cancer, depression). The background incidence of post-menopausal Hemorrhage decreases with increase in age, however, for the observed-to-expected (O/E) the same background incidence for all age groups was used due to limited information in published literature. All age stratified O/E analysis rate ratios were less than 1 when assuming 25% of cases were reported. In MAH US PASS P920, no evidence of increased HR of PMH was observed in the cohort exposed to elasomeran bivalent and influenza vaccine during the same time period, for risk windows of 1-21 days, 1-42 days, and 1-90 days; the incidence rates for PMH following medically attended COVID-19 diagnosis were higher than rates following elasomeran bivalent vaccination. Literature review did not provide sufficient evidence of a causal association between PMH and elasomeran vaccine administration. In conclusion MAH considered PMH in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the PI and/or RMP, including relevant risk minimization measures. HMB will continue		

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					to be monitored through routine PV surveillance.		
Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the US	27 Oct 2023	Closed	01 Nov 2023	Quality Complaint, Routine Signal Detection	Since Oct 2023, reports of overdose in the context of overfill of the SDV indicated for individuals 6 months to 11 years of age, were received from various sources, including spontaneous reports, quality complaints and HCP inquiries. This issue is restricted to the US and is limited to the US EUA of Moderna COVID-19 vaccine (2023-2024 formula) for individuals 6 months through 11 years of age. The pediatric SDV contains notably more than 0.25 mL of vaccine, which has led to provider confusion or administration errors, including overdose. Analysis of the MAH global safety database retrieved 128 reports related to overfill of vials (DLP 29 Oct 2023), of which 42 reports (33%) involved PTs related to overdose: all reports were from the US to the MAH, and all but one was reported from HCPs. All reports were non-serious, and mainly concerned individuals aged 6 months to 11 years. Apart from one overdose report describing pyrexia, none of the remaining overdose reports indicated any associated clinical adverse events. Analysis of Product Quality complaints identified 134 complaints related to overfill of the SDV, including one complaint involving 200 patients. Following investigation of the possible root causes, the MAH considered Overdose in children aged 6 months to 11 years in the context of overfill of SDV in the US as an important	Signal Evaluation Report, Response to Health Authority Request	Close Monitoring via Signal Detection, Dear Healthcare Professional Communication (DHPC), Regional SmPC Update only,Update to MAH Websites Important Potential Risk

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					potential risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified is it considered a potential risk. The MAH decided on the following risk minimization actions: • Update of the current US-Fact Sheet, to clarify the dosage and administration instructions to providers. • Update of corresponding websites to clarify dosage and administration information. • Communication of the findings to the appropriate health authorities, including CDC • Distribution of a DHCP letter in the US only In addition, the MAH is closely monitoring overdose in children in the context of overfill of the SDV and associated harms as part of signal detection activities.		

Rapporteur assessment comment:

The MAH reported on six closed signals.

Five signals were closed as refuted by the MAH ("IgA nephropathy flare-up", "Sensorineural Hearing Loss", "Breast swelling", "Mastitis", "Postmenopausal Haemorrhage"), and 1 signal was closed as important potential risk ("Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the US").

The signal "Sensorineural Hearing Loss" was closed post DLP in the previous PSUR and evaluated in corresponding PSUSA procedure (PSUSA/10897/202306), where it was concluded that no further actions beyond routine pharmacovigilance were warranted. As no new information is presented in the current PSUR, this closed signal will not be further discussed in this assessment report.

The signal "Postmenopausal Haemorrhage" was recently reviewed by the PRAC in procedure no: SDA 131 (EPITT 20015) where the PRAC concluded "*Having considered the available data, including from the cumulative review performed by the MAH, the PRAC has agreed that the overall evidence is insufficient to establish a causal association between SPIKEVAX and postmenopausal haemorrhage. No updates of the product information and/or risk management plan are warranted at present. The MAH of COVID-19 mRNA vaccine (nucleoside-modified) SPIKEVAX (Moderna Biotech Spain, S.L.) should continue to monitor postmenopausal haemorrhage through routine pharmacovigilance*". As no new information is presented in the current PSUR, this closed signal will not be further discussed in this assessment report.

For the remaining 4 closed signals, signal evaluation reports are presented and evaluated by the MAH. Please see below.

2.2.1. IgA nephropathy Flare-up

Table 20: IgA nephropathy flare-up

Signal evaluation criteria	Summary
Source	The Swissmedic requested a signal analysis of Immunoglobulin-A-Nephropathy (IgAN) – Flare-Up. The signal was based on the publication Canney et. al. The MAH was requested to comment on the present signal, considering the following aspects and questions: • Current figures on a flare-up of glomerular disease associated with mRNA vaccination, both nationally and internationally. • Presentation and discussion of relevant case reports of a flare-up of glomerular disease from home and abroad, e.g., from the WHO database. • Presentation of current and relevant technical literature • Submission of any evaluation reports already available (in-house, external) • Any current status of this signal abroad. • Can you confirm the signal? • If so, what risk-minimizing measures do you propose? *Swissmedic Assessment / Considerations* Several reports (Ritter et al,1 2022; Bronz et al, 2022 2] have described glomerular disease after 2019 coronavirus disease vaccination (COVID-19). Without adequate controls in these reports, assessment of a causal relationship is limited. In the population-based cohort of 1,105 adult patients [Canney et al., 2022] with stable glomerular disease, the first dose of COVID-19 vaccine was not associated with risk of relapse; however, a subsequent dose of vaccine was associated with a 2-fold increase in risk of relapse. The increase in absolute risk associated with vaccination was small (1%-5%). These results represent the first accurate assessment of the relative and absolute risk of glomerular disease relapse associated with COVID-19 vaccination. In summary, there was no robust evidence for a causal relationship between mRNA vaccination and IgAN. However, based on current data [Canney et al., 2022], an association between preexisting IgAN and relapse after mRNA vaccination was possible but very rare. Nevertheless, the favorable risk-benefit ratio of vaccination in patients

	with glomerular disease remains positive. Patients and professionals should be instructed, as the data strengthen, to closely monitor patients with pre-existing IgAN.
Background	Immunoglobulin-A-Nephropathy is the most common cause of primary glomerulonephritis. This is often a silent condition that may go undetected for many years. Most common symptom of IgA nephropathy is hematuria (blood in the urine.). IgA nephropathy is diagnosed by renal biopsy. There is no Brighton definition. Flares usually diagnosed by hematuria and/or proteinuria, without re-biopsy. PRAC has noted "IgA nephropathy can follow a benign course, however, slow progression to end stage disease occurs in 25 to 30 percent of patients within 20 to 25 years of presentation." More common in men than women, IgA nephropathy can occur at all ages but is most common in the second and third decades of life. 80% of patients are ages 16-35 years at time of diagnosis. Brief Regulatory History of IgA Nephropathy and elasomeran: PRAC Assessment Report of PBER #2: It was acknowledged that there were cases reported indicating a potential causal association between elasomeran and IgA nephropathy, in particular flare up of underlying IgA nephropathy. This includes several cases reported in the scientific literature. However, the case number is low, especially considering that, by the DLP, an estimated 466,804,529 doses of elasomeran had been administered. Cumulative evidence is not sufficient to warrant amendment of the product information regarding IgA nephropathy at present. Immunoglobulin-A-Nephropathy can follow a benign course, however, slow progression to end stage disease occurs in 25 to 30 percent of patients within 20 to 25 years of presentation. Also, IgA nephropathy can be associated with acute kidney injury as well as rapidly progressive glomerulonephritis. The fact that IgA nephropathy was delineated from other renal PTs, both in disproportionality analyses as well as in case reviews, calls for a continuous alertness regarding this condition. The MAH is requested to add IgA nephropathy to the list of safety concerns as an important potential risk in the PSUR. As a consequence, a risk characterization and an evaluation of new information for the risk is expected in the next PSUR. The MAH was also requested to discuss in the next PSUR whether IgA nephropathy needs to be added to the list of safety concerns in the RMP." Consequently, validated signal on IgA Nephropathy was assessed and then closed by the MAH as a refuted signal on 29 Jul 2022. PRAC Assessment Report of PBER #3: The rapporteur thus agreed that at present there was not enough evidence to establish (nor to reject) a causal relationship between the administration of SPIKEVAX/elasomeran and the development of IgA nephropathy and that no changes to the product information regarding this issue are currently warranted. However, the PRAC rapporteur still finds it warranted to consider IgAN an important potential risk in the PSURs. Also, based on the limited number of cases and the lack of a clear association, no changes to the RMP, neither concerning de novo IgAN nor flare of known IgAN, are currently considered warranted. PRAC Preliminary Assessment Report PBRER #4: The rapporteur concluded that reporting of IgAN is rare and that the evidence was 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 was therefore expected that the MAH will present new information on IgA nephropathy and risk characterization in PSUR section 16.3 and 16.4, respectively.

Methodology	The assessment of IgAN – Flare-Up 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: Three ModernaTx, Inc sponsored clinical studies (mRNA-1273-P203, mRNA-1273-P204 and mRNA-1273-P301) were queried as part of the response to the agency's request for information. For study mRNA-1273-P203 the data cutoff was 27 Jan 2022; for mRNA-1273-P204 the data cutoff date was 21 Feb 2022, and for mRNA-1273-P301 the data cutoff date was 04 May 2021. The topic of Glomerulonephritis and nephrotic syndrome was cumulatively reviewed for any PTs including in the HLT Glomerulonephritis and Nephrotic Syndrome in above mentioned studies. 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. Epidemiological studies: NA. External Databases: There is not a MedDRA PT for IgAN Flare-Up. Therefore, disproportionality for this event cannot be assessed in VAERS or EVDAS. Review of the Pharmacovigilance Database: Post marketing data for Glomerulonephritis and nephrotic syndrome was cumulatively reviewed in the MAH GSDB with a DLP of 17 Dec 2022. The term IgAN – Flare-Up was analysed by using a HLT glomerulonephritis and nephrotic syndrome Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Cases from all sources and supplemented with relevant literature case reports not yet in Moderna GSDB were included. Information presented in results section includes analyzes performed on cases received by ModernaTx, Inc., for the elasomeran and for the elasomeran/davesomeran and elasomeran/imelasomeran. Literature search review: The MAH performed a focused search of PubMed for elasomeran and IgA Nephropathy to retrieve relevant literature during this reporting period.
Results	Clinical Trial Data: Overall, there were zero cases listed for any of these PTs from HLT of Glomerulonephritis and Nephrotic Syndrome. External Databases: NA

	Review of the Pharmacovigilance Database: Cumulatively as of the DLP (17 Dec 2022), a total of 237 cases (272 events) were retrieved using the MedDRA HLT of "Glomerulonephritis and Nephrotic Syndrome". 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. 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%). 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 IgAN 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. 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 adverse events 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. Currently, with the limited number of reports, this finding is an observation, as there is no clear biological explanation. The MAH has evaluated cumulatively all cases with IgA nephropathy, De Novo and flare, temporally associated with elasomeran according to the WHO-UMC causality assessment. Most of the cases (37; 54.4%) were considered possible due to temporal association and lack of adequate information for complete clinical evaluation. Review of counts of IgA nephropathy cases by initial receipt date and PSUR reporting period shows that in the PSUR#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. The cumulative reporting rate remains < 1 case per 10 million doses. **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 search review:

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 [32]

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

Abstract. Diebold et al 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 (IR 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 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% CI 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) [32].

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.

Following receipt of a signal letter from Swissmedic, triggered by the publication Canney et al: A Population-Based Analysis of the Risk of Glomerular Disease Relapse after COVID-19 Vaccination., the MAH has opened a signal of IgA nephropathy flare-up and evaluated the information presented in this article. Using a centralized clinical and pathology registry (2000-2020) in British Columbia, Canada, this study identified patients who had been previously diagnosed with biopsy-proven glomerular disease. The primary study outcome was disease relapse based on eGFR and proteinuria. The investigators identified, patients whom they determined had stable disease, without a relapse in the year prior to 14 Dec 2020, the first day that COVID-19 vaccines became available in British Columbia. Total study follow-up duration was 281 days, ending on 21 Sep 2021. Of the 1,105 patients, 1,016 (92%) received at least one dose, and 986 (89%) received two or three doses of COVID-19 vaccine.

The most common vaccine types were BNT162b2 (Pfizer-BioNTech, 67%) and mRNA-1273 (ModernaTx, Inc, 30%). Vaccine type was not a study focus. Of the 1,105 patients, 134 (12.1%) experienced a relapse; the relapse of 24 of these patients occurred within the 30-day window following vaccination. These 24 patients were a key element to this study, however the amount of detail about them was relatively sparse. The type of glomerular disease was reported as: ANCA-related, 3 patients: lupus nephritis, 4 patients; minimal change disease, 2 patients; membranous nephropathy, 5 patients; FSGS, 3 patients; and IgA nephropathy, 7 patients. The investigators reported: "Although a first vaccine dose was not associated with relapse risk [HR]=0.67; 95% CI, 0.33 to 1.36), exposure to a second or third dose was associated with a two-fold risk of relapse (HR=2.23; 95% CI, 1.06 to 4.71). The pattern of relative risk was similar across glomerular diseases." They concluded their abstract by noting the "low absolute increased risk of relapse". The authors also noted that, of the 24 patients with relapse post-vaccination, only four had a change in immunosuppression, and none underwent repeat biopsy.

The study by Canney et al has some important limitations that are further described below: The lower bound of the 95% CI of the HR that combines dose 2 and dose 3 was 1.06, as noted above, barely exceeding unity to achieve conventional statistical significance. As the authors stated, "It should be acknowledged that the HR estimates had wide CIs and need to be validated in an independent cohort with larger sample size to generate more precise estimates." The MAH agrees that this study's findings require confirmation in rigorous studies; such rigorous studies should also include clinical details of important cases of interest.

The investigators reported that their interaction analyzes, with P-values for interaction of ~0.5, "suggested that the relative risk of disease flare associated with any vaccine exposure was not significantly different on the basis of the type of glomerular disease." Given that there were only 24 patients with relapse linked to vaccination in the prior 30 days and that the study included six different glomerular disease types, the MAH questions whether this analysis had sufficient statistical power to be reliable. Canney et al article noted that on the study index date there were 4,390 adults with biopsy-proven glomerulonephritis. The vast majority of these were excluded from the main study analyses; only 1,105 patients (25%) were included in the study cohort. Large numbers of patients were excluded from study based on end-stage kidney disease (957

	patients), recent relapse (550 patients), and <2 proteinuria measurements in 12 months prior to index date (1,734 patients). The exclusion of 75% of glomerular disease patients is a basis for a major caveat that the authors did not communicate. The authors did not note that their study protocol was registered. In an attempt to address the possibility of ascertainment bias, the authors reported "similar proportion of patients had a laboratory test performed within 30 days before vaccination and within 30 days after vaccination (41.6% versus 43.5%; P=0.39), suggesting that testing frequency was not correlated with vaccination status." However, the unexposed time used for calculating HRs in the main study analyses included all other study time outside the 30-day exposure window after each vaccine dose, not only the 30 days prior to vaccination. Thus, this seemingly reassuring methodological analysis is incomplete. A potential need for increased monitoring was raised by the authors. In this regard, it is relevant to note that this study included 1,016 COVID-19-vaccinated glomerular disease patients and reported that among them only four (0.4%) needed a change in immunosuppression following vaccination at some time in the 30-day period prior to relapse; no patient had a repeat biopsy. The glomerular diseases of these four patients were not reported. Regardless of vaccination, standard practice is that all glomerular disease patients should self-monitor for signs and symptoms of relapse. The data reported by Canney do not provide a sufficient basis for new recommendations or product labelling changes about IgA nephropathy in association with COVID-19 vaccine administration [31].
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 through 17 Dec 2022 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 bivalents (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. Final assessment report of this signal evaluation was received from SwissMedic, on 12 Jun 2023 confirming that no additional activities were requested, as stated in their notification letter: "Swissmedic examined your documents and came to the following conclusion: According to available data (clinical data, literature, post-marketing data, including O/E analyses), there are e.g., Currently there is no reliable evidence of a causal connection between an mRNA vaccination and an IgAN - be it de novo or an exacerbation of one existing IgAN. 1. No action is currently required regarding this signal. 2. The signal is completed."
Conclusion	Overall, based on the analysis of all available safety data as of 17 Dec 2022 including the literature articles discussed above, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran, or the bivalent ModernaTx, Inc vaccines, and the development of IgA nephropathy. No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor IgA Nephropathy events using routine pharmacovigilance surveillance. The data reported by Canney et al, reviewed in detail above, do not provide a sufficient basis for new recommendations or product labelling changes with regard to IgA nephropathy flare-up in association with COVID-19 vaccine administration. The signal of IgA nephropathy flare-up is closed and refuted.

Rapporteur assessment comment:

The MAH opened the signal of IgA nephropathy flare-up, following receipt of a signal letter from Swissmedic, triggered by the publication Canney et. al: A Population-Based Analysis of the Risk of Glomerular Disease Relapse after COVID-19 Vaccination. The signal was closed and refuted post DLP of the previous PSUR.

IgA Nephropathy was evaluated in PRAC Assessment Report of PSUR #2, #3, and #4, where it was acknowledged that there were cases reported indicating a potential causal association between elasomeran and IgA nephropathy, in particular flare up of underlying IgA nephropathy. However, the evidence was at that time inconclusive regarding a possible causal role of vaccination with elasomeran.

The MAH presents that cumulatively as of the DLP (17 Dec 2022), a total of 237 cases (272 events) were retrieved using the MedDRA HLT of "Glomerulonephritis and Nephrotic Syndrome". Medical review identified 68 cases involving IgA nephropathy; 43 cases were new onset (DeNovo) IgA nephropathy, and 25 cases were considered IgA nephropathy flares. There were no reports of fatalities in the medically confirmed IgA Nephropathy cases. The Rapporteur notes that the MAH has used the same DLP as for the evaluation of this topic in PSUR no. 4 without providing a justification for not including more recent data.

As the signal was detected on 21 Apr 2023, the used DLP (17 Dec 2022) is not considered appropriate. However, as the Rapporteur did not identify new and significant safety information from the MAH's presentation of neither the 8 cases reporting the PT "IgA nephropathy" in the previous PSUR (no. 5) nor from the MAH's presentation of the four cases reporting the PT "IgA nephropathy" in the current PSUR, further action is not currently warranted.

The MAH presents that a total of 177 literature articles was retrieved. However, it appears that the MAH has not updated its literature review since its presentation of this topic in PSUR no. 4, as the number of retrieved articles and the sole publication deemed significant are exactly the same. However, the Rapporteur notes that according to the MAH, the number of publications with new and significant safety information regarding the important potential risk "IgA Nephropathy" is 0 in both PSUR no. 5 and 6 (i.e. since the topic was presented in PSUR no. 4), and therefore further action is not considered warranted currently.

In future PSURs, the MAH is requested to use a DLP as recent as possible in signal evaluations, cumulative reviews etc. to ensure that the evaluation is as complete and up to date as possible. DLPs that are several months old will not be accepted without a reasonable justification.

Medical review of these articles conducted by the MAH identified one article that provided new and significant safety findings; 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. With regard to the study by Canney et al, which triggered the signal, several important limitations were noted by the MAH. The study ascertained the risk of glomerular disease relapse after COVID-19 vaccination and the Rapporteur notes the following weaknesses of the study. It is noted that the observed increased risk after the 2nd and 3rd dose is just borderline statistically significant (lower bound of the 95% confidence interval of the HR is 1.06). No increased risk was found after the first dose. Furthermore, it is noted that disease relapse was ascertained based on a significant increase in proteinuria or creatinine. The Rapporteur deems that significantly increased proteinuria or creatinine in a patient with a medical history of glomerular disease is likely to be a sign of relapse of the index disease, however, increased proteinuria or creatinine are unspecific findings and as relapse has not been confirmed with kidney biopsy, it cannot be excluded that false positive cases of "disease relapse" have been included in the analysis. Furthermore, Szeto et al. found that of 72 patients with histologically confirmed IgA nephropathy, 33% developed proteinuria and 7% developed impaired renal function during a median follow-up of 7 years (study conducted prior to the pandemic). Increased proteinuria and decreased kidney function therefore appear to be a common complication in patients with IgA nephropathy regardless of exposure to elasomeran. For these reasons, the study by Canney et al. is not deemed to provide significant evidence of a causal association between elasomeran exposure and IgA nephropathy flare-up.

No cases of IgA Nephropathy were identified in the MAH's Clinical Trials. The MAH argues that no pathophysiologic process has been shown to explain a causal association between elasomeran or the ModernaTx, Inc bivalent vaccines and IgA nephropathy. The Rapporteur agrees that no definitive pathophysiologic process has been identified, but it is noted that the publication by Ma and Xu presents proposed mechanisms of action by which COVID-19 vaccination might induce IgA nephropathy. This publication is also referenced by the MAH in PSUR section 16.4 in the characterisation of IgA nephropathy as an important potential risk.

Following evaluation of the MAH signal assessment report, SwissMedic concluded in their final assessment report (12 June 2023) that "currently there is no reliable evidence of a causal connection between an mRNA vaccination and an IgAN - be it de novo or an exacerbation of one existing IgAN". No further action was requested.

Overall, the MAH concluded that there is insufficient information in all available safety data to establish a

causal relationship between the administration of Spikevax, or the bivalent Moderna vaccines, and the development of IgA nephropathy. No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor IgA Nephropathy events using routine pharmacovigilance surveillance.

This is endorsed. Despite the MAH's suboptimal presentation of cumulative literature and case reports, based on the conclusion reached for IgA nephropathy in the 4th PSUSA procedure, and the data accumulated since (according to the presentation by the MAH in PSUR no. 5. and 6), the currently available evidence is not considered strong enough to establish a causal relation between IgA nephropathy and elasomeran exposure. The signal of IgA Nephropathy should be considered closed. IgA Nephropathy is an important potential risk in the PSUR list of safety concerns. Please refer to section 2.3.1.2.1 of this assessment report.

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2.2.2. Mastitis/Breast swelling

Table 21: Mastitis/Breast Swelling

Signal evaluation cirteria	Summary
Source	On 05 Jul 2023, ModernaTx, Inc received a request from the TGA (TRIM No. D23-2098241) to update the SPIKEVAX PI with mastitis and breast swelling (Moderna Australia Pty Ltd) including: Request to make safety-related changes to the Product Information (PI) and Consumer Medicine Information for: elasomeran [ARTG No: 370599, 388245, 406730, 399553, 389513, 388244, 399552, 396452]. The TGA's Pharmacovigilance Branch has recently assessed the risk of mastitis and breast swelling with elasomeran. Our assessment concluded that there are sufficient safety grounds to request an update to the SPIKEVAX PI with mastitis and breast swelling.
Background	**Mastitis** Mastitis is a relatively common breast condition [42]. It can affect patients at any time but predominates in women during breastfeeding. It is defined as an inflammatory condition that may be due to several different etiologies, infectious or not, but most breast inflammation is expressed as a hard, swollen, and red breast area, accompanied by a fever above 38.5°C, chills, and general flu-like symptoms [43]. Mastitis with infection may be lactational (puerperal) or non-lactational (e.g., duct ectasia) [42]. *Types of mastitis*

Lactational or *Puerperal mastitis*

In lactational mastitis, it is likely that bacteria (often originating from the mouth of the infant) gain entry via cracks or fissures in the nipple surface. Once the primary defenses are breached, organisms have an ideal culture environment in nutrient rich maternal milk leading to rapid replication. This process can be augmented by milk stasis and overproduction leading to mastitis. The pathological process is similar to any acute inflammatory event, although the nature of the lactating breast architecture with its loose parenchyma and stagnation of milk in an engorged segment may allow the infection to spread quickly both within the stroma and through the milk ducts. Risk factors include previous mastitis, sore/cracked nipples, wearing tightfitting bra, improper nursing techniques, poor nutrition, and tobacco usage [42] and [44].

Non-lactational or *Non-puerperal Mastitis (periductal)*

In non-lactational or non-puerperal infectious mastitis (NLIM), it can be caused by different infectious agents. Staphylococcus is the main genus of bacteria associated with non-lactational infectious mastitis and up to 30% may be polymicrobial (e.g., Enterobacteriaceae, Peptostreptococcus, Propionibacterium, Bacteroides) [45]. In duct ectasia, the mammary duct-associated inflammatory disease sequence involves squamous metaplasia of lactiferous ducts causing blockage (obstructive mastopathy) with peri-ductal inflammation and duct rupture. Inflamed ducts are prone to bacterial infection [42]. Risk factors include chronic use of oral contraceptives, tobacco usage, long-term steroids, thoracic surgery, cat scratches, breast implants, reduction mammoplasty, diabetes mellitus, obesity, and tuberculosis [43,44,46].

Non-infectious mastitis

Non-infection mastitis may result from underlying duct ectasia (periductal mastitis or plasma cell mastitis) and infrequently from foreign material (e.g., nipple piercing, breast implant, or silicone). Causes of non-infectious mastitis include idiopathic granulomatous inflammation, autoimmune disorders (e.g., sarcoidosis, thyroiditis, systemic erythematosus lupus, Sjogren's syndrome, Crohn's disease), trauma, hyperprolactinemia, and other inflammatory conditions (e.g., foreign body reaction) [42,44,47].

Epidemiology

Worldwide, lactational mastitis occurs in 2%-30% of breastfeeding women. In the United States, the reported incidence is between 7%-10%. The incidence is highest in the first three weeks postpartum [48]. The global prevalence of mastitis in lactating women ranges from 1-10%; however, a Cochrane review suggested that the incidence of mastitis could be as high as 33%. The incidence is highest in the first few weeks of postpartum and decreases gradually after that. Duct ectasia (peri-ductal mastitis or dilated ducts associated with inflammation) occurs in 5-9% of non-lactating women [42]. Breast inflammation during breastfeeding requires immediate and appropriate treatment [43].

Clinical Features and Diagnosis

Common signs and symptoms are fever, breast signs/symptoms (pain, swelling, warmth, thickening of skin, lump, tenderness, firmness, erythema, abscess), decreased milk outflow, enlargement of axillary lymph nodes, chills, myalgias, and malaise [42,44], [48].The diagnosis is usually based on history and clinical findings. However,

	useful diagnostic tools include ultrasound, fine needle aspiration, biopsy, milk sample, cultures, mammography, laboratory studies, and tuberculin skin test [42]. *Clinical course* If mastitis is left untreated, it may cause tissue destruction resulting in an abscess associated with bacteremia and sepsis. Lactational abscesses tend to be in the peripheral breast and are often a progression of mastitis or lactational breast inflammation. Non-lactational breast abscesses are often sub-areolar and were first described as fistulas of lactiferous ducts; this is proceeded by inflammation of the surrounding duct, infection of these terminal lactiferous ducts, duct rupture and subsequent peri-areolar fistula and sub-areolar breast abscess formation. These abscesses have a chronic course, often with recurrent obstruction of the ducts with keratin plugs and tend to form extensive fistulas [42]. *Treatment* Supportive treatment included effective milk removal, lymphatic massage, hot compresses, rest, nutrients, and increased fluid intake. Also, the following pharmacological treatment have been used in conjunction with supportive treatment: analgesics, antibiotics, topical antifungal preparations, and steroid combination ointment [43]. Surgical intervention may be required for mature fluctuant abscess [42]. **Breast Swelling/Breast Oedema** Breast oedema is fluid accumulation within breast tissue that may lead to visible swelling, increased breast parenchymal density, inflammation, skin dimpling (peau d'orange) and thickening, breast pain, and sagging of the breast. This fluid buildup is largely a result of compromised outflow due to an obstruction or disruption of lymphatic vessels that drain the breast, which may occur from a diverse spectrum of etiologies. *Etiology* The predominant cause is breast cancer treatment referred to as breast-conserving therapy (BCT) whereby breast-conserving surgery (also called lumpectomy or segmental mastectomy) is performed, followed by radiotherapy. Often coexistent with breast oedema attributable to BCT is lymphoedema of the arms, an entity that has been far more recognized and treated clinically as well as extensively explored and discussed in the literature. Less common causes of breast oedema include inflammatory breast carcinoma, congestive heart failure, mastitis, lymphatic obstruction (by axillary, chest wall, or intrathoracic lesions), metastasis, breast lymphoma, and trauma [49] .In addition, breast enlargement has been associated with medications (e.g., antiandrogen/inhibitors of androgen synthesis, chemotherapeutic agents, cardiac medications, hormones, psychoactive drugs, antiretrovirals) [48]. *Diagnosis* Current methods to detect breast oedema incidence tend to be suboptimal, often limited to subjective assessments (such as surveys, questionnaires, and self-reports) and clinical assessments based on cursory physical examinations. Diagnostic studies are plain radiology, mammograms, MRI, ultrasound imaging, and contrast-enhanced digital mammography (CEDM) [48]. *Treatment*

	Management of breast oedema can be facilitated if both the patient and clinician are aware of its presentation, its course, and [49] methods used for its detection and monitoring. If left untreated, breast oedema can have psychological effects leading to decreased quality of life, body image issues, and fear of cancer reoccurrence, as well as continued breast discomfort and pain. Treatment options include manual lymphatic drainage, compression banding, lymph-reducing exercises, and skin care [48].
Methodology	The assessment of Mastitis and Breast swelling in association with the use of elasomeran-containing vaccines in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources are described below. **Methodology for Mastitis and Breast Swelling:** The MAH's clinical database and the global safety database were queried for valid case reports of Mastitis and Breast Swelling received from HCP, HA, consumers, and literature, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) using the following PTs: "Mastitis, Breast swelling, Breast oedema, and Breast enlargement." Two different Medical Dictionary of Regulatory Activities (MedDRA) version were used. For the CTs MedDRA version 23.0 and 24.0 were used and for querying the global safety database, cumulative as of 17 Jun 2023, the MedDRA version 26.0 was used. Clinical Trial Data: The Company clinical database was queried cumulative from 18 Dec 2020 to 17 Jun 2023. Safety data from four CTs in different age groups (adults, adolescents, and children) was reviewed to identify unsolicited events (serious and nonserious) reported using the MedDRA (version 26.0) PTs "Mastitis," "Breast swelling," "Breast Oedema," and "Breast enlargement." The topics of Mastitis and Breast Swelling were cumulatively reviewed in the clinical trial datasets, within the following studies: • mRNA-1273-P301, data as of 04 May 2021 • mRNA-1273-P203 Part 1A and Part 1B, data as of 31 Jan 2022 Part 1C, data as of 15 Aug 2022 Part 3 Day 29 interim analysis (IA) (FDA Single Dose IR). Data as of 05 Jun 2023 • mRNA-1273-P204 Part 1 and Part 2, data as of 07 Sep 2022 • mRNA-1273-P306 Part 1 and Part 2, data as of 05 Dec 2022 • Booster sBLA (Part 2), data as of 21 Mar 2023 External Databases: Disproportionality was performed for the external safety databases VAERS and EVDAS. Review of the Pharmacovigilance Database: The MAH GSDB was queried cumulative as of 17 Jun 2023, for valid case reports of mastitis and breast swelling received from HCP, HA, consumers, and literature, worldwide for Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, using the MedDRA dictionary, version 26.0 PT: "Mastitis, Breast swelling, Breast enlargement, and Breast oedema". Given that there is no established case definition for mastitis or breast swelling/breast

	oedema, the MAH created a case definition to establish a certainty level of whether a report could be classified as a case of mastitis or breast swelling. For mastitis, based on the case definition presented below, all identified cases meeting the case definition, were medically reviewed (regardless of seriousness or medically confirmed): Mastitis: This is an inflammatory condition that may be due to several different etiologies, infectious or not, but most breast inflammation is expressed as a hard, swollen, and red breast area, accompanied by a fever above 38.5°C, chills, and general flu-like symptoms. In addition, the mastitis cases were classified as lactational or non-lactational based on the information provided. Breast swelling: Breast swelling/edema is fluid accumulation within breast tissue that may lead to visible swelling, increased breast density, inflammation, skin dimpling and thickening, breast pain, and sagging of the breast. In order to identify cases that met the case definition of breast swelling/breast enlargement/breast oedema, the medical review was focused on: • Serious cases (medically confirmed/not medically confirmed) • Non-serious medically confirmed cases • Non-serious not medically confirmed cases that contained diagnostic information (e.g., mammogram, breast ultrasound) • Male gender cases, and cases with ages < 18 years old. Breast swelling/breast edema/breast enlargement cases reported for males are often reported as events of gynecomastia. For thoroughness, the MAH global safety database was also queried cumulative as of 17 Jun 2023, for valid case reports of gynecomastia received from HCP, HA, consumers, and literature, worldwide, for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, using the MedDRA dictionary, version 26.0 PT: "Gynecomastia." There is no established case definition for gynecomastia. The MAH created a case definition to establish a certainty level of whether a report could be classified as a case of gynecomastia, and all identified cases meeting the case definition, were medically eviewed (regardless of seriousness or medically confirmed): Gynecomastia is an increase in the amount of breast gland tissue in boys or men, caused by an imbalance of the hormones estrogen and testosterone that may cause pain (particularly in adolescents), swollen breast tissue, breast tenderness, and nipple sensitivity. The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system was used for causality assessment for all cases of mastitis, breast swelling/breast oedema/breast enlargement, and gynecomastia. In the absence of an established risk window and established biological plausibility, MAH has chosen to use 42 days as the upper limit for TTO following vaccination consistent with risk window used for other AESIs for COVID-19 vaccines. Literature search review: A cumulative literature search was performed from 18 Dec 2020 to 17 Jun 2023 using PubMed for search strategies used to identify articles related to mastitis and breast swelling and COVID-19 mRNA vaccine, elasomeran.
Results	Clinical Trial Data:

mRNA-1273- P301 Study

Study mRNA-1273-P301 (randomized, stratified, observer-blind, placebo-controlled study) included healthy adults ≥ 18 years of age. 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. There were two participants in P301, reporting one event of "Breast swelling" and one event of "Breast enlargement".

mRNA-1273-P203 Study

Study mRNA-1273-P203 (Phase 2/3, randomized, observer-blind, and placebo controlled) included healthy adolescents in the age group 12 to < 18 years, there was one participant reporting an event of "Mastitis" was observed.

mRNA-1273-P204 Study

Study mRNA-1273P204 (Phase 2/3, 2-part, open-label, dose-escalation, age deescalation, and randomized, observer-blind, placebo-controlled expansion) included healthy pediatrics between 6 months to < 12 years. In mRNA-1273-P204, there was one participant reporting an event of "Mastitis".

mRNA-1273-P306 Study

Study mRNA-1273-P306 (An Open-Label, Phase 3 Study) included healthy pediatrics between 6 months to < 6 years. In study P306, there were no participants reporting any events of Mastitis and Breast swelling.

Summary of clinical trial Data

No imbalance was observed in any of the 4 studies for the PTs "Mastitis," "Breast swelling," "Breast oedema," or "Breast enlargement". Four participants identified with events of interest. All four cases were considered as "not related to product Investigational product" by the investigator.

External Databases:

VAERS: No disproportionate reporting of events was observed using EB05 > 2 (mRNA-1273 versus All vaccines in adults) in VAERS. EVDAS: The PTs for breast swelling, breast edema, and breast enlargement demonstrated disproportionality as the ROR was >1. Breast swelling (ROR= 2.17; n=260), Breast oedema (ROR=1.77; n=31) and Breast enlargement (ROR=1.31; n=135). While disproportionality is not uncommon in EVDAS, results should be taken with caution given the limitations in EVDAS and based on low case counts.

Review of the Pharmacovigilance Database:

Review of Mastitis Cases

Cumulatively, as of 17 Jun 2023, the MAH received a total of 117 cases (120 events) with the PT of "mastitis". There were 66 serious cases (66 serious events). There were no fatal events, and 43 cases were medically confirmed. There were 113 cases (96.6%) reporting 116 events (65 serious) following vaccination with elasomeran; 4 cases (3.4%) reporting 4 events (1 serious) following vaccination with elasomeran/imelasomeran; no cases were reported following vaccination with elaosmeran/davesomeran. The majority of cases were reported in females (116 cases;

99.1%) especially among women of reproductive age (specifically 18-49 years of age), and no reports in the adolescent's group (12 to 17 years of age); there was 1 case (0.9%) reported in a male. In the 115 cases that provided age data, the mean patient age was 41.6 years (SD: 13.3) with a median age of 37.0 years (age range: 23.0 to 82.0 years). A considerable proportion of reports were received from regulatory authorities and in such cases, follow-up is not possible due to privacy restrictions. When TTO and dose number were known most events had a TTO within 7 days regardless of dose number. The median TTO was 2.5 days (range: 0 to 62 days) with an average TTO of 6.1 days (SD: 10.0) which reflects expected vaccine reactogenicity. Most of the events (71 events; 59.2%) reported an outcome of resolved/ resolving. According to the case classification of mastitis cases there were 31 lactational cases; and 32 non-lactational cases; 53 were classified as unknown; and 1 (male patient) was considered not applicable.

In most of the cases (108; 92.3%), mastitis was reported without breast swelling, breast oedema, or breast enlargement. In 5 cases, the diagnosis of mastitis was confirmed by breast ultrasound and/or mammogram. In three cases (WW Identifier: [redacted], the patients had a positive rechallenge with subsequent mRNA vaccines; however, all the patients had confounding factors such as concurrent breastfeeding and history of mastitis. In one case (WW Identifier: [redacted], the patient had a negative rechallenge with a subsequent mRNA vaccine. Overall, most cases, key missing information included medical history, concomitant medications, pregnancy status, onset of the event, clinical course, physical examination, treatment, dechallenge/rechallenge information, and diagnostic studies. There was one case (WW Identifier: [redacted]) reporting events of mastitis in a male patient. The case involved a 34-year-old male with a history of hypogonadism who experienced mastitis in conjunction with pyrexia the same day he received his third dose of elasomeran vaccine. Concomitant medications included testosterone. Key information such as diagnostic studies, physical examination, and treatment were not provided. The reported outcome was "Not resolved" at the time of this report.

Risk Factors/ Confounders

Review of 117 cases, shows that for 74 cases (63.2%), the patients had risk factors and/or confounders for mastitis including: concurrent breastfeeding (29 cases), concurrent lymphadenopathy (18 cases), concomitant medications associated with gynecomastia/breast swelling (12 cases), thyroid disease (8 cases), COVID-19 infection (5 cases), previous mastitis (3 cases), menstrual disorder (3 cases), diabetes mellitus (2 cases), previous breast disorder (1 case), breast cancer (1 case), prolactin producing pituitary tumor (1 case), obesity (1 case), endometriosis (1 case), breast prothesis user (1 case), galactostasis (1 case), unspecified autoimmune disorder (1 case), and herpes zoster (1 case). In 13 cases (11.1%), the patients had received prior COVID-19 vaccinations with Pfizer-BioNTech COVID-19 vaccine and/or AstraZeneca COVID-19 vaccine.

Serious Events of Mastitis

Out of the 65 serious events of mastitis, there were three cases (WW Identifier# [redacted] concerning patients who were hospitalized for mastitis. One case (WW Identifier# [redacted] concerned a 37-year-old female with a history of mitral valve prolapse

who developed mastitis one day after receiving the third dose of elasomeran vaccine. It was unknown if the mastitis was associated with breastfeeding or a recent pregnancy. The patient was first treated with antibiotics; however, she was hospitalized 30 days later for a breast abscess due to mastitis. A breast biopsy revealed mixed acute suppurative inflammation, necrotizing granulomatous inflammation, micro abscess formation, focal granulation tissue formation, and no micro-organisms. Treatment included incision/drainage and debridement. The patient improved and was discharged. The remaining two cases (WW Identifier# [redacted] and [redacted]) contained limited information regarding the hospitalization. According to the WHO-UMC causality assessment, the 65 serious events were assessed as follows: "Probable" (2 events), "Possible" (11 events), "Unlikely" (4 events), and "Unassessable" (48 events).

WHO Causality Assessments

According to the WHO (World Health Organization)-UMC causality assessment, review of the 120 events were assessed as follows: "Probable" (4 events), "Possible" (17 events), "Unassessable" (94 events), and "Unlikely" (5 events).

Breast Swelling Cases (including Breast Oedema, and Breast Enlargement):

Cumulatively, as of 17 Jun 2023, the MAH received 616 cases (631 events) of breast swelling, breast oedema, and breast enlargement following vaccination with an elasomeran-containing vaccine. There were 90 serious cases (53 serious events), with no cases reporting a fatal outcome, and 188 cases were medically confirmed. There were 605 cases (98.2%), reporting 620 events (50 serious) following vaccination with elasomeran; 9 cases (1.5%) reporting 9 events (3 serious) following vaccination with, elasomeran/imelasomeran and 2 cases (0.3%) reporting 2 non-serious events following vaccination with and elasomeran/davesomeran. Most cases were reported in females (575 cases; 93.3%) when compared to males (33 cases; 5.4%); with 8 cases (1.3%) not reporting gender. Most cases (380; 66.2%) were among women of reproductive age (specifically 18-49 years of age). There were 2 reports received in the adolescent group of 12-17 years of age and one report in pediatric group of 0-5 months old. In the 574 cases that provided age data, the mean age was 44.5 years (SD: 14.3) with a median age of 43.0 years (age range: 9 days to 97 years). The most reported PTs were Breast swelling (440 events; 69.7%), Breast enlargement (152 events; 24.1%), and Breast oedema (39 events; 6.2%). A considerable proportion of reports were received from regulatory authorities. In such cases, follow-up is not possible due to privacy restrictions.

Based on the case definition and on the evaluation, criteria presented above, for cases with reported PTs of breast swelling/breast oedema/breast enlargement, 320 cases involving 323 events were identified for focused medical review. Most of these 320 cases were reported in females (284 cases; 88.8%) with 33 cases (10.3%) reported in males and 3 cases (0.1%) that did not report gender. Most cases (158; 49.4%) were among women of reproductive age (specifically 18-49 years of age). In the 301 cases that provided age data, the mean age was 48.6 years with a median age of 48.0 years (age range: 9 days old to 97 years).

When TTO and dose number were known (323 events), events most frequently occurred within 7 days of vaccination regardless of dose number. The median TTO was 2.0 days (range: 0 to 214 days) with an average TTO of 7.6 days (SD: 18.6) which

	reflects expected vaccine reactogenicity. There were 33 cases (7 serious) in which events of breast swelling, breast oedema, or breast enlargement were reported in a male patient. In the 30 cases that provided age data, the mean age was 57.5 years with a median age of 49.5 years (age range: 25 to 89 years). In 21 cases (63.6%), the patients had one or more risk factors and/or confounders for breast swelling, breast enlargement, or breast oedema as follows: concurrent lymphadenopathy/peripheral oedema (12 cases), concomitant medications associated with gynecomastia (9 cases), gynecomastia (2 cases), diabetes mellitus (2 cases), breast mass (2 cases), herpes zoster (1 case), weight increased (1 case), prostate cancer (1 case), and tobacco usage (1 case). In the remaining 12 cases, limited information was provided. The reported outcomes of the events were as follows: "Resolved" (3 events), "Not resolved" (20 events), "Resolving" (2 events), and "Unknown" (8 events). There were 3 non-serious cases in which breast swelling or breast enlargement occurred in patients younger than 18 years of age. Case (WW Identifier: [redacted] involved 9-day-old female, with an unknown medical history, who experienced bloody nipple exudate 24 days after the mother received the third dose of elasomeran vaccine; the event subsequently resolved after an unspecified period. Case (WW Identifier: [redacted] involved a 12-year-old female with an unknown medical history who experienced breast swelling associated with pyrexia 1 day after receiving an unspecified dose of elasomeran; the event was reported as "Resolving". Case ([redacted]) involved 16-year-old female with an unknown medical history who experienced breast enlargement in conjunction with unspecified menstrual disorder an unknown time after receiving an unspecified dose of the Elasomeran vaccine; the event was reported as "Not resolved". According to the WHO-UMC causality assessment, all events were assessed as "Unassessable". **Risk Factors/ Confounders from Breast Swelling Cases** Review of the 320 cases, showed that 241 (75.3%) cases were heavily confounded by the patient's risk factors and/or confounders for breast swelling, breast oedema, and breast enlargement including: concurrent lymphadenopathy/ lymphoedema/lymphadenitis (107 cases), concurrent medications associated with gynecomastia/breast swelling (65 cases), concurrent peripheral oedema/fluid retention (50 cases), menstrual disorder (41 cases), thyroid disease (19 cases), diabetes mellitus (13 cases), breast cancer (9 cases), breast mass (6 cases), herpes zoster (6 cases), obesity/overweight (6 cases), amenorrhea (5 cases), concurrent breastfeeding (4 cases), breast prothesis user (4 cases), endometriosis (4 cases), axillary mass (2 cases), tobacco user (3 case), concurrent COVID-19 infection (3 cases), previous breast disorder (2 cases), concurrent pregnancy (2 cases), polycystic ovarian syndrome (2 cases), gynecomastia (2 cases), weight increased (2 cases), fibrocystic disease (1 case), concurrent pulmonary embolism (1 case), concurrent deep vein thrombosis (1 case), unspecified autoimmune disorder (1 case), chronic kidney disease (1 case), benign pituitary tumor (1 case), and increased prolactin level (1 case).

	In 43 cases (13.4%), the patients had received prior COVID-19 vaccinations with Pfizer-BioNTech COVID-19 vaccine and/or AstraZeneca COVID-19 vaccine. In 9 cases (2.9%), breast swelling, or breast enlargement was reported in conjunction with mastitis. In 6 of those 9 cases, concurrent lymphadenopathy (5 cases) and/or concurrent breastfeeding (3 cases) were reported. In 283 cases (88.4%), breast swelling/breast enlargement/breast oedema were reported in conjunction with other PTs (e.g., pyrexia, chills, lymphadenopathy, axillary pain, lymph node pain, erythema, breast tenderness, breast mass, breast cyst, breast discharge, breast pain, breast implant infection, influenza like illness, lactation insufficiency, autoimmune thyroiditis, fluid retention, peripheral swelling, weight increased, COVID-19 infection, herpes zoster). In addition, 41 oedema cases (6.7%) were associated with menstrual disorders (e.g., unspecified menstrual disorder, polymenorrhea, menstruation delayed, intermenstrual bleeding, heavy menstrual bleeding, menometrorrhagia, menstruation irregular, vaginal hemorrhage) suggestive of physiological hormonal changes due to estrogen and progesterone. Additionally, for 9 cases, the patients had either pre-existing breast cancer (8 cases) or newly diagnosed breast cancer (1 case). The first case (WW Identifier#: [redacted] involved a 57-year-old female with a history of breast cancer (status post mastectomy) who experienced breast swelling associated with lymphadenopathy and peripheral oedema; treatment and outcome were not provided. The second case (WW Identifier#: [redacted] involved a 46-year-old female breast cancer (status post bilateral mastectomy) who experienced breast swelling associated with lymphadenopathy 2 days after receiving the first elasomeran vaccine; treatment and outcome were not provided. The third case (WW Identifier#: [redacted] involved a 58-year-old female with a history of breast cancer who experienced breast swelling associated with axillary pain and peripheral oedema the same day she received an unknown dose of Elasomeran vaccine; the reported outcome was "Not resolved" and treatment was not provided. The fourth case (WW Identifier#: [redacted] involved a 75-year-old female with a history of breast cancer who experienced breast swelling associated with lymphadenopathy 3 days after receiving the first dose of elasomeran; the reported outcome was "Not resolved" and treatment was not provided. The fifth case (WW Identifier#: [redacted] involved a 63-year-old female with a history of breast cancer who experienced breast swelling associated with lymphadenopathy and breast discoloration 9 days after receiving the second dose of elasomeran vaccine; the patient was treated with cephalexin and outcome was not provided. The sixth case (WW Identifier#: [redacted] involved a 51-year-old female with a history of breast cancer who experienced breast swelling associated with lymphoedema and peripheral swelling; the reported outcome was "Not resolved" and treatment was not provided.

	The seventh case (WW Identifier#: [redacted] involved a 57-year-old female with a history of breast cancer who experienced breast swelling associated with weight increased within 27 days of receiving the second dose of elasomeran vaccine; treatment and outcome were not provided. The eighth case (WW Identifier#: [redacted]) involved a 65-year-old female with a history of breast cancer who experienced breast swelling associated with pyrexia and erythema 1 day after receiving the second dose of COVID-19 vaccine; the reported outcome was "Resolved", and treatment was not provided. The ninth case (WW Identifier#: [redacted] involved a 54-year-old female with an unknown medical history who was diagnosed with breast cancer 33 days after receiving the second dose of elasomeran vaccine; treatment and outcome were not provided. In the 95 events that reported location of breast swelling/breast enlargement/breast oedema events, the locations were as follows: unilateral event with unknown vaccination site (46 events), unilateral event ipsilateral to the vaccination site (35 events), bilateral with unknown vaccination site (11 events), unilateral event contralateral to the vaccination site (2 events), and bilateral with vaccination site on left side (1 event). **WHO Causality assessment** According to the WHO- UMC causality assessment, 323 events were assessed as: "Probable" (8 events), "Possible" (65 events), "Unassessable" (238 events), "Unlikely" (11 events), and "Not applicable" (1 event occurred with another vaccine). In many cases, key missing information included medical history, concomitant medications, pregnancy status, onset of the event, clinical course, physical examination, treatment, dechallenge/rechallenge information, and diagnostic studies. **Literature review** The PubMed search retrieved 118 unique articles, including the six literature articles cited in the TGA request letter (4 case reports, 1 prospective cohort study, 1 literature review). But none of these articles were indicative or suggestive of a potential for a causal association or a potential MoA. Below is a summary of the six literature articles cited by the TGA. *Management Strategies for Patients Presenting with Symptomatic Lymphadenopathy and Breast Oedema After Recent COVID-19 Vaccination [50]* The authors reviewed the two recent publications on the combination of axillary lymphadenopathy and breast oedema after COVID-19 mRNA vaccination that subsequently resolved. Ipsilateral lymphadenopathy was often incidentally detected onmultimodality imaging; sonographic findings included enlarged nodes with cortical thickening, loss of normal fatty hilum, and possible hypervascularity. They discussed a case of symptomatic lymphadenopathy confounded by profound unilateral breast swelling after recent vaccination with subsequent biopsy revealing invasive lobular carcinoma and nodal metastasis. They stated that although ipsilateral axillary and breast oedema associated with COVID-19 vaccination was uncommon, it was critical to consider differential diagnosis of unilateral breast oedema including both malignant (e.g., inflammatory breast cancer, primary or metastatic breast cancer, breast lymphoma) and benign

	(e.g., mastitis, congestive heart failure, venous occlusion, trauma, previous surgery, or radiation treatment) causes. Patients presenting with axillary lymphadenopathy and with other breast symptoms or additional abnormal imaging findings should be considered in a high-risk category and need prompt diagnostic evaluation and consideration of tissue sampling with punch biopsy. *Breast implant seroma: A SARS-CoV-2 mRNA vaccine side effect [51]* This was a case report of a 48-year-old female patient with a history of textured silicone gel breast implants for aesthetic reasons (5 years ago) who experienced bilateral breast swelling associated with breast pain and warmth 10 days after a second Pfizer-BioNTech SARS-CoV-2 mRNA vaccine dose. A clinical breast examination revealed enlarged, firm breasts without skin abnormalities. A breast ultrasound showed diffuse fluid collection surrounding the breast implants, no breast tissue abnormality, and no implant rupture. Laboratory tests revealed elevated C-reactive protein (6.3 mg/L) and positive rheumatoid antibodies (AntiENA, AntiSSA). The patient noticed symptom improvement 48 hours after nonsteroidal anti-inflammatory drug treatment and complete disappearance of symptoms after 10 days with seroma disappearance detected on ultrasound. The authors hypothesized that a breast implant seroma as post-SARS-CoV-2 mRNA vaccine adverse event since other diagnoses had been excluded. *Mammographic and sonographic findings in the breast and axillary tail following a COVID-19 vaccine [52]* This was a case series of 3 female patients (ages 36, 60, 83 years old) who had abnormal findings on diagnostic mammography within 1-11 days after receiving an unspecified COVID-19 vaccination. In the literature, axillary lymphadenopathy on breast imaging after recent COVID-19 vaccination has been reported as immunization has become morewidespread. While muscle oedema at the injection site has been observed on MRI secondary to an immune response, ipsilateral breast imaging observations of oedema have not been reported to be seen with the COVID-19 vaccinations. Mammographic findings such as trabecular and skin thickening, along with increased echogenicity on ultrasound, can be seen with oedema secondary to capillary leak or poor lymphatic drainage. The authors stated that these findings should be considered as a possible etiology for the observed breast oedema following a recent COVID-19 vaccine. Inflammatory changes observed in the breast and axillary tail post vaccination described in this case series were transient, but clinically relevant for patients who experience swelling following injection. Similar to evaluations for suspected mastitis, a short interval imaging follow-up to confirm resolution may be appropriate for patients with ipsilateral vaccination histories and could potentially reduce the number of false positive examinations in this clinical scenario. The authors concluded that inflammatory breast cancer can mimic inflammation and infection, therefore, close follow-up to resolution was critical as to not miss cancer. *Breastfeeding Mother and Child Clinical Outcomes After COVID-19 Vaccination [53]* This was a prospective cohort study of 88 lactating healthcare workers in Singapore who received two doses of BNT162b2 vaccination (Pfizer/BioNTech). The aims of the study were to determine solicited adverse effects (e.g., axillary lymphadenopathy, mastitis, and breast engorgement) as well as systemic and local adverse effects of BNT162b2 mRNA vaccine in mothers and potential effects on their breastfed infants. The outcomes of mother–child dyads within 28 days after the second vaccine dose were determined through a participant-completed questionnaire. The results revealed minimal effects related to breastfeeding were reported by the study cohort. Three of 88 (3.4%) participants had mastitis, one (1.1%) participant experienced breast engorgement, five

	of 88 (5.7%) participants reported cervical or axillary lymphadenopathy. There was no change in human milk supply after vaccination. The most common side effect was pain/ redness/swelling at the injection site, which was experienced by 57 (64.8%) participants. There were no SAEs of anaphylaxis or hospital admissions. There were no short-term adverse effects reported in the infants of 67 lactating participants who breastfed within 72 hours after BNT162b2 vaccination. The authors concluded that BNT162b2 vaccination was well tolerated in lactating participants and was not associated with shortterm adverse effects in their breastfed infants. *Transient ipsilateral breast oedema following COVID-19 vaccination [54]* This was a case report of a 60-year-old female patient with an unknown medical history who experienced ipsilateral breast oedema 2 days after receiving her second booster dose of ModernaTx, Inc COVID-19 vaccination. The screening mammography revealed a new global asymmetry in the left axillary region comprised of trabecular thickening suggestive of oedema. Approximately 13 days later, the patient had repeat diagnostic studies which revealed that the breast findings had resolved included the lymphadenopathy. While ipsilateral lymphadenopathy following COVID-19 vaccination is a relatively common finding on mammography, breast ultrasound transient ipsilateral breast oedema is rare with only a few published case reports. Radiologists should be aware of this potential imaging appearance of the breast and axilla following COVID-19 vaccination given the imaging features of oedema such as trabecular thickening, skin thickening, and increased echogenicity can overlap with benign and malignant breast conditions such as mastitis and inflammatory breast cancer. *Mammographic Findings of Diffuse Axillary Tail Trabecular Thickening After the Second Booster of COVID-19 Vaccination [55]* This was a case report of a female patient of unknown age with a history of hypertension, diabetes mellitus, hyperlipidemia, and morbid obesity who had a diffuse axillary tail trabecular thickening of the left breast on a screening mammogram 4 days after receiving her second Pfizer booster COVID-19 vaccination. Of note, the patient had completed the primary COVID-19 vaccination series and received a first booster (specific vaccines were not provided). Concomitant medications included nifedipine, furosemide, spironolactone, and unspecified diabetic medications. Four weeks, the patient had a diagnostic mammography which revealed that the breast findings had resolved including lymphadenopathy. The authors stated that both breast cancer and mastitis may present similar findings; however, ipsilateral injection of COVID-19 vaccine/booster and spontaneous resolution on follow-up provided clues to the etiology. It has been hypothesized that proinflammatory conditions (e.g., hypertension, obesity, and diabetes) may predispose to axillary tail trabecular thickening on mammography post-COVID-19 vaccination. The authors concluded that it was important to recognize these findings in the context of COVID-19 vaccinations and boosters to avoid unnecessary biopsies that would strain the healthcare system and to avoid needless patient anxiety. Overall conclusion, there were few articles describing mastitis and/or breast swelling as mostly transient events occurring within 14 days following administration of mRNA vaccine against COVID-19. Most articles described events of mastitis and breast swelling as a secondary manifestation stemming from the presence of axillary lymphadenopathy following vaccination. Overall, the literature review did not provide

	sufficient evidence of a direct causal association between mastitis and breast swelling and elasomeran vaccine administration. However, the articles suggest the presence of axillary lymphadenopathy following mRNA COVID-19 vaccine administration (which is a labeled adverse event for elasomeran) may be the precursor that contributes to events of mastitis and/or breast swelling.
Discussion	The MAH conducted an extensive evaluation of two validated signals of mastitis and breast swelling triggered by a request from a health agency received on 05 Jul 2023, requesting to update the SPIKEVAX PI to include these two medical topics in the warning and precautions section. The signal evaluation included a cumulative review of all safety data available to the MAH, including non-clinical data, clinical trial information, post-marketing reports as well as cumulative review of the literature. The review was conducted using four MedDRA PTs (Mastitis, Breast swelling, Breast oedema, and Breast enlargement) with a DLP of 17 Jun 2023. Mastitis is a relatively common breast condition that can affect patients at any time but occurs mainly in women who are breastfeeding; it is defined as inflammation of the breast with or without infection. The most common signs and symptoms of mastitis are fever, chills, breast pain, breast swelling, and enlargement of axillary lymph nodes. There are three types of mastitis (e.g., lactational, non-lactational, non-infectious). Common causes of mastitis include bacterial infection, oral contraceptives, long-term steroids, and breast implants. Mastitis is usually diagnosed based on history and clinical findings; however, useful diagnostic tools include breast ultrasound and mammograms. If mastitis is left untreated, it may cause tissue destruction resulting in an abscess associated with bacteremia and sepsis. Breast oedema is fluid accumulation within breast tissue that may lead to visible swelling, increased breast parenchymal density, inflammation, breast pain, and sagging of the breast. This fluid buildup is largely a result of compromised outflow due to an obstruction or disruption of lymphatic vessels that drain the breast. Common causes of breast oedema include lymphatic obstruction, breast cancer, breast cancer treatment, congestive heart failure, mastitis, trauma, and concomitant medications. Breast oedema is usually diagnosed based on physical examination, mammograms, MRI, and plain radiology. The lymphatic system is a critical part of the immune system and consists of lymph fluid, vessels, and lymphoid tissues (e.g., lymph nodes, tonsils, spleen). In addition, lymph nodes play a key role in triggering the body's immune response to vaccines via development of lymphocytes (e.g., B cells and T cells). Figure-4 contains images of the lymphatic system in men and women as well as an image of the axillary nodes in a woman. At the injection site, there are several interactions between cells and the vaccine components that leads to the production of antibodies, effector cells, and memory cells. In the "draining lymph node" (lymph node downstream from the vaccination site), sites of B-cell development form in the B-cell zones of the lymph nodes. Immediately following vaccination, local innate cells release cytokines into the circulation to enable a coordinated response [56]. Information from the ModernaTx, Inc combined developmental and perinatal/postnatal reproductive toxicity study, there were no vaccine-related adverse effects on females, fetal development, or postnatal development. In non-clinical studies in rats, the highest mRNA concentrations were observed at the injection site followed by the popliteal and axillary lymph nodes, consistent with distribution via the lymphatic system. Also,

	repeat-dose toxicity studies in rats revealed macroscopic findings of enlarged lymph nodes and skin thickening at the injection site. Across ModernaTx, Inc sponsored clinical trials, there were 4 non-serious cases of mastitis. In one case, the TTO was 2 days after the second mRNA-1273 which resolved after 4 days without treatment. In the remaining 3 cases, the TTO was > 42 days which is suggestive of an alternative etiology. However, there was an imbalance between mRNA and placebo with regards to lymphadenopathy in both males and females as well as across all age groups. In the GSDB, the search criteria for mastitis yielded 117 cases (120 events) reported primarily with elasomeran (113 cases). Of the 120 events, 65 events were serious, and none had a fatal outcome. Most events involved females between the ages of 23-82 years old with most cases involving women of reproductive age. There was one case in a male patient; however, there were no reports of mastitis in the adolescent or pediatric groups. In 63.2% of the cases, the patients had risk factors and/or confounders for mastitis. In the cases that reported pregnancy status, there were an equal number of lactational and non-lactational mastitis events. In 27 cases, unilateral breast swelling was reported with 11 events occurring ipsilateral to the vaccination site. Most mastitis events (54.7%) occurred in conjunction with other reactogenicity events (i.e., lymphadenopathy, pyrexia, chills, influenza like illness). In addition, 7 mastitis cases were associated with menstrual disorders suggestive of physiological hormonal changes due to estrogen and progesterone. Most of events occurred after Doses 1 and 2 with a TTO that ranged from same day to 60 days (median of 2.5 days; mean of 6.1 days). Seventy-one (71) events reported an outcome of either "resolved", "resolving", or "resolved with sequelae". Three patients were hospitalized for mastitis; one patient was hospitalized for a breast abscess due to mastitis 30 days after receiving third dose of elasomeran; the remaining two cases contained limited information regarding the hospitalization. Three patients had a positive rechallenge (all 3 patients had confounding factors) and one patient had a negative rechallenge with a subsequent mRNA vaccine. The WHO causality assessments were "probable" (4), "possible" (16), "unassessable" (95), and "unlikely" (5). The search criteria and case definition for breast swelling, breast enlargement, and breast oedema, yielded 320 cases (90 serious, 230 non-serious) involving 323 events reported predominantly with elasomeran (315 cases). Most of the events involved females between the ages of 9 days old and 97 years old with most cases involving women of reproductive ages. There were 33 male patients and 3 patients < 18 years of age. In the 70.6% cases, the patients had risk factors and/or confounders for breast swelling events. Most of the events (88.1%) of breast swelling events occurred in conjunction with other reactogenicity events (i.e., lymphadenopathy, pyrexia, chills, influenza like illness). Most of events occurred after Doses 1 and 2 with a TTO that ranged from same day to 120 days (median of 2.0 days; mean of 7.6 days). One hundred events (100) reported an outcome of either "resolved", "resolving", or "resolved with sequelae". Two patients were hospitalized for breast swelling / breast oedema associated with a possible vaccination reaction and chest pain. One patient had a positive rechallenge and two patients had a negative rechallenge with subsequent mRNA-1273 vaccines. The WHO causality assessments were "probable" (8), "possible" (65), "unassessable" (238), and

	"unlikely" (11), and "not applicable" (1 event occurred with another vaccine). Due to a plausible temporal relationship between the events of mastitis and breast swelling/breast oedema/breast enlargement and 4 cases of positive rechallenge after subsequent vaccinations with mRNA-1273, a contributory role of elasomeran could not be excluded. However, there were 3 cases of a negative rechallenge after subsequent vaccinations. Based on the information provided in the cases, the events of mastitis, breast swelling, breast oedema, and breast enlargement are most likely secondary to post-vaccinal lymphadenopathy, which is a labeled event of elasomeran, triggered by the immune response to the vaccine. Since the immune response to the elasomeran vaccine is robust, the degree of lymphadenopathy is more pronounced [57]. The lymphadenopathy is typically observed in the axilla lymph nodes ipsilateral to the vaccination site. Due to the large scale COVID-19 vaccination campaign, there has been a marked increase in the identification of the lymphadenopathy associated with the vaccines [58]. Of note, vaccine-related lymphadenopathy has been reported with other vaccines (e.g., measles, anthrax, H1N1 influenza, human papilloma virus, Bacille Calmette-Guerin [BCG], smallpox) [59-61]. Furthermore, there were two cases of breast swelling that occurred after receiving Tozinameran and TicoVac vaccines; in both cases, the events occurred prior to receiving the first dose of elasomeran vaccine. For mastitis, the O/E analysis was only conducted in women due to lack of expected incidence in men. In overall mastitis (lactational and non-lactational), the number of observed cases were lower than expected cases for all age strata. However, the number of observed cases were higher than expected for two age groups (25-39 years old and 40-49 years old) in non-lactational mastitis. Of note, this did not meet the threshold for disproportionality. For breast oedema, the observed to expected analysis was not conducted due to lack of expected incidence of breast oedema. In VAERS, none of PTs for mastitis and breast swelling were disproportionately reported for both elasomeran and elasomeran/davesomeran. In EVDAS, there was disproportionately observed for mastitis and breast swelling PTs for elasomeran. Also, disproportionately was observed for breast swelling for elasomeran/imelasomeran, however, these data should be interpreted with caution due to the low counts. The literature review revealed a small number of articles describing mastitis and/or breast swelling in conjunction with lymphadenopathy as mostly transient events occurring within 14 days following administration of mRNA vaccine against COVID-19. Most articles described the events of mastitis and breast swelling as a secondary manifestation stemming from the presence of axillary lymphadenopathy following vaccination which were detected on imaging studies (e.g., mammogram, ultrasound).
Conclusion	Based on the analysis of all available safety, non-clinical studies, clinical trial, external database, and literature data as of 17 Jun 2023, the MAH considers that events of mastitis, breast oedema, breast swelling, and breast enlargement are most likely secondary to vaccination-related lymphadenopathy which is well-known ADRs observed with all vaccines. In addition, these events have been detected in mammograms and breast ultrasounds in post-COVID-19 vaccinated women. No new or emerging safety concerns were identified since lymphadenopathy is included as a very common ADRs in the SPIKEVAX PI and the current SPIKEVAX PI is considered to adequately reflect the safety profile of elasomeran. ModernaTx, Inc. concludes that no further action is warranted at this time and will continue to monitor events of

	Mastitis and Breast swelling using routine surveillance. The benefit-risk valuation remains positive.

Rapporteur assessment comment:

During the reporting interval, the MAH closed and refuted the signals "breast swelling" and "mastitis". The MAH clarifies that due to the clinical similarities between mastitis and breast swelling, the two signals were analysed together. On the 5th July 2023, the MAH received a request from the Therapeutic Goods Administration (TGA) [the Australian Medicines Agency] to update the PI with mastitis and breast swelling. These signals were raised as the TGA had observed disproportionate reporting of mastitis and breast swelling with elasomeran in its Adverse Event Management System (AEMS). Of note, neither "mastitis", "breast swelling", "breast oedema" nor "breast enlargement" are mentioned in the product information for elasomeran currently available on TGA's website.

Clinical trial data

Regarding clinical trial data, the MAH reports that no imbalance was observed in any of the four studies for the PTs "Mastitis," "Breast swelling," "Breast oedema," or "Breast enlargement". In these four studies, four participants in total experienced an event of interest, but the MAH reports that all four cases were considered as "not related to investigational product" by the investigator. Of note, in the clinical trial "mRNA-1273-P301", approximately 15,000 patients received elasomeran, but only two participants reported events relevant for this signal evaluation.

Mastitis cases from MAH's safety database

Cumulatively, the MAH identified 117 cases in its safety database that reported the PT "mastitis". Of note, three of these cases reported positive re-challenge. However, the MAH argues that in all these three cases there were confounding factors such as concurrent breastfeeding and history of mastitis. The MAH reports that, overall, most cases lacked essential information such as medical history, onset of the event, re-challenge information, examination results etc. Furthermore, the MAH reports that in 74 cases (63.2%) the patients had risk factors and/or confounders for mastitis. Of these risk factors, the assessor deems that the most noteworthy examples are: 29 cases with concurrent breastfeeding, 12 cases with concomitant medications associated with gynecomastia/breast swelling and three cases reporting previous mastitis. However, it is also noted that the MAH classifies concurrent lymphadenopathy which is reported in 18 cases as a risk factor/confounder. The Rapporteur disagrees with this notion. It is deemed likely that lymphadenopathy occurs concurrently with mastitis or breast swelling if it is caused by infection, lymphatic obstruction or similar. Furthermore, if the lymphadenopathy occurred prior to vaccination then it could suggest that the aetiology behind the mastitis/breast sweeling is not the vaccination but the same as what caused the lymphadenopathy in the first place. However, if the lymphadenopathy occurred at approximately the same time as the mastitis/breast swelling (and after vaccination), then the vaccination cannot be ruled out as the cause of both events unless a more obvious cause is identified. The MAH assessed the 120 events (in 117 cases) according to the WHO-UMC causality criteria as follows: "Probable" (4 events), "Possible" (17 events), "Unassessable" (94 events), and "Unlikely" (5 events).

Breast swelling cases from MAH's safety database

Cumulatively, the MAH identified 616 cases in its safety database that reported breast swelling, breast oedema or breast enlargement. Based on MAH's case definition, 320 cases involving 323 events were identified for focused medical review. The MAH argues that 241 (75.3%) of these cases were confounded by the patient's risk factors and/or confounders. However, the Rapporteur does not agree with the MAH on all the conditions listed as risk factors/confounders. Notably, the Rapporteur does not agree that

concurrent lymphadenopathy/lymphoedema/lymphadenitis as reported in 107 cases and concurrent peripheral oedema/fluid retention as reported in 50 cases may explain the breast swelling without further arguments. As also noted for the mastitis cases, these phenomena may be related to the same underlying condition which has also caused the breast swelling (e.g. lymphatic obstruction) and if they pre-existed before vaccination, then vaccination appears to be an unlikely cause of the breast swelling. However, if these conditions occurred at approximately the same time as the breast swelling and after vaccination, then the vaccination cannot be ruled out by default as the cause. Of the 323 events (in 320 cases) identified for focused medical review, the MAH assessed the events according to the WHO-UMC causality criteria as follows: "Probable" (8 events), "Possible" (65 events), "Unassessable" (238 events), "Unlikely" (11 events), and "Not applicable" (1 event occurred with another vaccine). The MAH notes that many cases lacked essential information such as medical history, concomitant medications, pregnancy status, onset of the event etc.

Rapporteur's comment on MAH's case causality assessment

Based on the assessors' review of several of the mastitis case narratives presented in PSUR appendix 3b and several of the breast swelling case narratives presented in PSUR appendix 4b, the MAH's case causality assessment appears rather conservative. It appears that several of the cases assessed as "possible" have only received this designation due to a plausible time-to-onset, as key information on risk factors/other potential causes are missing. Furthermore, in some of the cases assessed as "possible" by the MAH, potential other causes of the event are present (e.g. breastfeeding). The Rapporteur does not consider any of the mastitis cases (3) or the breast swelling cases (7) assessed as "probable" by the MAH to be of "probable" causality due to one or more of the following reasons: Prior history of mastitis, concurrent breastfeeding, sparse information about the event or sparse information about other potential causes.

Literature

The MAH's PubMed search retrieved 118 articles including six publications cited in the TGA's request letter to the MAH. The MAH concludes that none of these articles were suggestive of a causal association.

Regarding the publication by Hao et al., the Rapporteur agrees that it is not suggestive of a causal association, as the biopsy confirmed invasive lobular carcinoma of the breast is deemed to be a more likely explanation for the observed breast swelling.

Kayser et al. report a patient with bilateral breast swelling due to peri-implant seroma 10 days after her second COVID-19 mRNA vaccination and 5 years after breast implant surgery. The case is well-documented and relevant alternative explanations had been excluded. Furthermore, it is noted that a somewhat similar phenomenon is listed in the SmPC: Facial swelling has been observed in vaccine recipients with dermatological fillers. However, late presentation of breast implant seromas with no obvious cause have been reported in the literature (e.g. Chourmouzi et al.). One study found that late seroma occurred 18 to 44 months after surgery in 1.68% of the patients who had undergone breast implantation surgery (Mazzocchi et al.). Therefore, the Rapporteur deems that the single well-documented case report by Kayser et al. does not warrant further action at present.

Locklin et al. presents three cases of abnormal mammographic findings shortly after COVID-19 vaccination. However, as the observed abnormalities are primarily radiographic, it is not entirely clear whether the abnormalities could have started prior to vaccination.

In Low et al., three of 88 (3.4%) participants experienced mastitis and one (1.1%) participant experienced breast engorgement after BNT162b2 vaccination (Pfizer/BioNTech). All study participants were breastfeeding, which the Rapporteur deems as a more likely explanation for the observed mastitis, as the incidence in the study population is similar to the global estimate of lactational mastitis referenced

in the publication (2.5% to 20%). Furthermore, the publication does not provide individual case details suggestive of vaccination as a more likely cause.

In the case report by McGrath et al., a woman with a palpable fullness and tenderness in her left axilla had a screening mammography undertaken, which demonstrated asymmetry in the left axillary region comprised of trabecular thickening. Ultrasound showed prominent axillary lymph nodes on the same side. Mammographic and sonographic findings including lymphadenopathy had resolved at the follow-up evaluation 13 days later.

In the case report by Adam et al., the screening mammography of an asymptomatic patient showed diffuse axillary tail trabecular thickening of the left breast four days after COVID-19 vaccination. At re-evaluation four weeks later, the axillary tail trabecular thickening had resolved.

Rapporteur's comment on literature presented by the MAH

The Rapporteur would like to highlight the publications by Locklin et al., McGrath et al. and Adam et al., as they presented case reports of abnormal mammograms shortly after vaccination which could be of clinical relevance, in the event that the association is causal. In all five cases presented in these three publications, the mammograms showed "trabecular thickening" in the part of the breast that lies in close relation to the axilla. However, for the following reasons and considering the enormous exposure of elasomeran and the frequent use of mammograms, the Rapporteur deems that further evaluation of this topic is not currently warranted:

- The MAH has only received five case reports cumulatively reporting the PT "mammogram abnormal" (according to PSUR appendix 3 "Cumulative and Interval Summary Tabulation From Post-Marketing Data Sources").
- Only two case reports reporting the PT "mammogram abnormal" are available in Eudravigilance and these are not considered relevant for this topic as the abnormal mammograms in both cases appear to be related to breast cancer.
- The number of relevant publications on PubMed appears limited and the vast majority of these appears to describe lymphadenopathy rather than abnormal findings in the breast tissue proper.

Rapporteur's conclusion

None of the cases assessed as "probable" by the MAH are considered well-documented enough to provide evidence of causal association between elasomeran vaccination and mastitis/breast swelling. From the cases assessed as "possible" by the MAH, the assessors chose a random sample for review - none of these reviewed "possible" cases provided evidence of a causal association either. Similarly, neither the clinical trial data nor the publications presented by the MAH are deemed to provide evidence of a causal association between mastitis and/or breast swelling and elasomeran exposure. The MAH argues that the events of mastitis, breast swelling, breast oedema, and breast enlargement are most likely secondary to post-vaccinal lymphadenopathy and it is implied that because lymphadenopathy is a labeled event, a risk of the aforementioned adverse events is also reflected by the SmPC. The Rapporteur disagrees with this notion. However, as the currently available evidence does not support the existence of a causal association, no regulatory action is considered warranted and the topic should be monitored via routine pharmacovigilance.

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2.2.3. Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the US

Table 22: Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the United States

Signal evaluation criteria	Summary
Source	The Signal Management Team (SMT) identified an increase in the number of reports from the United States only related to medication errors and/or overfilling of the SDV of the Moderna COVID-19 Vaccine (2023-2024 Formula) for children 6 months to 11 years of age. In some cases, this overfilling has led to overdosing, without concerning adverse events reported to date. Regarding safety, the issue is the potential for overdose (as much as 0.65 mL instead of 0.25 mL) if the total volume is administered to a child aged 6 months to 11 yrs. During the routine signal detection reviews, the review of medication error reports for mRNA-1273.815 on 12 Oct 2023, the signaling team flagged the issue of overfill for discussion at SMT meeting and during the SMT, this topic was escalated to discuss with product quality compliance team and perform a detailed analysis.
Background	Moderna COVID-19 Vaccine (2023-2024 Formula) was developed by ModernaTx, Inc, as a monovalent vaccine encoding the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5. The Moderna COVID-19 Vaccine is made in the same way as the

	Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent, but it encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). Moderna COVID-19 Vaccine (2023-2024 Formula) is authorized by the FDA, under an EUA for ages 6 months through 11 years is supplied in SDV. SPIKEVAX (2023-2024) Formula approved for ages 12 years and older is supplied in SDV and single dose pre-filled syringes. Overdose in children in the context of overfill of the SDV mRNA-1273.815 indicated for individuals 6 months through 11 years of age.
Methodology	The assessment of Overdose in children in the context of overfill of the SDV- mRNA-1273.815 indicated for individuals 6 months through 11 years of age was performed using the company's GSDB. The methods of evaluation used in the analysed data is described below. There is no clinical data related to use of the mRNA-1273.815 vaccines at the various doses for individuals 6 months through 11 years of age: Review of data from VAERS IDs provided by FDA: A cumulative search in VAERS, through 27 Oct 2023 using the family names mRNA-1273.815 was conducted with the following search strategies: • Product name: Andusomeran • Family name: mRNA-1273.815 • MedDRA PT: Incorrect dose administered. • Date: 27 Oct 2023 (FAD cut-off date was 30 Oct 2023). Review of the Pharmacovigilance Database: A cumulative search in GSDB, through 29 Oct 2023 using the family names mRNA-1273.815 was conducted with the following search strategies: • Product name: Andusomeran • Family name: mRNA-1273.815 • MedDRA PTs: Accidental overdose, Overdose, Circumstance or information capable of leading to medication error, Intercepted medication error, Product packaging quantity issue, Product packaging issue, Incorrect dose administered, Incorrect dosage administered, Extra dose administered. • Cut-off date: 29 Oct 2023. Literature search review: General review of the PubMed literature database as of 27 Oct 2023 was performed
Results	*VAERS Database Review:* There were 237 VAERS reports ID numbers that involved the PT "incorrect dose administered" in the information provided by the FDA on 03 Nov 2023. Ten reports were not yet available in CDC Wonder as of the DLP 27 Oct 2023. Overall, review of these 227 reports of medication error with PT 'Incorrect dose administered' showed 5 reports with additional adverse events. All these 5 reports were non-serious. Here are the details of these five (5) VAERS reports: VAERS ID [redacted] This non-serious report, involved a female age 8 years who was "on the tail end of antibiotics for sinusitis." After concurrent vaccination for COVID-19

	and influenza, it was reported that the child was "dizzy when she showered" and that it "hurt to breathe", which was reported as resolving. Patient was afebrile with pulse oximetry 98-100%. Also, it was reported that she had 1" injection site reactions to both vaccines." The information was reported after an office visit. VAERS ID [redacted]: This non-serious report, involved a male patient with a medical history of recurrent otitis media and acute bilateral bacterial conjunctivitis, who developed otitis media again 2 days after vaccination. Office visit. No additional information was provided. VAERS ID [redacted] This non-serious report, is from a consumer that involves a 15-month-old male who the same day after receiving 0.5 mL of the vaccine experienced pyrexia and swelling at the injection site. He was administered paracetamol, and the outcome of the events was reported as not resolved. VAERS ID[redacted]: This non-serious report shows redness/swelling/fatigue; events resolved, involved standard vaccine reactogenicity. VAERS ID [redacted]: This non-serious report shows pain and fatigue, involved standard vaccine reactogenicity. <u>Review of Data from Product Quality Compliance (PQC) Team</u> Product Quality complaints team have identified 134 complaints related to overfill of the SDV, including one complaint involving 200 patients. All these reports from PQC are sent to case processing team and individual case safety report are created as appropriate. All these ICSRs are reviewed within the ModernaTx, Inc Pharmacovigilance Database Review. <u>Review of the Pharmacovigilance Database:</u> Review of the GSDB with the MedDRA PTs identified 252 reports. All were spontaneously reported (no regulatory agency, literature, or solicited reports). These 252 reports were individually reviewed to identify a true case of medication error. The review was conducted to verify if there was any incidence of overfill in these cases and any such case was marked as true medication error case. The review of these 252 reports, identified 127 reports of true overfill medication error from united states. Of these 127 reports, one was a consumer report, and the rest all were from healthcare professionals. Overall, review of these 128 medication error reports identified one clinical adverse event report ([redacted] that noted Pyrexia (non-serious). Summary of this case is provided below. <u>*Summary of case with Additional Adverse Event:*</u> [redacted] (WWID# [redacted]: This spontaneous report was submitted by health care professional concerning infants (7 to 15 months) of unknown age and gender. The infants received mRNA-1273.815 (andusomeran; batch no. AU5509B), on an unknown date for COVID-19 prophylaxis. No relevant concomitant medications or medical history were reported. On an unknown date they experienced Pyrexia (*fever*), also had medication errors such as, Product Packaging Quantity Issue (*there is significant overfill in the single dose vials*) and Accidental Overdose (*HCP states that a few patients [maybe 8 or 9] received over the 0.25 mL recommended dosage*). The case report was considered invalid due to involvement of multiple patients without identifiers. The reporter did not provide any

	causality assessments and no treatment medication were reported. Outcome of these events were unknown. Literature search review: General review of the PubMed literature database as of 27 Oct 2023, identified one article that reported an extensive and comprehensive VAERS review of excess dose of vaccination by Moro et al. 2019. Article Summary: The study examined the VAERS for reports of excess vaccine doses administered from 2007-2018. Out of 5067 reports, 76.9% did not describe an adverse health event (AHE). The most common vaccines reported were trivalent inactivated influenza, varicella, hepatitis A, and measles, mumps, rubella, varicella. The most common AHEs reported were pyrexia, injection site erythema, injection site pain, and headache. Of the 5067 reports, 3898 (76.9%) did not describe an AE or any sign or symptom and 1169 reported excess dose, and a clinical review of these 1,169 reports, determined that 64 cases involved an excess vaccine dose, but no specific pattern of adverse events was found. The most common reactions reported were local or systemic reactions, with no increased risk of adverse events or birth outcomes found in a study of women who received Tdap during pregnancy. In conclusion, the study found that the administration of excess doses of vaccines, did not result in any new or unexpected safety issues. No specific pattern of adverse events was found in cases involving an excess vaccine dose. This suggests that administering excess doses of vaccines does not generally lead to serious health risks. However, the study highlights the importance of careful record-keeping and adherence to vaccine recommendations to avoid administration of unnecessary excess doses [67].
Discussion	This safety signal issue is restricted to the US. The MAH conducted a signal evaluation of the potential signal of Overdose in children in the context of overfill of the single dose vial. The signal evaluation included a cumulative review of the MAH safety database with a DLP of 29 Oct 2023 and VAERS data as of 27 Oct 2023. Analysis of the MAH global safety database related to overfill of vials as of 29 Oct 2023, retrieved 128 reports. All but one was reported from HCPs. All reports were non-serious, and mainly concerned individuals aged 6 months to 11 years. Apart from one overdose report describing pyrexia, none of the remaining overdose reports indicated any associated clinical adverse events. Additionally, the Product Quality complaints team identified 134 complaints related to overfill of the SDV, including one complaint involving 200 patients; these complaints led to the creation of individual case safety reports if the information in the complaint merited this, and such reports were included in our analysis. In summary, the review of the safety information received as of 29 Oct 2023, showing that events of medication errors associated with the risk of overdose related to pediatric single dose vials indicated for individuals 6 months through 11 years of age distributed in the US, did not find that these medication errors have led to clinical harm in any individual. This clinical finding agrees with a large retrospective 2007-2017 CDC/FDA

	VAERS study that concluded "More than three-fourths of reports of an excess dose of vaccine did not describe an AHE. Among reports where an AHE event was reported, we did not observe any unexpected conditions or clustering of AEs [67]" The MAH considered Overdose in children aged 6 months to 11 years in the context of overfill of SDV in the US as an important potential risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified, it is considered a potential risk.
Conclusion	This safety signal issue is restricted to the US. Based on the findings of the safety assessment evaluation regarding Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age, the MAH considered that this was an Important Potential Risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified, it is considered a potential risk. This topic was classified as Priority 2 High Priority Safety Issue: Issues which may impact the product's benefit / risk profile, but which do not require urgent action. The MAH decided on the following risk minimization actions: • Update of the current Fact Sheet, to clarify the dosage and administration instructions to providers. • Update of corresponding websites to clarify dosage and administration information. • Communication of the findings to the appropriate health authorities, including CDC • Distribution of a DHCP letter in the US only. In addition, the MAH is closely monitoring overdose in children in the context of overfill of the SDV and associated harms as part of signal detection activities and pharmacovigilance.

Rapporteur assessment comment:

The signal "Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the US" was closed and substantiated during the reporting period. According to the MAH, this safety signal issue is restricted to the US.

In order to investigate this, the assessors searched Eudravigilance for relevant case reports using the substance name: "elasomeran", "elasomeran multivalent NOS", "elasomeran NOS", "elasomeran/davesomeran", "elasomeran/imelasomeran" and "andusomeran" and the PTs "overdose", "accidental overdose", "circumstance or information capable of leading to medication error", "intercepted medication error", "product packaging quantity issue", "product packaging issue", "incorrect dose administered", "incorrect dosage administered" and "extra dose administered". This search yielded only one case report, where the patient's age was known and was between 6 months and 11 years. The case was from the US. Based on this, the Rapporteur agrees that it appears that the safety issue is restricted to the US. Furthermore, it is noted that the EU SmPC states that single-dose vials of 0.5 ml should not be used to deliver a partial dose of 0.25 ml.

The MAH Signal Management Team identified an increase in the number of reports from the United States related to medication errors and/or overfilling of the Single dose vial (SDV) of the Moderna COVID-19

Vaccine (2023-2024 Formula) for children 6 months to 11 years of age. In some cases, this overfilling has led to overdosing (as much as 0.65 mL instead of 0.25 mL).

The MAH global safety database yielded 127 reports associated with overfill of vials, originating from the US. Almost all reports were submitted by healthcare professionals, and all were nonserious in nature. Review of these 127 medication error reports for clinical adverse events identified only one report ([redacted]) which noted an AE of Pyrexia (non-serious), which is labeled and standard reactogenicity.

The MAH classified this issue as an Important Potential Risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified, it is considered a potential risk.

In response to these findings, the MAH has adopted several risk minimization actions, including updating the Fact Sheet and relevant websites to provide clearer dosage and administration information, communicating the findings to appropriate health authorities, including the CDC, and distributing a DHCP letter in the US only.

The MAH will continue to closely monitor overdose in children in the context of overfill of the single dose vial and associated potential harms as part of ongoing pharmacovigilance and signal detection activities.

This is endorsed. The signal should be considered closed and no further action is currently warranted.

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Evaluation of risks

2.3.1.1. Important identified risks

2.3.1.1.1. Anaphylaxis (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the known identified risk of Anaphylaxis, has not identified any additional clinically relevant new safety information for this topic. The characterization of this important risk as described in PSUR Section 16.4, remains valid.

Rapporteur assessment comment:

The MAH did not identify any new and significant safety information changing the characterisation of Anaphylaxis (safety concern in PSUR only).

In future PSURs the MAH is requested to present new information evaluated during the reporting interval related to anaphylaxis, in PSUR section 16.3.1, in the same format and detail level as for the remaining safety concerns.

2.3.1.1.2. Myocarditis and Pericarditis

Evaluation of information received during the PBRER reporting interval relating to the known important identified risks of myocarditis and pericarditis, has not identified any additional clinically relevant new safety information for these topics. The characterization of these important risks as described in the current RMP and in PSUR Section 16.4, remains valid.

ModernaTx, Inc. Supplemental Follow-up Questionnaire for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of a marketed Moderna vaccine targeting SARS-CoV-2

During the reporting period of this PBRER a total of 165 follow-up questionnaires (FUQs) for collecting supplementary information on cases of potential/confirmed Myocarditis/Pericarditis were sent by the MAH to the reporters, of which 0 FUQ responses were received. The response rate to this questionnaire was 0%. Cumulatively, a total of 730 Myocarditis/ Pericarditis FUQs have been sent to reporters, of which only 25 FUQs were received, for a response rate of 3%.

This very low response rate may be an indicator of the reporter's difficulties to address all the requested follow-up information. The length of the questionnaire and the redundancy of certain information already provided by the reporter may also discourage reporting. In addition, reporters may not understand the importance of documenting cases to inform and further characterize these already known risks.

Since its implementation in Jul 2021, the cumulative review of FUQs experience, shows an extremely low reporting rate. Hence, ModernaTx, Inc. concludes that the current format of the FUQ included in Annex 4 of the SPIKEVAX RMP is not adequate. In order to improve data collection for these 2 important identified risks, ModernaTx, Inc. proposes an updated version of the FUQ streamlining the information requested in the form and avoiding duplication of the information related to patients' demographic.

The proposed updated questionnaire is included in Annex 4 of the updated EU-RMP version 8.3 submitted with this PBRER.

Table 23: Myocarditis and Pericarditis

Important Identified Risk	**Myocarditis and Pericarditis**
Source of new information	• ModernaTX, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 120 o New and Significant Safety Information: None (0).
Background	An association between myocarditis and pericarditis and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events, particularly among adolescent and young-adult males within 14 days after Dose 2.
Methods	Cases are classified using both the BC Myocarditis/ Pericarditis case definition [68,69], and the CDC working case definition [70] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	It is important to note a considerable decrease in the number of reported cases of myocarditis/pericarditis during this reporting period. Many of the case reports received from consumers lack important information including medical history, concomitant medications, as well as dose number and TTO; information that is critical for medical review and informed causality assessment. *Myocarditis and Pericarditis Cases Involving elasomeran* During the review period, the MAH received 63 serious cases (64 events) of myocarditis and pericarditis with all cases considered serious cases. There were 3

	cases reporting a fatal outcome (See Appendix 12.11). There were 46 medically confirmed cases involving elasomeran. A total of 41 (65.1%) cases involved males and 15 cases (23.8%) involved females; 7 cases (11.1%) were missing gender information. The mean age of the patients was 37.7 (SD:15.4), with a median 35.0 years (range 14.0 to 87.0 years); 12 cases were missing age data. A total of 21 events (32.8%) were reported as "Recovered/Recovering." Limitations exist in capturing follow-up information about individual events from spontaneous reports, such that the category of "Not recovered/Not resolved" likely represents an over-estimate for this category of outcome, as the assessment is based on the reporting date rather than a prescribed interval following symptom onset (i.e., it should not be interpreted as representing the entire episode of care). According to the BC case definition for myocarditis and pericarditis, 5 cases met Level 1 definition, 13 cases met Level 2 definition, 3 cases met Level 3 definition, 39 cases met Level 4 definition, and 3 cases met Level 5 definition. Appendix 12.11. According to the CDC working definition [70] 2 cases were classified as "Confirmed"; 18 cases were classified as "Probable"; 40 cases were classified as "Unassessable"; and 3 cases were considered "Not a case" of myocarditis or pericarditis. (See Appendix 12.11). According to the WHO causality assessment, there was 1 case considered "Probable"; 18 cases considered "Possible"; 40 cases considered "Unassessable", 1 case considered "Unlikely" related to the vaccine, and 3 cases were not assessed as they were not considered a case of myocarditis or pericarditis. (Appendix 12.11). The 3 cases with fatal outcomes are summarized below: [redacted]: *(WWID:* [redacted] This is a spontaneous case concerning a 50-year-old female patient, with no medical history reported (however autopsy findings confirmed chronic conditions), received elasomeran vaccine (first dose). One day after vaccination the patient complained of chest pain and nausea, vomited multiple times. The patient was taken to the hospital. She was treated with amiodarone and epinephrine for atrial fibrillation. The patient suffered from a circulatory arrest. Resuscitation measures failed and she died. The autopsy was performed. The reported cause of death was acute left heart failure/circulatory arrest with acute blocked lung with serious alveolar pulmonary edema. On autopsy, myocarditis was suspected; additional findings revealed past liver injury, chronic pancreatitis, emphysema (chronic nicotine use), chronic bronchitis, moderate to serious condensate pneumopathy, arteriosclerosis and shocked kidney were also determined. This case confounded by medical history (per autopsy): Moderate biventricular myocardial hypertrophy, arteriosclerosis coronary artery, chronic bronchitis, emphysema, liver injury, chronic pancreatitis. This case was considered Level 1 according to BC case definition, probable according to CDC case definition and possible case of myocarditis according to WHO causality assessment. [redacted] *(WWID:* [redacted] This is a spontaneous fatal case concerning a male patient of an unknown age with no reported medical history. It was reported that the patient fainted and died approximately 20 days after receiving a dose of elasomeran vaccine, received as the

	first dose of COVID-19 vaccination schedule. Myocarditis was reported as the cause of death, and it is unknown if an autopsy was performed. No further information was disclosed. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment. [redacted] *(WWID:* [redacted]*):* This is a fatal report from regulatory authority reported by consumer (subsequently medically confirmed) on a 30-year-old male patient with the relevant medical history of COVID-19, extrasystoles and heart pounding, who experienced loss of consciousness, circulatory collapse, cardiac arrest, unexpected events of hypersensitivity, palpitations (2 episodes), malaise, nausea, chest discomfort, anxiety, and dizziness, which occurred 18-23 days after the first dose of elasomeran vaccine. Patient died 23 days after vaccination and causes of death were reported as acute circulatory failure and myocarditis. An autopsy was performed, but no results were provided. No further clinical information was provided. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment. *Myocarditis and Pericarditis Cases involving elasomeran/imelasomeran* During the review period, the MAH received 13 serious cases (13 events) of myocarditis and pericarditis involving elasomeran/imelasomeran. All cases were considered serious, and 6 cases were medically confirmed. There was 1 case with a fatal outcome. A total of 8 cases (61.5%) involved males and 3 cases (23.1%) involved females; 2 cases (15.4 %) was missing gender information. The mean age of the patients was 64.2 (SD: 19.7), with a median 63.0 years (range 26.0 to 90.0 years); 4 cases were missing age data. There were 3 events (23.1%) reporting an outcome of "Recovered/ Recovering." According to the BC case definition for myocarditis and pericarditis, 1 case met Level 2 definition, 2 cases met Level 3 definition, and 10 cases met Level 4 definition. According to the CDC working definition (Gargano 2021), 1 case was considered "Acute pericarditis", 2 cases were considered "Probable"; and 10 cases were considered "Unassessable." According to the WHO causality assessment, there were 2 cases considered "Possible", 8 cases considered "Unassessable", and 3 cases considered "Unlikely" related to the vaccine. The one case with fatal outcomes is summarized below: [redacted] *(WWID:* [redacted]*):* This is a spontaneous fatal case concerning a 26-year-old male patient with medical history of bradycardia, syncope, and suicidal ideation, who experienced dizziness and myocarditis 2 days after the 4th dose with elasomeran/imelasomeran vaccine. Patient died 3 days after vaccine was given. It is unknown if an autopsy was performed. No further details were provided for medical review. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment.

	Myocarditis and Pericarditis Cases involving elasomeran/davesomeran During the review period, the MAH received 2 serious medically confirmed cases (2 events) of myocarditis and pericarditis involving elasomeran/imelasomeran. There was 1 case with a fatal outcome. Both cases (100%) involved males, the mean age of the patients was 37.0 (SD: 12.7), with a median 37.0 years (range 28.0 to 46.0 years). One event was reported as "Fatal", and the other event was reported as "Recovered/Recovering". According to the BC case definition for myocarditis and pericarditis in patients, 1 case met Level 3 definition, and 1 case met Level 4 definition. According to the CDC working definition [70], 1 case was considered "Probable" and the other case was considered "Unassessable." According to the WHO causality assessment, 1 case was considered "Possible", and the other case was considered "Unassessable." The one case with fatal outcomes is summarized below: [redacted] *(WWID:* [redacted]*):* This case was received from Regulatory Authority: A 46-year-old male with medical history of hyperlipidemia and hepatitis received elasomeran/davesomeran vaccine, third dose. Approximately 25 days after the third dose of vaccine, the patient experienced syncope and heart arrest. After resuscitation measures the heart function was recovered, however the patient remained in coma. Acute heart failure and multiple organ failure followed. The reported cause of death was Myocarditis. No information disclosed about diagnostic tests performed or treatments received. There was no autopsy performed. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment. *Myocarditis and Pericarditis Cases involving andusomeran* It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant andusomeran. Since its approval, the MAH has received 6 serious cases (7 events) of myocarditis and pericarditis involving andusomeran. All cases were considered serious, and 4 cases were medically confirmed. There were no cases with a fatal outcome. A total of 4 cases (66.7%) involved males and 2 cases (33.3%) involved females. The mean age of the patients was 49.5 (SD: 33.2), with a median 48.5 years (range 13.0 to 91.0 years). There were 5 events (71.5%) reporting an outcome of "Recovered/ Recovering." According to the BC case definition for myocarditis and pericarditis in patients, 1 case met Level 1 definition, 1 case met Level 2 definition, 3 cases met Level 4 definition, and 1 case met Level 5 definition. According to the CDC working definition [70], 2 cases were considered "Probable", 3 cases were considered "Unassessable" and 1 case was considered "Not a case" of myocarditis.

	According to the WHO causality assessment, 1 case was considered "Possible", 3 cases were considered "Unassessable", 1 case was considered "Unlikely", and 1 case was not assessed as it was not considered a case of myocarditis or pericarditis. *Myocarditis and Pericarditis Cases Involving SPIKEVAX (NOS)* It is important to note that during the reporting period for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran). During the review period, the MAH received 10 serious cases (10 events) of myocarditis and pericarditis under the SPIKEVAX (NOS) classification. All cases were considered serious, and 4 cases were medically confirmed. There were no cases with a fatal outcome. A total of 6 cases (60.0%) involved males and 3 cases (30.0%) involved females; 1 case (10.0%) was missing gender information. The mean age of the patients was 43.6 (SD: 24.8), with a median 27.0 years (range 25.0 to 78.0 years); 4 cases were missing gender information. There were 2 events (20%) reporting an outcome of "Recovered/ Resolved." According to the BC case definition for myocarditis and pericarditis in patients, 1 case met Level 1 definition, and 9 cases met Level 4 definition. According to the CDC working definition [75], 1 case was considered "Confirmed", and 9 cases were considered "Unassessable." According to the WHO causality assessment, 1 case was considered "Possible", 8 cases were considered "Unassessable", and 1 case was considered "Unlikely" a case myocarditis or pericarditis. See PSUR Appendix 12.11 for additional information.
Discussion	A review of the data received during this reporting period showed no meaningful changes in the characteristics of the events of myocarditis and pericarditis reported after vaccination with marketed Moderna vaccines targeting SARS-CoV-2. To date, the safety profile of those reports of myocarditis and pericarditis after vaccination does not differ from the known safety profile of all marketed Moderna vaccines targeting SARS-CoV-2. Please refer to PSUR Section 8 for results from the PASS study on the evaluation of myocarditis and pericarditis. Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of myocarditis and pericarditis to be consistent with the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2 and the benefits of vaccination far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. A review of the data received cumulatively and during this reporting period showed a continuous decreasing trend in the number of reported cases and that events of myocarditis and pericarditis continue to primarily

	occur in young males shortly after the second dose of the vaccine with a reported TTO less than 7 days. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including PASS to further characterize them. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Myocarditis and Pericarditis

The MAH has provided a review for myocarditis and pericarditis for the latest review period from 18 June 2023 to 17 December 2023 comprising cases and literature.

Source of information

Literature: A focused literature search has been performed and 120 papers were retrieved; the MAH did not identify any new and significant information.

The Global Safety Database (GSDB) was searched for all cases of myocarditis and/or pericarditis following vaccination against COVID-19 with elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran. Data from the review period are presented.

The MAH evaluated 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

For the review period 18 June 2023 to 17 December 2023, a total of 84 cases (86 events) of myocarditis and/or pericarditis were identified.

Of these, 63 cases (64) were following vaccination with the monovalent elasomeran vaccine, 13 cases (13 events) following the bivalent vaccine elasomeran/imelasomeran, 2 cases (2 events) were following the bivalent elasomeran/davesomeran vaccine, and 6 cases (7 events) following andusomeran. All cases were considered serious, and 5 had fatal outcome. Of those with a fatal outcome, 3 were following elasomeran, 1 following elasomeran/imelasomeran, 1 following elasomeran/davesomeran, and none following andusomeran. All fatal cases were presented.

Gender was known in 64/84 cases (71.2%), and the distribution by gender was 55 (65.5%) males, 20 (23.8%) females, while gender was not reported for 9 (10.7%). The age range was 13 to 91 years.

Dose number and TTO was presented if possible for all fatal cases. There is sufficient cumulative data regarding dosage and TTO; therefore, it is fully acknowledged that these details are not further specified here.

Conclusion

The MAH has provided a review for the latest period from 18 June 2023 to 17 December 2023. Myocarditis and pericarditis are well-described and known rare side effects to the vaccine. The information retrieved in this period does not give rise to new concern regarding the risk for myocarditis and/or pericarditis following vaccination with Spikevax (elasomeran-containing vaccines and andusomeran).

2.3.1.2. Important potential risks

2.3.1.2.1. IgA Nephropathy (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the known important potential risks of IgA Nephropathy for marketed Moderna vaccines targeting SARS-CoV-2 has not identified any additional clinically relevant new safety information for this topic. The characterization of this important risk as described in Section 16.4, remains valid. IgA Nephropathy is monitored in accordance with a request from a Health Authority.

Table 24: IgA Nephropathy (Safety concern in PBRER only)

Important Potential Risk	**IgA Nephropathy**

Source of New Information	• ModernaTx, Inc. GSDB
	• Literature Sources
	  o Search Criteria Applied: Appendix 13.4
	  o Retrieved: 129
	  o New and Significant Safety Information: None (0).

Background	Following review of PBRER#4, a Health Authority requested the following information on IgAN: • *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 or bivalent. Thus, the MAH should maintain IgAN as an important potential risk in the future PBRERs. In the next PBRER, it is therefore expected that the MAH will present new information on IgA nephropathy and risk characterization in PBRER section 16.3 and 16.4, respectively.*
Methods	Neither the BC nor CDC has established a case definition for IgA nephropathy. The MAH has 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. The Company case causality assessment is provided utilizing the WHO-UMC standard causality categories and criteria.
Results	Refer to Appendix 12.12 for information about the medical topic. During the review period, the MAH received 18 reports (19 events) that had PTs within the HLT of Glomerulonephritis and Nephrotic Syndrome (note: the following case [redacted] was captured for elasomeran and for those reports under the SPIKEVAX [NOS]) classification. Of these 18 cases, 15 cases involved elasomeran, and 1 case each involved elasomeran/imelasomeran, elasomeran/davesomeran, and SPIKEVAX (NOS). There were no reports involving andusomeran.

	All the 18 reports were medically reviewed. Four cases were classified as confirmed IgA nephropathy; the remaining 14 cases involved other types of nephropathy or other conditions (e.g., glomerulonephritis minimal lesion, glomerulonephritis membranous, nephrotic syndrome, glomerulonephritis rapidly progressive, and C3 glomerulopathy). Out of the 4 cases involving IgA nephropathy, no cases involved fatal outcomes. All 4 cases involved elasomeran and considered were serious. Three (3) cases were new onset (de novo) of IgA nephropathy, and 1 case was considered IgA nephropathy flares because the patient was reported to have experienced exacerbation of IgA nephropathy that had been diagnosed prior to vaccination. Equal numbers of cases in females (2 cases; 50.0%) and males (2 cases; 50.0%) were reported. The mean age was 20.8 years (SD: 1.7) and median age was 20.5 years (range: 19.0 to 23.0 years). Time to onset was missing in 3 cases and in 1 case TTO was on Day-1.
Discussion	During the reporting period in the MAH's GSDB, there were 4 cases of IgA nephropathy that were identified through medical review, all these 4 cases involved elasomeran. Of the 4 cases of IgA nephropathy, 3 cases involved new onset (de novo) IgA nephropathy, of these 3 cases WHO causality assessment was considered possible for 2 due to positive biopsy, but important information was missing including medical history. Additionally for one of the cases, IgAN was detected within 24 hours of vaccination with elasomeran which is not biologically plausible. The other report is also confounded by previous administration of Comirnaty 6 months before vaccination with a booster dose of elasomeran. The third case was considered Unlikely as the event occurred almost 3 months post vaccine with no biopsy. The fourth case was reported as IgA nephropathy flare which was assessed Possible according to WHO causality assessment due to temporal relationship as the biopsy showed chronic GN and the patient presented in chronic RF. No new patterns were observed with regard to IgA nephropathy-related data for marketed Moderna vaccines targeting SARS-CoV-2. Renal patients are at increased risk of serious illness and death due to COVID-19 disease; thus, vaccination is of great benefit to them. Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of IgA nephropathy to be consistent with the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The benefits for vaccination far outweigh any possible vaccine-associated risks.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2. Information presented in those reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to monitor eventsfor IgA Nephropathy using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

During the reporting period there were four cases of IgA nephropathy identified through medical review by the MAH. All four cases involved Elasomeran and were considered serious. No cases involved fatal outcomes.

Three cases were new onset (de novo) of IgA nephropathy, and one case was considered IgA nephropathy flare. According to the medical review presented in PSUR appendix 12.12a and b, three of the four cases were assessed as WHO-UMC "Possible", while none were considered of "Probable" or "Certain" causality. One case was considered WHO-UMC "unlikely".

This is endorsed. From MAH's evaluation of cases reported in appendix 12.12a and b, the rapporteur did not identify new and significant safety information.

2.3.1.3. Missing information

2.3.1.3.1. Use in pregnancy

Evaluation of information received during the PBRER reporting interval relating to missing information of marketed Moderna vaccines targeting SARS-CoV-2 of "Use in pregnancy" has not identified any additional clinically relevant new safety information for this topic. The characterization of these important risks as described in the approved RMP as of the DLP of this PBRER and in PSUR Section 16.4, remains valid.

Table 25: Use in pregnancy

Missing Information	**Use in pregnancy**
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 563 o New and Significant Safety Information: None (0).
Background	Use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy is an area of missing information in the RMP; no clinical trials 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. The use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy is embedded in clinical practice and included in relevant health guidelines. No specific safety concerns for pregnancy have been identified.
Methods	Refer to Appendix 12.13 for Methods of Evaluation
Results	Refer to Appendix 12.13 for additional information. **Overview of Pregnancy Cases Who Received elasomeran** It is important to note that the MAH terminated the distribution of Elasomeran vaccine worldwide after Jun 2023. Therefore, during this review period, there was a considerable decrease in the number of reported pregnancy cases for elasomeran vaccine.

	During the review period, the MAH received 53 pregnancy cases (246 events) with 42 serious cases (115 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. One (1) case reported a fatal outcome, and a total of 26 cases were medically confirmed. During the review period, a higher proportion (79.2%) of cases were reported as "serious" compared to the cumulative period (35.2%). Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" in addition to known reactogenicity events and are reported as "serious" cases; See below in the Serious and Fatal Cases and Serious Pregnancy-related events-elasomeran 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 all events as serious in a given serious case. Most (22; 48.9%) pregnancy-specific cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been seen in previous review periods. During the review period, the most frequently reported PTs (3 events or more) indicating an adverse event/outcome for pregnancy cases were fatigue, myalgia, malaise, injection site pain, arthralgia, COVID-19, injection site swelling, abortion spontaneous, chills, nausea, headache, pain in extremity, vomiting, and dizziness. Most events were reactogenicity events, consistent with the product safety profile and similar between the reporting period and the cumulative periods. During the review period, there were no pregnancy cases reporting events of myocarditis and/or pericarditis after receipt of elasomeran. *Pregnancy-specific events – elasomeran* During the review period, of the 53 pregnancy cases received by the MAH, 45 pregnancy cases reported a pregnancy-specific adverse event/outcome in individuals who received or had a medical history of maternal exposure to elasomeran. (Please note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ). These 45 cases reported 59 pregnancy-specific events with 35 serious cases (44 serious events). No cases with pregnancy-specific adverse events reported a fatal outcome, and 20 cases were medically confirmed. After the exclusion of PTs that did not indicate an adverse pregnancy-specific event/outcome, "Abortion spontaneous" remained the most frequently reported adverse pregnancy event/outcome for both the reporting and cumulative periods. (Refer to Spontaneous abortions, Stillbirths, and Foetal 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 PSUR Appendix 12.13.

	Serious Pregnancy-specific Events and Fatal Cases– elasomeran During the review period, of the 32 reported serious pregnancy cases, when restricted to pregnancy cases reporting only pregnancy-specific events/outcomes, 27 serious cases were identified as including serious pregnancy-specific events (34 events). No cases reported a fatal outcome, and 11 cases were medically confirmed. 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, gestational age 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, concomitant medications, comorbidities (such as chronic hepatitis, autoimmune thyroiditis, substance abuse) and previous relevant obstetric history including fetal loss] were present. *Fatal Pregnancy Cases– elasomeran* During the review period, 1 pregnancy case was coded as fatal following receipt of elasomeran. This case of maternal death is summarized below: [redacted]**:** This literature non-study case concerns a 38-year-old pregnant (reported as 20 weeks gestational age) female with concurrent medical conditions of chronic hepatitis B and autoimmune thyroiditis (under treatment with prednisolone), who experienced hepatitis B reactivation, antiphospholipid syndrome, multi-organ failure, hepatic failure, lactic acidosis, vaginal haemorrhage, and hypotension 8 days after receiving the first dose of elasomeran [vaccine date and event date were not provided]. Five days after vaccination, the patient presented with icteric sclera and yellowish skin discoloration. Hepatitis B flare was detected and tenofovir disoproxil fumarate was prescribed. Nonetheless, the patient developed progressive hepatic decompensation, vaginal bleeding, profound hypotension, and lactic acidosis and was admitted to the intensive care unit. Vaccine-related catastrophic anti-phospholipid syndrome with multi-organ failure was suspected by a rheumatologist. Treatment for the events included plasma exchange, continuous venovenous hemodiafiltration, belimumab, cyclosporin, abatacept, leflunomide, and methylprednisolone. Relevant diagnostic tests included alanine aminotransferase at baseline was 14 U/L, onset/peak of 1745/1860 U/L (no reference ranges provided); aspartate aminotransferase at onset/peak of 1387/1387 U/L (no reference ranges provided); no baseline HBV DNA was tracible, peak of HBV DNA of >1,000,000,000 IU/mL (no reference ranges provided); total bilirubin of 4.1 mg/dL (no reference ranges provided); international normalized ratio of 1.74 >10 on Day 12 and >10 on Day 13 (no reference ranges provided). Unfortunately, the patient died on Day 26. The reported causes of death were hepatitis B reactivation, catastrophic antiphospholipid syndrome, multi-organ failure, vaginal bleeding, hypotension, hepatic decompensation and lactic acidosis. It is unknown if an autopsy was performed. The outcome of the fetus was not reported.

	MAH Comment: Catastrophic antiphospholipid syndrome is most often associated with thrombosis risk factors such as infection, surgery, or pregnancy, in an individual with pre-existing antiphospholipid antibodies or a genetic complement abnormality. This pregnant woman had pre-existing autoimmune disease and chronic hepatitis B infection which became reactivated, which may provide an alternative explanation for the events. This case was assessed as "Unlikely" given the limited information provided regarding obstetric history, complete diagnostic evaluation, and clinical course; and the concurrent medical conditions that provided an alternate etiology. *Fetal Deaths– elasomeran* The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth." Fetal deaths are classified as spontaneous abortion if they occur before 20 weeks gestational age (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 [71]. *Spontaneous and Missed Abortions – elasomeran* During the review period, 6 serious pregnancy cases with a medical history of maternal exposure to elasomeran reported spontaneous abortion with 6 serious events. Of the 6 cases, 2 cases were medically confirmed, and no cases were coded as fatal. The mean age of the cases was 35.4 years (SD: 3.4) with a median age of 36.0 years (range 30-39 years). Analysis of event clustering by dose number and TTO was not meaningful as 4 of the 6 events (66.7%) did not report dose number or TTO. Of the 2 remaining cases, 1 case reported dose number (Dose 3) and TTO (4 days) and the other case reported TTO (443 days) but not dose number. *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 stillbirth as fetal death after 20 weeks gestational age [71]. 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 are 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. During the review period, no pregnancy cases reported stillbirth following maternal exposure to elasomeran. 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. *Congenital Anomaly– elasomeran*

	During the review period, 13 pregnancy cases that reported a PT from the Congenital, familial, and genetic disorder SOC were identified. After medical review, no reporting patterns or safety concerns were identified. Of the 13 pregnancy cases, 7 cases occurred among foetuses and neonates who were maternally exposed to elasomeran in utero and 6 cases were determined to be "non-pregnancy cases" as they either represented medical history miscoded as an adverse event, or a pre-existing congenital anomaly detected in a non-pregnant person. Of the 7 pregnancy cases, 3 cases reported a live birth at delivery. One case ([redacted] reported the event outcome as "Resolved", 1 case [redacted] reported the event outcome as "Resolved with sequelae", and 1 case ([redacted]) reported the event outcome as "Unknown." Further review of the congenital anomalies, considering the GA at vaccination and fetal development, contributed to the assessment of causality. Many cases lacked GA at the time of vaccination and thus causality was considered "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. Even when considering the cumulative data, there were no significant patterns or safety concerns identified. **Subpopulation Analyzes-elasomeran:** *Children <6 years of Age with a medical history of maternal exposure to Elasomeran during pregnancy* During the review period, the MAH received 2 serious cases (3 events) among children under 6 years of age with a medical history of maternal exposure to elasomeran during pregnancy. Neither case reported a fatal outcome nor was medically confirmed. [redacted] was previously reported in the prior PBRER review period but had event updates made to the case narrative during this reporting period. The PT "Maternal exposure during pregnancy" was removed from the list of reported PTs and was then captured in infant's medical history. This update did not affect the MAH's original causality assessment. [redacted] This regulatory authority case reported by a consumer, concerns a 1-year-old female infant, with no medical history reported, who experienced the serious (due to medically significant) event of Foetal growth restriction (reported as stunted intrauterine growth due to poor placental blood flow), which occurred on an unknown date related to elasomeran vaccine. This vaccine was administered to the mother as the second dose within the COVID-19 vaccination schedule. No information was disclosed regarding diagnostic tests performed or treatments received. At the time of the report, the event had not resolved. MAH Comment: Causality was considered "Unassessable" given the limited information provided regarding obstetric history, diagnostic evaluation, and clinical course that precludes a meaningful causality assessment. No unusual

patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period.

Pregnancy Cases Among Adolescents (12-17 Years of Age – Elasomeran During the review period, no pregnancy cases were received by the MAH among adolescents (12-17 years of age) who received elasomeran.

Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified cumulative.

Pregnancy Cases After Receiving a Booster Dose with elasomeran/imelasomeran

During the review period, the MAH received 1 serious pregnancy case (2 events) for an individual who received a booster dose of elasomeran/imelasomeran.

This case is summarized below:

[redacted] this regulatory authority retrospective pregnancy case reported by a consumer concerns the occurrence of Abortion spontaneous in a 35-year-old female following receipt of elasomeran/imelasomeran. This vaccination was reported as the fourth dose in the COVID-19 vaccine series. The report indicated that vaccination occurred when the mother "was 11 weeks pregnant and had miscarried 3 days later." However, no dates confirming last menstrual period or estimated date of delivery to confirm GA were reported. Concomitant medication included Folic acid.

MAH Comment: Causality was considered "Unassessable" given the limited information provided; including missing data regarding maternal medical, family, and obstetric history, diagnostic evaluation, and clinical course that precludes an informed case and a meaningful causality assessment.

Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified during the reporting and cumulative periods.

Pregnancy Cases After Receiving a Booster Dose with elasomeran/davesomeran

During the review period, the MAH received 7 pregnancy cases (13 events) with 1 serious case among individuals who received a booster dose of elasomeran/davesomeran. No case reported a fatal outcome, and 5 cases were medically confirmed.

Cumulatively and during the review period, there have been no pregnancy cases reporting a fatal outcome, stillbirth, or foetus/infant with congenital anomalies following exposure to a dose of elasomeran/davesomeran. The most frequently reported events/PTs represent expected reactogenicity for elasomeran. The only pregnancy-specific PTs reported have been "Maternal exposure during pregnancy" and "Gestational hypertension." The one serious case reported during the review period is summarized below:

[redacted] This regulatory case concerns a 28-year-old female patient, pregnancy reported, who experienced the serious (hospitalization) event of Gestational hypertension,

	approximately 3 months after a dose of elasomeran/davesomeran. This vaccination was reported as the fourth dose in the COVID-19 vaccination series. Last menstrual period and estimated date of delivery were not provided. No details of previous doses were provided. No treatment information was provided. No further clinical information was available for medical review. Company causality assessed the event of gestational hypertension as not related due to long latency and that the pathophysiology of the reported pregnancy was considered the main risk factor for the event. MAH Comment: Causality was considered "Unassessable" given the limited information provided; including missing data regarding maternal medical, family, and obstetric history, diagnostic evaluation, and clinical course that precludes an informed case and a meaningful causality assessment. Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified during the reporting and cumulative periods. **Pregnancy Cases After Receiving a Booster Dose with andusomeran** It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant XBB 1.5. Therefore, this will be the first PBRER review period where pregnancy cases following andusomeran vaccination will be reviewed. Since its approval, the MAH has received 24 pregnancy cases (75 events) with 3 serious cases (3 events) among individuals who received a booster dose of andusomeran. No cases have reported a fatal outcome, and 22 cases were medically confirmed. Most (14; 58.3%) pregnancy cases reported after receipt of Andusomeran occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been seen with elasomeran-containing vaccines in previous review periods. The most frequently reported PTs have been predominantly reactogenicity events, consistent with the product safety profile for elasomeran-containing vaccines and consistent with events reported for elasomeran-containing vaccines in prior review periods. No pregnancy cases after receipt of andusomeran have reported events of myocarditis and/or pericarditis. *Pregnancy-specific Events –andusomeran* Of the 24 pregnancy cases received by the MAH, 23 pregnancy cases reported a pregnancy-specific adverse event/outcome in individuals who received or had a medical history of maternal exposure to andusomeran. (Please note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ). These 23 cases reported 25 pregnancy-specific events with 3 serious cases (2 events). No cases with pregnancy-specific adverse events reported a fatal outcome, and 22 cases were medically confirmed. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome the only PTs reported were "Abortion spontaneous," "Haemorrhage in pregnancy," and "Morning sickness." [Note: Case [redacted] reported the pregnancy-specific event of "Morning sickness." However, assuming the age of the patient was reported correctly, it appears this case may have been incorrectly coded as a pregnancy case given the individual's age (75 years)].

	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 PSUR Appendix 12.13. *Serious Pregnancy-specific Events– andusomeran* Of the 3 serious pregnancy cases reported, when restricted to pregnancy cases reporting only pregnancy-specific events, 2 serious cases were identified as including serious pregnancy-specific events (2 events). No cases reported a fatal outcome, and both cases were medically confirmed. The 2 serious cases are summarized below: [redacted] This spontaneous prospective pregnancy case concerns a 36-year-old female with relevant medical history of retroplacental haematoma in the first trimester and concomitant receipt of the flu vaccine who experienced the serious event of "haemorrhage in pregnancy." The event occurred 2 days following receipt of andusomeran. This vaccination was reported as the sixth dose within the COVID-19 vaccination series. The event duration was 2 days, and the outcome was reported as "Recovered." Vaccination occurred at 17 weeks GA, and it was reported that "baby's heartbeat was heard" upon visit to the hospital. No further clinical information was reported. MAH Comment: Causality was assessed as "Unassessable" given limited data provided; including missing data regarding maternal medical/surgical, family, and obstetric history; diagnostic evaluation; and clinical course that precludes a meaningful causality assessment. Medical history of retroplacental haematoma in the first trimester and concomitant receipt of flu vaccine on the same day as andusomeran are also potential confounders for this event. [redacted] This spontaneous retrospective pregnancy case concerns the occurrence of Abortion spontaneous in a 34-year-old female with the relevant medical history of a recent flu vaccination ["Flu Shot (1 week ago)"]. The event occurred approximately 1 month after receipt of andusomeran. Vaccination was reported as the fifth dose within the COVID-19 vaccination series. No information was disclosed regarding GA of the fetus, diagnostic tests performed, or treatments received. MAH Comment: Causality was assessed as "Unassessable" given the limited data provided; including missing data regarding maternal medical, family, and obstetric history, diagnostic evaluation and clinical course that precludes an informed case and a meaningful causality assessment. The receipt of a flu vaccination 1 week prior to the report of the event also confounds this case. *Fatal Pregnancy Cases– andusomeran* No pregnancy cases have reported a fatal outcome following receipt of andusomeran. *Fetal Deaths– andusomeran* The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth." Fetal deaths are classified as spontaneous abortion if they occur

	before 20 weeks GA, and as stillbirth if they occur after 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [71]. *Spontaneous and Missed Abortions – andusomeran* Since its' approval, 1 serious pregnancy case with a medical history of maternal exposure to andusomeran reported spontaneous abortion with 1 serious event. Case [redacted] is summarized in the Serious Pregnancy-specific Events-andusomeran section above. *Stillbirth – andusomeran* No pregnancy cases have reported stillbirth following maternal exposure to andusomeran. *Congenital Anomaly– andusomeran* No pregnancy cases have reported congenital anomaly following maternal exposure to andusomeran. **Subpopulation Analyses-Andusomeran:** No pregnancy cases have been reported for the following subpopulations during the review period: • Children <6 years of Age with a medical history of maternal exposure to andusomeran during pregnancy • Children 6 to 11 years of age • Adolescents (12-17 Years of Age) Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified during the reporting and cumulative periods. **Pregnancy Cases Receiving a vaccine under the SPIKEVAX (NOS) classification** During the reporting period of this PBRER, for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran). During the review period, the MAH received 5 pregnancy cases (9 events) with 2 serious cases (2 serious events) among individuals under the SPIKEVAX (NOS) classification. No cases reported a fatal outcome, and 4 cases were medically confirmed. Most (3; 60.0%) pregnancy cases occurred in the 18 to 39-year age group which is consistent with typical childbearing age. *Pregnancy-specific Events – SPIKEVAX (NOS)* After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome the only PTs reported were "Abortion spontaneous," and "Fanconi syndrome." 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 PSUR Appendix 12.13. *Serious Pregnancy-specific Events– SPIKEVAX (NOS)* During the review period, 2 serious pregnancy cases (2 events) were reported following receipt or maternal exposure to a vaccine under the SPIKEVAX (NOS) classification. No cases reported a fatal outcome, and 1 case was medically confirmed. **Case** [redacted] concerned a 42-year-old female who experienced the medically significant event of Fanconi syndrome at an unspecified time following SPIKEVAX (NOS). This report appears to be misclassified as a pregnancy case as there is no indication within the case narrative that the patient was pregnant (i.e., no mention of last menstrual period, estimated delivery date, or obstetric medical history). The remaining serious pregnancy case is summarized below: [redacted]: This spontaneous case concerns an occurrence of abortion spontaneous in a 33-year-old female with medical history of miscarriage, which occurred in context administration of a vaccine under the SPIKEVAX -NOS classificatio. This vaccination was reported as the second dose in the COVID-19 series. It was reported that the event occurred approximately 1 month after becoming pregnant. Last menstrual period and estimated date of delivery were not reported. It was reported that the patient was vaccinated approximately 1 month before becoming pregnant. The PT "Maternal exposure before pregnancy" was also noted in the case. The only concomitant medication reported was folic acid for an unspecified indication. No further details regarding maternal medical, family, and obstetric history, diagnostic evaluation and clinical course were provided for review. The event outcome was reported as "Unknown" at the time of report. MAH Comment: Causality was assessed as "Unlikely" given the patient was vaccinated 1 month prior to pregnancy (second dose of the COVID-19 series) and miscarried approximately 2 months after vaccination (approximately 1 month after becoming pregnant). The patient's medical history of miscarriage is also a potential confounder as history of past miscarriage may represent an increased risk of spontaneous abortion for future pregnancies. *Fatal Pregnancy Cases– SPIKEVAX (NOS)* No pregnancy cases have reported a fatal outcome following receipt a vaccine under the SPIKEVAX (NOS) classification. *Fetal Deaths– SPIKEVAX (NOS)* The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth." Fetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA, and as stillbirth if they occur after 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [71]. *Spontaneous and Missed Abortions – SPIKEVAX (NOS)* During the review period, 1 serious pregnancy case with a medical history of maternal exposure to a vaccine under the SPIKEVAX (NOS) classification.

	reported spontaneous abortion with 1 serious event. **Case** [redacted] is summarized in the Serious Pregnancy-specific Events-SPIKEVAX (NOS) section above. *Stillbirth –SPIKEVAX (NOS)* During the review period, no pregnancy cases reported stillbirth following maternal exposure to a vaccine under the SPIKEVAX (NOS) classification. *Congenital Anomaly*– SPIKEVAX (NOS) During the review period, 1 serious case (1 event) reported congenital anomaly following receipt of a vaccine under the SPIKEVAX (NOS) classification. Case [redacted] concerned a 42-year-old female who experienced the medically significant event of Fanconi syndrome at an unspecified time following exposure to a vaccine under the SPIKEVAX (NOS) classification. This report appears to be misclassified as a pregnancy case as there is no indication within the case narrative that the patient was pregnant (i.e., no mention of last menstrual period, estimated delivery date, or obstetric medical history). **Subpopulation Analyses-SPIKEVAX (NOS):** During the review period, no pregnancy cases were reported for the following subpopulations: • Children <6 years of age with a medical history of maternal exposure to vaccination during pregnancy • Children 6 to 11 years of age • Adolescents (12-17 years of age) Based on current available information, no unusual patterns or pregnancy-specific safety concerns were identified during the reporting period.
Discussion	During the reporting period, the MAH received a total of 90 pregnancy cases (345 events) among individuals who received a marketed Moderna vaccine targeting SARS-CoV-2 during pregnancy. The pattern of the reports remained generally consistent when compared with the cumulative data. While there was a higher proportion of serious cases reported following receipt of elasomeran vaccine, review of serious pregnancy-specific events and non-pregnancy-specific events for all marketed Moderna vaccines targeting SARS-CoV-2 during the review period did not identify any new safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of marketed Moderna vaccines targeting SARS-CoV-2 with no other causal association to vaccination. Reported cases reflect obstetric events observed after administration of marketed Moderna vaccines targeting SARS-CoV-2. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of adverse event(s), diagnostics, treatment and/or outcome. Where data were available, noted confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy included advanced maternal age, concomitant medications, comorbidities, underlying medical conditions, previous relevant obstetric history, and congenital anomalies which predated the vaccination.

	Spontaneous abortion remained the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster has been identified during the reporting and cumulative periods. During the review period, no cases reported stillbirth. Cases of stillbirth from the cumulative period had clear alternate etiologies, with 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 marketed Moderna vaccines targeting SARS-CoV-2 and stillbirth. The MAH will continue to review and evaluate cases of spontaneous abortion, fetal death, and stillbirth, using routine surveillance as well as PASS. Review of the cases reporting congenital anomalies following maternal exposure to any marketed Moderna vaccine targeting SARS-CoV-2 during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. After approval of andusomeran, it was observed that reports predominantly represent reactogenicity events, which is consistent with the product safety profile for elasomerancontaining vaccines and consistent with events reported for elasomeran-containing vaccines in prior review periods. The only pregnancy-specific events indicating an adverse clinical outcome following andusomeran vaccination have been "Abortion spontaneous" and "Haemorrhage in Pregnancy." No pregnancy cases following andusomeran vaccination have reported a fatal outcome, stillbirth, or congenital anomaly. No pregnancy cases have been reported in children or adolescents under 18 years of age. In-depth literature reviews performed have not identified any new safety concerns for the use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy. Thus far, published literature has not identified any evidence of an increased risk of fetal or neonatal complications related to maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. Furthermore, published literature has reported that there is transfer of maternal antibodies, reduction in SAR-CoV-2 infection in vaccinated pregnant women and early evidence that infants benefit from passive protection from SARS-CoV-2 infection and severe disease following maternal COVID-19 vaccination. It is acknowledged that SAR-CoV-2 infection may be more serious and cause complications for both the mother and the fetus and published literature supports the favourable benefit/risk profile of maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. Data continues to provide supporting evidence for theuse of marketed Moderna vaccines targeting SARS-CoV-2 before and during pregnancy. After careful review of all new safety data received during the reporting period for the safety topic of Use in Pregnancy, the benefit-risk profile for marketed Moderna vaccines targeting SARS-CoV-2 remains favourable.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the safety topic of Pregnancy reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any new safety concern. The MAH

	will continue to monitor events for pregnancy using routine surveillance and ongoing post authorization studiesmRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Use in pregnancy

The MAH has presented information regarding use of Moderna Spikevax vaccines targeting SARS-CoV-2 during pregnancy for the latest period 18 June 2023 through 17 December 2023. Data are achieved from the MAH's global safety database and from the literature.

Use in pregnancy has been an area of missing information. However, animal studies do not indicate any harmful effects, and both real world evidence from use of Spikevax vaccines during pregnancy, as well as the literature, do not rise specific safety concerns for use in pregnancy.

Results

Results from the Global Safety Database

In the review period 18 Jun to 17 Dec 2023 there were 90 pregnancy cases (345 events) reported after receiving a Spikevax vaccine against COVID-19. Of these, 53 cases (246 events) were reported for elasomeran, 1 case (2 events) for elasomeran/imelasomeran, 7 cases (13 events) for elasomeran/davesomeran, 24 cases (75 events) for andusomeran, and 5 cases (9 events) following an unspecified Spikevax vaccine (Spikevax NOS).

Pregnancy cases are concerning maternal exposure during pregnancy.

Cases have been defined 'serious' on a wide background, there is possibly a tendency of defining cases as serious due to the fact that they are pregnancy-related.

Adverse reactions

Reactogenicity: Many cases were related to known reactogenicity; most PTs were reactogenicity-related events, consistent with the product safety profile.

Lack of vaccine efficiency: COVID-19 has been reported as an adverse reaction following vaccination during pregnancy, this can be defined as lack of efficiency of vaccine.

Spontaneous abortion: Spontaneous abortion, stillbirth, and foetal death are pregnancy-related PT. Fetal death before 20 weeks gestational age (GA) are defined as spontaneous abortion. Fetal death from 20 weeks gestational age are defined as stillbirth. Cases of fetal death were not reported as fatal cases.

Congenital Anomaly: Cases related to congenital anomaly. Some were covering pre-existing congenital anomaly/miscoded. However, the cases did not raise concern for causality, which is supported by that no significant patterns or safety concerns are identified in the cumulative data.

Fatal cases: In the review period 1 case was defined a fatal case, this was a case of maternal fatality. There were severe medical conditions, and there was no indication of causal association between the vaccine and the death of the pregnant woman.

Literature search:

The MAH reported that the performed literature search gave 563 manuscripts. Despite the many retrieved papers, the MAH did not find any new and significant information in these.

Conclusion

In the review period 18 June to 17 December 2023 there were 90 pregnancy cases (345 events) reported after receiving a Spikevax vaccine.

Many of the reported symptoms were related to reactogenicity and are consistent with milder side effects to vaccination. Furthermore, there were reported gynaecological and/or obstetric complications/events which are temporally associated but not causally associated to vaccination. One case was reported as fatal, the pregnant woman died; there was not a causal relationship to the vaccine.

No unusual patterns or pregnancy-specific safety concerns were identified during reporting period, nor for the cumulative period.

The findings from the global safety database do not raise new concerns, just as the MAH's literature review did not identify articles that provided any new information of concern. Previous animal studies have not indicated any harmful effects.

Pregnancy cases will continue to be monitored by routine surveillance and via ongoing post-authorisation studies mRNA-1273-P905 and mRNA-1273-P919.

2.3.1.3.2. Use while breastfeeding

Evaluation of information received during the PBRER reporting interval relating to the known missing information of marketed Moderna vaccines targeting SARS-CoV-2 of "Use while breastfeeding" has not identified any additional clinically relevant new safety information for this topic. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in PSUR Section 16.4, remains valid.

Table 26: Use while Breastfeeding

Missing information	**Use in Breastfeeding**
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 563 o New and Significant Safety Information: None (0)
Background	The topic of Breastfeeding is summarized because the use of marketed Moderna vaccines targeting SARS-CoV-2 among breastfeeding women is an area of missing information in the currently approved RMP. Real world evidence and literature demonstrate that marketed Moderna vaccines targeting SARS-CoV-2 are well tolerated by lactating women and their children, and side-effects experienced are similar to side-effects in the general population. No specific safety concerns for breastfeeding have been identified.
Methods	Refer to Appendix 12.14 for Methods of Evaluation
Results	**Overview of Lactation Cases Who Received elasomeran** It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide after Jun 2023. Therefore, during this review period, there was

	a considerable decrease in the number of reported pregnancy cases for elasomeran vaccine. During the review period, the MAH received 7 lactation cases (54 events) with 1 serious case among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran. Two (2) of the 7 lactation cases were medically confirmed. No lactation cases reported a fatal outcome. A higher percentage (6 cases; 85.7%) of the cases reported during this reporting period were non-serious compared to the prior review period (74.3%). During the reporting period, no meaningful changes were observed in the age distribution of the cases of lactating women and their breastfeeding children and are consistent with the expected age of lactating women and their breastfeeding children. Please note cases coded as males likely represent children who were exposed to breastmilk from mothers who had been vaccinated with elasomeran vaccine. During the review period, the most frequently reported PTs were consistent with reactogenicity events and common breastfeeding issues such as lactation insufficiency. When restricted to lactation-specific adverse events/outcomes, the only PTs reported were "Lactation insufficiency" (1 event), and "Galactostasis" (1 event). There was not a significant change in the pattern of PTs reported during the reporting period when compared to cumulative data. Most of the lactation-related events were transient and occurred within 2 days of vaccination. Medical review of the HLT "Lactation Disorders" was performed and the data for the review period are similar to the previous cumulative experience; no concerning patterns or notable trends were identified. During the reporting period 1 serious lactation case was received. Case [redacted] described the serious event of Guillain-Barre syndrome in a 39-year-old female. This case was reported in the previous review period but added the nonserious concurrent event of COVID-19 infection and other updates to the narrative (reporter information, patient details, medical history, lab data, and event information) during this review period. The only lactation-specific PT reported was "Exposure via breast milk." There were no lactation-specific events reported indicating a clinical adverse event/outcome for an infant/child or lactating woman in this case. **Subpopulation Analyses** *Lactation Cases Under 6 Years of Age–elasomeran* During the review period, the MAH received 3 non-serious cases (11 events) 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). No cases reported a fatal outcome and 1 case was medically confirmed. Similar to the previous review period, the most frequently reported clinical events reported among children under the age of 6 years of age were fatigue, pyrexia,

	diarrhoea, vomiting, rash, malaise, and body temperature increased which are consistent with reactogenicity events expected for elasomeran. When restricted to only lactation-specific PTs, the most frequently reported lactation-specific PT continued to be "Exposure via breast milk." During the reporting period, the mean age of lactation cases among children under 6 years was 0.4 years (SD: 0.3) and median age was 0.4 years (range: 0.0 to 0.7 years). The sample size was small so there was no meaningful difference in the number of reports involving males (1; 33.3%) and females (1; 33.3%); with 1 case (33.3%) not reporting gender. When TTO was known, most of the lactation-related events were transient and all events occurred within two days after vaccination. During the review period, no lactation cases reporting seizure were received. Cumulatively, all serious cases with lactation specific events have been medically reviewed and summarized. Many cases lack information on clinical course, outcome, pediatric medical history, or alternate etiologies/concurrent clinical events. Thus, based on the temporal relationship, causality cannot be excluded. To date, no concerning patterns or notable trends have been identified to suggest a vaccine-associated safety concern. *Lactation Cases Among Adolescents (12-17 years of Age)- elasomeran* No lactation cases were reported among adolescents during this review period. Cumulatively and during the reporting period, no unusual patterns or lactation specific safety concerns have been identified after receipt of elasomeran. **Lactation Cases After Receiving Booster Dose with elasomeran/imelasomeran** During the review period, no lactation cases were reported among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with a booster dose of elasomeran/imelasomeran. **Lactation Cases After Receiving Booster Dose with elasomeran/davesomeran** During the review period, the MAH received 2 non-serious lactation cases (4 events) among individuals who received elasomeran/davesomeran. No cases reported a fatal outcome, and both cases were medically confirmed. During the review period, when restricted to lactation-specific events, the only PT reported was "Maternal exposure during breastfeeding." **Lactation Cases Among Adolescents (12-17 years of Age)- elasomeran/davesomeran** No lactation cases were reported among adolescents during this review. Cumulatively and during the reporting period, no unusual patterns or lactation specific safety concerns have been identified after receipt of a booster dose with elasomeran/davesomeran. **Lactation Cases After Receiving Booster Dose with andusomeran**

	It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant XBB 1.5. Therefore, this will be the first PBRER review period where lactation cases among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with a booster dose of andusomeran will be reviewed. Since the approval of andusomeran, the MAH has not received any fatal or serious cases. The MAH has received 5 non-serious lactation cases (17 events) among individuals who received a booster dose of andusomeran. Four (4) of the 5 cases were medically confirmed and 3 cases did not report an adverse clinical event/outcome. When restricted to lactation-specific events, the only PTs reported were "Maternal exposure during breast-feeding" and "Exposure via breast milk." Assuming that the age of the patients was reported correctly, it is important to note that cases [redacted] and [redacted] may have been incorrectly coded aslactation cases given the patient's age (56 years and 70 years, respectively). **Lactation Cases Among Adolescents (12-17 years of Age)- andusomeran** No lactation cases were reported among adolescents during this review. No unusual patterns or lactation-specific safety concerns were identified after receipt of a booster dose with andusomeran. **Lactation Cases After Receiving SPIKEVAX (NOS)** During the reporting period, no lactation cases were reported that were classified as exposed to a vaccine under the SPIKEVAX (NOS) classification.
Discussion	During the reporting period, ModernaTx, Inc. received a total of 14 lactation cases (75 events) among individuals who received or were exposed to breast milk from mothers who had been vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2; of which 3 cases were among children under 6 years of age with exposure to elasomeran via breast milk and the remaining cases (11) were reported for adult females older than 18 years of age. There were no lactation cases reported among adolescents (12-17 years age group) during this reporting period. There was 1 serious lactation case received (reporting the serious event of Guillain-Barre syndrome) for an adult female, however no serious lactation-specific events were reported, and the case was heavily confounded by concurrent medical history of COVID-19 infection. No cases reporting a fatal outcome were received. While vaccination can induce cytokines, which can be passed via breast milk, vaccination while breastfeeding has not been linked to adverse events in infants. In fact, women with fever and illness are encouraged to continue breastfeeding 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 [72] [73] [74].

	The most frequently reported terms were exposure during breast-feeding or maternal exposure during breast-feeding. 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 were available, many of the events occurred within 2 days after vaccination, and most events were mild/moderate, transient events. 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 marketed Moderna vaccines targeting SARS-CoV-2 or what is expected in the general population [75] [76] [75]. No specific safety concerns were identified after receipt of a booster dose with Andusomeran by breastfeeding women and their children who are exposed to this vaccine through breast milk. The current safety profile of andusomeran is consistent with the safety profile of the other marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to review cases that received the andusomeran vaccines using routine surveillance. Review of the literature to date has not identified any safety concerns related to marketed Moderna vaccines targeting SARS-CoV-2 during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated breastfeeding 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 favourable benefit/risk profile of COVID vaccination during lactation which continues to provide supporting evidence for HA recommendations for the use of COVID-19 vaccines including marketed Moderna vaccines targeting SARS-CoV-2 during lactation. The MAH is closely monitoring the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in this population through routine pharmacovigilance [77-79]. After careful review of all new safety data received during the reporting period for the safety topic of Use while Breastfeeding, the benefit-risk profile for marketed Moderna vaccines targeting SARS-CoV-2 remains favourable.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Use while Breastfeeding reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any safety concern. The MAH will continue to monitor events associated with breastfeeding women who receive marketed Moderna vaccines targeting SARS-CoV-2 and their children who are exposed to these vaccines through breast milk using routine surveillance and ongoing post-authorization studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation for this sub-population continues to remain positive.

Rapporteur assessment comment:

The MAH has presented and evaluated data received during the reporting interval regarding the missing information topic "Use while breastfeeding".

Regarding breastfeeding, section 4.6 of the SmPC states: "No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to Spikevax is negligible. Observational data from women who were breastfeeding after vaccination have not shown a risk for adverse effects in breastfed newborns/infants. Spikevax can be used during breastfeeding."

During the reporting period, the MAH received a total of 14 lactation cases concerning either breastfeeding women vaccinated with Spikevax or breastfed children whose mothers were vaccinated with Spikevax. Of these 14 cases, three concerned children under 6 years of age with exposure to elasomeran via breast milk and the remaining eleven cases were reported for adult females older than 18 years of age.

The Rapporteur deems that the MAH's presentation of this missing information topic has some weaknesses. The MAH primarily focuses on lactation-specific adverse events (e.g. "lactation insufficiency"). The Rapporteur agrees that such adverse events are of interest, and this focus is endorsed in the cases concerning breastfeeding women, as it is deemed unlikely that the general safety profile is markedly different in lactating women compared to non-lactating women. However, with regard to the cases concerning breastfed infants, as these infants are potentially exposed to Spikevax via the breastmilk and in many cases will be younger than children in which Spikevax is authorised (from 6 months), any adverse event observed in this population is of interest.

The MAH presents the most frequently reported clinical events in the three interval cases concerning children exposed via breast milk (e.g. pyrexia, diarrhoea, vomiting, rash), and the MAH argues that these events are consistent with reactogenicity events expected for elasomeran. The Rapporteur does not consider this argumentation valid. As noted above, the SmPC states that the systemic exposure of the breastfeeding woman to Spikevax is negligible, for this reason the Rapporteur deems that it would be expected that the exposure via breastmilk is also negligible, and therefore, reactogenicity events is not expected in the infant. However, as the interval cases are non-serious, only totals three and as the reported events are common in unexposed infants, this particular issue does not currently warrant further action. **However, in evaluations of the missing information topic "Use while breastfeeding" in future PSURs, the MAH is requested to present the adverse events reported in children exposed via breastmilk (as in the current PSUR). Furthermore, the MAH should provide an overall discussion of the reported cases, conclude on the causality between elasomeran exposure and the reported adverse events and provide specific arguments for this conclusion.** Based on the current product information for elasomeran, vaccine reactogenicity is not considered a valid argument for dismissing cases of adverse events in infants exposed via breastmilk.

The MAH concludes that its analysis of all safety data received during the reporting period for the missing information topic "use while breastfeeding" did not raise any safety concern. Based on the presented data, the Rapporteur has not identified safety concerns that warrant further action at this point. The MAH will continue to monitor this topic via routine surveillance and the ongoing post-authorisation studies mRNA-1273-P905 and mRNA-1273-P919. This is endorsed.

2.3.1.3.3. Long-term safety

Evaluation of information received during the PBRER reporting interval relating to the missing information risks of long-term safety, has not identified any additional clinically relevant new safety information for

these topics. The characterization of these important risks as described in the current RMP and in Section 16.4, below, remains valid.

Missing Information	**Long-term Safety**
Source of New Information	As of the DLP of this PBRER, 26 CTs were ongoing 16 of which are sponsored by ModernaTx, Inc. Cumulatively, 59,907 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, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 (including its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administered with mRNA-1010 or co-administered with mRNA-1345, or co-administered active licensed sFLU vaccines (Fluzone HD or Fluarix) in the mRNA-1083 clinical development program sponsored by ModernaTx, Inc.
Background	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-P203, mRNA-1273-P204, mRNA-1273-P205 (Parts A.1, B, C, D, F, and G), and the completed studies mRNA-1273-P101 (DMID 20-0003), and mRNA-1273-P201. Per protocols, safety follow-up period for mRNA-1273-P205 (Parts A.2, H and J) is 6 months and for the competed study mRNA-1273-P301 was 24 months. Post-authorization safety studies in real world that evaluate long-term safety include ongoing studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911.
Methods	The long-term safety profile remains to be characterized through continued trial followup, routine pharmacovigilance, and PASS as indicated in the current RMP. The Phase 3 study mRNA-1273-P301, completed during the current review period of this PBRER, included a total of 24 months follow-up; no long-term safety concerns were identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days).
Results	No long-term safety concerns were identified after completion of the clinical pivotal study mRNA-1273-P301. Post-authorization safety studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911 are ongoing, and no findings related to long-term safety have yet been identified. As of the DLP of this PBRER, no clinically important safety concerns have been identified upon review of long-term follow-up data in CTs.
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 Marketed Moderna vaccines targeting SARS-CoV-2.

	Ongoing Studies: • Study mRNA-1273-P904 (final CSR: 31 Sep 2024) • Study mRNA-1273-P910 (final CSR: 30 Jun 2025) • Study mRNA-1273-P911 (final CSR: 31 Oct 2028) • Study mRNA-1273-P203 (final CSR: 15 Jul 2025) • Study mRNA-1273-P204 (final CSR; 31 Dec 2024) • Study mRNA-1273-P205 (final CSR: 07 Nov 2024) **Completed Studies**: • Study mRNA-1273-P301 (final CSR: 20 Oct 2023)
Conclusion	As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor the 1 completed study (mRNA-1273-P301) which are being assessed to characterize long-term safety of Marketed Moderna vaccines targeting SARS-CoV-2.

Rapporteur assessment comment:

The MAH has provided information on several ongoing clinical trials which all aim to study long-term safety. The long-term safety profile remains to be characterized through continued trial follow-up, routine pharmacovigilance, and PASS as indicated in the current RMP.

One Phase 3 study (mRNA-1273-P301) completed during the current review period, included a total of 24 months follow-up. No long-term safety concerns were identified. Ongoing studies have not demonstrated significant safety findings.

The information provided is acknowledged.

2.3.1.3.4. Use in immunocompromised subjects (Safety concern in PBRER only)

Evaluation of information received during this PBRER reporting period relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in relation to immunocompromised individuals, has not identified any additional clinically relevant new safety information for this subpopulation.

Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

The characterization of the missing information within the PSUR on Use in Immunocompromised Individuals, as of the DLP of this PBRER, and in Section 16.4, remains valid. The number of fatal cases received during this reporting period and the associated MAH comment are presented by product in PSUR Appendix 12.15.

Table 27: Use in immunocompromised subjects (Safety concern in PBRER only)

Missing information	Use in immunocompromised subjects
Source of New Information	• ModernaTx, Inc GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 53 o New and Significant Safety Information: There was no new and significant safety information identified for the immunocompromised population.
Background	The topic of Immunocompromised is summarized because it is considered missing information in the PBRER. No specific safety concerns for immunocompromised individuals have been identified. It is important to note that the use of marketed Moderna vaccines targeting SARS-Cov-2 in immunocompromised individuals is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a request from the PRAC.
Methods	For the purposes of this PBRER reporting period, the following search criteria 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 haematological malignant tumors SMQ, transplantation, primary/innate and acquired immunodeficiency syndromes (including Human Immunodeficiency Virus) and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs. The "General Population" (all marketed Moderna vaccines targeting SARS-CoV-2 data) in the ModernaTx, Inc's. 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.
Results	Refer to Appendix 12.15 for additional information. **Overview of Cases for Immunocompromised Individuals Who Received elasomeran** It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide after Jun 2023. Therefore, during this review period, there was a considerable decrease in the number of reported cases for immunocompromised individuals who received elasomeran vaccine. During this review period, the MAH received 91 cases (360 events) with 54 (59.3%) serious cases (179 serious events) among immunocompromised individuals who received elasomeran. A total of 51 (56.0%) cases were medically confirmed, and 2 cases (2.2%) reported a fatal outcome.

	Similar to the prior reporting period, there were more cases involving females (45; 49.5%) compared to males (43; 47.3%), with 3 cases (3.3%) that did not report gender information. The median age of patients was 58.0 years (range: 23.0 -83.0 years). Similar to the previous review period, the most frequently reported MedDRA PTs in the immunocompromised subpopulation included headache, fatigue, pyrexia, chest pain, myalgia, and dyspnoea. These PTs were comparable to those reported in the general population and reflected expected reactogenicity. Events of COVID-19 infection were the most frequently reported event during this review period (17; 4.7%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. Note that during the review period, 25 cases (including 15 serious and 1 fatal case) overlapped 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. **Subpopulation Analyzes:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – elasomeran)* During the review period, no cases were reported among immunocompromised individuals in these age groups who received elasomeran. *Fatal Cases in Immunocompromised Individuals – elasomeran* Evaluation of the 2 cases reporting fatal outcome showed that both cases concerned males; one was 75 years of age and the other was 53 years of age. Both cases had comorbidities including malignancies that were chronic conditions, and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Using the WHO-UMC causality assessment tool, both cases were assessed as "Unlikely" (due to long TTO outside the risk window/unspecified latency and concurrent medical conditions that provided an alternate etiology). Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran. **Overview of Cases for Immunocompromised Individuals Who Received elasomeran/imelasomeran** During the review period, the MAH received 15 cases (49 events) with 14 (93.3%) serious cases (46 serious events) for immunocompromised individuals who received a booster dose of elasomeran/imelasomeran. One (1) case (6.7%) was medically confirmed, and no cases reported a fatal outcome. A higher proportion of cases were reported for females (9; 60.0%) than males (5; 33.3%) with 1 case (6.7%) that did not report gender information. The median age of patients was 56.0 years (range: 20.0 to 75.0 years). During the review period, the most frequently reported PTs (>4.0%) in immunocompromised individuals who received elasomeran/imelasomeran were

	pain in extremity, headache, fatigue, pyrexia, dyspnoea, and palpitations. These events reflect expected reactogenicity and were comparable to events reported in the general population receiving elasomeran/imelasomeran. Events of COVID-19 infection were also frequently reported during this review period (2; 4.1%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. Note that during the review period, 6 cases (including 5 serious cases) overlapped 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. **Subpopulation Analyses:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – elasomeran/imelasomeran* During the review period, no cases were reported among immunocompromised individuals in these age groups who received elasomeran/imelasomeran. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran/imelasomeran. **Overview of Cases for Immunocompromised Individuals Who Received elasomeran/davesomeran** During the review period, the MAH received 12 cases (28 events) with 1 (8.3%) serious case (1 serious event) for immunocompromised individuals who received elasomeran/davesomeran. All 12 cases were medically confirmed, and no case reported a fatal outcome. Similar to the previous review period, there were no meaningful changes in the gender distribution of reports as a slightly higher proportion of cases continued to be reported in females (7; 58.3%) than males (5; 41.7%). The median patient age was 70.5 years (range: 14.0 to 86.0 years). During the review period, the most frequently reported events were issues related to product expiration, medication error (extra dose administered), or product storage error. These events reflect similar events observed during the reporting period in the general population receiving elasomeran/davesomeran. Additionally, during the review period, there was 1 case with a serious event of cerebrovascular accident in a person living with HIV, that was treated with antihypertensives and recovered. The case was assessed as unlikely related to the use of the product due to the short latency period and concurrent hypertension and HIV that provide alternate etiologies. Note that during the review period, 3 non-serious cases overlapped 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.

Subpopulation Analyses:

Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – elasomeran-davesomeran

During the review period, 1 non-serious case was reported for a 14-year-old immunocompromised female following receipt of elasomeran/davesomeran. Case [redacted] reported the events of product expiration and product storage error with no resulting clinical adverse event/outcome. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran/davesomeran.

Overview of Cases for Immunocompromised Individuals Who Received andusomeran

It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant XBB 1.5. Therefore, this will be the first PBRER review period where cases for immunocompromised individuals who received andusomeran will be reviewed.

During the review period, the MAH received 58 cases (179 events) with 26 (44.8%) serious cases (75 serious events) for immunocompromised individuals who received andusomeran. A total of 24 (41.4%) cases were medically confirmed, and 1 case (1.7%) reported a fatal outcome.

There were more cases reported for females (36; 62.1%) compared to males (16; 27.6%), with 6 cases (10.3%) that did not report gender information. The median age of patients was 64.0 years (range: 23.0 – 93.0 years).

The most frequently reported events (>2.0%) included headache, fatigue, pain in the extremity, pyrexia, arthralgia, diarrhoea, dizziness, and product expiration issues. These PTs were comparable to those reported in the general population that received andusomeran and predominantly reflected expected reactogenicity. Events of COVID-19 infection were also frequently reported during this review period (5; 2.8%). This may be due to an already exiting COVID-19 infection prior to vaccination, and the susceptibility to constantly changing variants.

Note that during the review period, 10 cases (4 serious) overlapped 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.

Subpopulation Analyses:

Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – andusomeran)

No cases have been reported among immunocompromised individuals in these age groups who received andusomeran.

Fatal Cases in Immunocompromised Individuals –Andusomeran One (1) case reported a fatal outcome in an immunocompromised individual who received

	andusomeran. This regulatory authority case concerned an individual of unspecified age and gender with a medical history of immunodeficiency. The patient died on an unknown date and an unspecified latency period following vaccination with andusomeran. The cause of death was not reported, and no autopsy was performed. Using the WHO-UMC causality assessment tool, this case was evaluated as "Unassessable" given limited data provided; including missing data regarding age, gender, dose number, TTO, medical history, concomitant medications, clinical course of events, diagnostic evaluation, and clinical course that precludes a meaningful causality assessment. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received andusomeran. **Overview of Cases for Immunocompromised Individuals Who Received a vaccine under the SPIKEVAX (NOS) classification.** It is important to note that during the reporting period for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, or andusomeran). During this review period, the MAH received 6 cases (13 events) with 1 (16.7%) serious case (1 serious event) among immunocompromised individuals who received a vaccine under the SPIKEVAX (NOS) classification. A total of 5 (83.3%) cases were medically confirmed, and no cases reported a fatal outcome. All cases reporting gender involved females (4; 66.7%), with 2 cases (33.3%) that did not report gender information. The median age of patients was 45.5 years (range: 33.0- 58.0 years). The most frequently reported MedDRA PTs were anaemia, leukaemia, and weight decreased. Events of COVID-19 infection were the most reported event for this subpopulation (4; 30.8%) and the general population (62; 10.1%) during this review period. This may be due to an already exiting COVID-19 infection prior to vaccination, and the susceptibility to constantly changing variants. Note that during the review period, 1 non-serious case overlapped 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. **Subpopulation Analyzes:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – SPIKEVAX (NOS)*

	During the review period, no cases were reported among immunocompromised individuals in these age groups who received a vaccine under the SPIKEVAX (NOS) classification. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received a vaccine under the SPIKEVAX (NOS) classification.
Discussion	As of the DLP date of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in immunocompromised individuals. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, the general pattern of commonly reported AEs in those considered immunocompromised individuals is comparable to the general population. Evaluation showed that the most frequently reported AEs in the immunocompromised population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The adverse events observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population was generally similar. Epidemiological studies have not indicated any increased risk of AEs in immunocompromised individuals after vaccination with a marketed Moderna vaccine targeting SARS-CoV-2. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. During the review period, there was 1 case reported in a 14-year-old adolescent. No cases were reported for children under 12 years of age. Review of cumulative cases for these subpopulations have not revealed any new or unusual pattern of events or safety concerns. Cases with a fatal outcome in immunocompromised individuals during the reporting period (1.7%) were strongly confounded by long or unspecified latency and multiple comorbidities that provided alternate etiologies.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of a marketed Moderna vaccine targeting SARS-CoV-2 in immunocompromised individuals. Information presented in those reports does not differ from the known safety profile of the marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important safety information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Immunocompromised, reported in temporal association with the administration of a marketed Moderna vaccine targeting SARS-CoV-2 did not raise any new safety concerns.

	The MAH will continue to monitor events for immunocompromised individuals using routine surveillance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Use in immunocompromised subjects is a safety concern (missing information) in the PSUR only.

The MAH presented information regarding use of marketed Moderna vaccines targeting SARS-CoV-2 in immunocompromised individuals for the reporting interval (18 Jun 2023 to 17 Dec 2023). Data were retrieved from the MAH's global safety database and from a literature search.

Literature: The performed literature search retrieved 53 publications. No new and significant safety information was identified by the MAH.

MAH's safety database: During the reporting interval, 182 cases (3 fatal cases) with 629 adverse events were reported for immunocompromised individuals who received marketed Moderna vaccines targeting SARS-CoV-2. Most cases were observed for Elasomeran (91 cases of which 2 were fatal) and Andusomeran (58 cases of which 1 was fatal). Review of the three fatal cases concluded that they were unlikely related (n = 2) due to long TTO outside the risk window/unspecified latency and concurrent medical conditions that provided an alternative etiology, and unassessable (n = 1) due to limited information.

Conclusion

Overall, the general pattern of commonly reported AEs in those considered immunocompromised individuals is comparable to that of the general population. No clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received marketed Moderna vaccines targeting SARS-CoV-2.

The MAH will continue to monitor events for immunocompromised individuals using routine surveillance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904.

2.3.1.3.5. Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in the frail subpopulation has not identified any additional clinically relevant new safety information for this subpopulation. Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran). The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, remains valid.

Missing information	**Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)**
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources

	o Retrieved: Appendix 13.4 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	Frail patients are considered at higher risk for 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 co-morbidities were excluded from the registration CTs, the MAH is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Safety reports for frail subpopulation is summarized because it is an area of missing information in the PBRER, but it was removed from the RMP during the previous PBRER reporting period. No specific safety concerns have been identified.
Methods	The ModernaTx, Inc. GSDB was queried for reports of frail individuals using "Frail" custom search as defined in the Moderna Signalling Strategy plan (see Appendix 12.16), which included subjects of all ages with unstable health conditions and comorbidities (including COPD, HIV, diabetes, chronic neurological disease, cardiovascular disorders).
Results	Refer to PSUR Appendix 12.16 for more information. **Overview of Frail Cases Reported for elasomeran:** It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide. Therefore, during this review period, there was a considerable decrease in the number of reported cases for frail individuals who received elasomeran vaccine. During the review period, the MAH received 641 cases (3,077 events) reported in Frail subpopulation with 352 (54.9 %) serious cases (1,061 serious events), 279 cases (43.5%) were medically confirmed cases, and 17 (2.7%) cases with fatal outcome involving elasomeran. The majority of cases were reported in females (398, 62.1%) compared to males (225, 35.1%). The median patient age was 55.0 years (range: 0.4 to 97.0 years). A high proportion of reported cases in frail was among the elderly (192, 29.9%). The most frequently reported events (>2%) were fatigue, headache, pyrexia, myalgia, and vaccination site pains. These events were comparable to that reported in the general population that received elasomeran and reflected expected reactogenicity. Evaluation of the 17 cases (26.5%) with fatal outcomes showed that majority (10; 58.8%) were elderly above 65 years, and all 17 cases had comorbidities that were confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, most of the cases (13; 76.5%) were assessed as unlikely, due to TTO that was outside the risk window and concurrent medical conditions that provided alternate etiologies. Four cases were assessed as possible, due to temporal

	association. However, these 4 cases were confounded by concurrent polymorbid conditions. **Overview of Frail Cases reported for elasomeran/imelasomeran:** During the review period, the MAH received 64 cases (207 events) reported in Frail subpopulation, with 51 serious cases (154 serious events), 19 medically confirmed cases, and 4 cases with fatal outcome involving elasomeran/imelasomeran. Cases were almost equally distributed across gender, females (31 cases, 48.4%) compared to males (28 cases, 43.8%). The median patient age was 64.0 years (range: 22.0 to 91.0 years). The most frequently reported MedDRA PTs were fatigue, dyspnoea, headache, arthralgia, pain in extremity, dizziness, chest pain, injection site reaction, syncope, myocarditis and palpitations. The majority of these events were comparable to that reported in the general population that received elasomeran/imelasomeran and reflected expected reactogenicity. Myocarditis is an identified risk for elasomeran. Evaluation of the 4 cases with fatal outcomes showed that half (2; 50.0%) were elderly above 75 years, 1 was in a 25-39 year-old range, and 1 was missing information on age. All 4 cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, 3 of the cases were assessed as unlikely (due to TTO outside the risk window and concurrent medical conditions that provided alternate etiologies); and 1 case was assessed as possible, based on temporal association. However, concurrent comorbidities of bradycardia and syncope provide alternate etiology. **Overview of Frail Cases Reported for elasomeran/davesomeran:** During the review period, the MAH received 93 cases (260 events) reported in the frail subpopulation, with 36 serious cases (76 serious events), 77 medically confirmed cases, and 5 cases with fatal outcome involving elasomeran/davesomeran. A slightly higher proportion of cases were reported in females (51; 54.8%) compared to males (41; 44.1%). The median patient age was 71.0 years (range: 4.0 to 98.0 years) with highest cases seen in the elderly >65+ (62.6%). The most frequently reported MedDRA PTs in frail subpopulation receiving elasomeran/davesomeran were pyrexia, myalgia, pain in extremity, fatigue, vaccination site pain, headache, arthralgia, and malaise. These events are expected reactogenicity and consistent with reports in the general population that received elasomeran/davesomeran. Evaluation of the 57 frail/elderly cases showed a higher proportion of case in females (33; 57.9%) compared to males (24; 42.1%), with over half (31; 54.4%) reported in 75+-year age group.

	Evaluation of the 5 cases with fatal outcomes showed a higher number of cases reported in females (3; 60.0%). All of the cases were from Japan and 4 of the 5 were over 75 years of age. All cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Using the WHO-UMC causality assessment tool, all 5 cases were assessed as unlikely, due to TTO outside the risk window, and concurrent polymorbid medical conditions that provide alternate etiologies. **Overview of Frail Cases Reported for andusomeran:** During the review period, the MAH received 228 cases (811 events) reported in the frail subpopulation, with 94 serious cases (223 serious events), 129 medically confirmed cases, and 8 cases with fatal outcome involving andusomeran. A slightly higher proportion of cases were reported in females (129; 56.6%) compared to males (88; 38.6%). The median patient age was 70.0 years (range: 5.0 to 98.0 years) with the highest cases seen in the elderly >65+ (63.2%). The most frequently reported MedDRA PTs in frail subpopulation receiving andusomeran were fatigue, headache, pyrexia, chills, chest pain, nausea, myalgia, diarrhoea, seizure, and loss of consciousness. Most of these events are expected reactogenicity (except for seizure, loss of consciousness, and chest pain) and were consistent with reports in the general population that received andusomeran. Over half of the cases (57.0%) were from the US. Evaluation of the 144 frail/elderly cases showed a higher proportion of case in females (75; 52.1%) compared to males (63; 43.8%). with over half (77; 53.5%) reported in 65-74 year age group. Most of the deaths were reported in females (5; 62.5%). Four cases were from Japan. All 8 cases had significant comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Seven of the individuals were over 80 years of age. Using the WHO-UMC causality assessment tool, 5 cases were assessed as unlikely, due to concurrent polymorbid conditions that provided alternated etiologies. Three cases were assessed as possible, based on temporal association, and reported clinical features of myocarditis and anaphylaxis. However, there were underlying cardiovascular, respiratory, and chronic renal disease confounders/risk factors. Myocarditis and anaphylaxis are identified risk for elasomeran. **Overview of Frail Cases Reported Involving a Vaccine Under the SPIKEVAX (NOS) Classification.:** During the review period, the MAH received 19 cases (50 events) reported in the frail subpopulation, with 6 serious cases (8 serious events), 14 medically confirmed cases, and 1 case with a fatal outcome involving a vaccine under the SPIKEVAX (NOS) classification. Cases were similarly reported in females (8; 42.1%) and males (9; 47.4%). The median patient age was 67.5 years (range: 23.0 to 83.0 years) with the highest events seen in the elderly >65+ years (42.1%) followed by the 50-64-year age group (21.1%).

	Most cases were non-serious (68.4%) with the most frequently reported MedDRA PTs in frail subpopulation receiving a vaccine under the SPIKEVAX (NOS) classification were fatigue, pyrexia, arthralgia, pain in extremity, and weight decreased. Most of these events are expected reactogenicity (except for weight decreased) and consistent with reports in the general population. COVID-19 infection was reported as a clinical event. The majority of cases (84.2%) were from the United States. Evaluation of the 8 frail/elderly cases showed equal distribution across gender (4 cases each; 50%) with the majority (6; 75.0%) reported in 65-74 year age group. Among serious cases, the majority had missing outcome. There was 1 case with fatal outcome in a 23-year-old male with a medical history of chronic asthma, who experienced respiratory distress, dyspnoea, and chest pain after vaccination of a dose of a vaccine under the SPIKEVAX (NOS) classification, with an unknown TTO. There was no report of concomitant medications, clinical course of events, and diagnostic results, The cause of death was not reported nor was an autopsy performed. Using the WHO-UMC causality assessment tool, the case was assessed as unassessable due to insufficient information on TTO, clinical course of events, diagnostic results. This case is confounded by concurrent asthma.
Discussion	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. Most of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, 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. Evaluation showed that the most frequently reported AEs in the frail population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The pattern of events observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals after vaccination with elasomeran. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events or safety concern. Cases with fatal outcome in the frail subpopulation in the reporting period (3.2%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiologies.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2 in the frail subpopulation. Information presented in those reports does not differ

	from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important safety information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in the frail subpopulation. Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Frail, reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any new safety concern. The MAH will continue to monitor events for Frail using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Frail subjects with unstable health conditions and co-morbidities is a safety concern (missing information) in the PSUR only.

The MAH has presented information regarding use of marketed Moderna vaccines targeting SARS-CoV-2 in frail subjects with unstable health conditions and co-morbidities for the latest review period (18 Jun 2023 to 17 Dec 2023). Data were retrieved from the MAH's global safety database and from a literature search.

Frail patients are considered at higher risk for complications due to COVID-19 infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. Since frail subjects with unstable health conditions and co-morbidities were excluded from the registration CTs, the MAH is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. No specific safety concerns have been identified.

Literature: There was no new and significant safety information identified, according to the MAH.

MAH's safety database: In the review period, 1,045 cases (4,405 adverse events) were identified for marketed Moderna vaccines targeting SARS-CoV-2, of which 35 were fatal cases. Most cases were observed for Elasomeran (641 cases of which 17 were fatal) and Andusomeran (228 cases of which 8 were fatal). The MAH did not identify any patterns or specific safety concerns in frail individuals. Most of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, the general pattern of commonly reported AEs in those considered frail individuals or with unstable health conditions and comorbidities is comparable to that of the general population. Cases with fatal outcome (3.2%) were strongly confounded by multiple comorbidities and/or advanced age, which provided alternate etiologies.

Conclusion

The reported events in frail individuals are consistent with the known safety profile for marketed Moderna vaccines targeting SARS-CoV-2.

The MAH will continue to monitor these events through routine surveillance. This is endorsed.

2.3.1.3.6. Use in subjects with autoimmune or inflammatory disorders (AI/ID) (Safety concern in PBRER only)

Evaluation of information received during the present PBRER reporting interval relating to individuals with known history of autoimmune and inflammatory disorders (MedHx AI/ID) and vaccination with a

marketed Moderna vaccine targeting SARS-CoV-2, has not identified any additional clinically relevant new safety information for this population. Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

The characterization of this missing information within this PSUR as of the DLP of this PBRER and in Section 16.4, remains valid. The number of cases received during reporting period are presented by product in Table 28. Refer to Appendix 12.17 for further information on fatal cases.

Table 28: Use in subjects with Autoimmune or Inflammatory Disorders (AI/ID) (Safety concern in PBRER only)

Missing information	**Use in subjects with autoimmune or inflammatory disorders (AI/ID)**
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 73 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	To date, clinical trials have not identified any specific safety risks in individuals with AI/AD. Because there was limited data from CTs on the use of elasomeran COVID-19 vaccines, in individuals with AI/ID, the MAH has been closely monitoring the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in this population through routine Pharmacovigilance. Important to note that use of these vaccines in individuals with AI/ID is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a request from the PRAC. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in AI/ID 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. Furthermore, some countries are suggesting additional doses after primary series in individuals with MedHx of AI/ID. Thus far, there have been no specific safety concerns for individuals with MedHx of AI/ID. Epidemiological studies have not indicated any increased risk of side-effects in individuals with AI/ID after vaccination with marketed Moderna vaccines targeting SARS-CoV-2 and have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general population receiving marketed Moderna vaccines targeting SARS-CoV-2.

Methods	The ModernaTx, Inc GSDB was queried for valid clinical and spontaneous reports for marketed Moderna vaccines targeting SARS-CoV-2 in people with a medical history of autoimmune and/or inflammatory disease, received for review period (18 Jun 2023 to17 Dec 2023). Reports from individuals with a MedHx AI/ID were identified from MAH GSDB using Immune-mediated/autoimmune disorder SMQ "Immune-mediated/autoimmune disorders SMQ" PTs identified in past medical history. Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	Refer to Appendix 12.17 for additional information. **Overview of MedHx AI/ID Cases Reported for elasomeran** During this reporting period, 367 cases (209 serious, 147 medically confirmed, 5 fatal cases) with 1,700 events (663 serious) were reported in individuals with a known MedHx AI/ID after receiving elasomeran. Majority of cases (264; 71.9%) were reported in females compared to males (88 cases; 24.0%), with a small proportion of cases (15; 4.1%) having no gender reported. The mean patient age was 51.4 years (SD: 15.8) and median age was 51.0 years (range: 16.0 to 97.0 years). Of note, 36 cases (9.8%) were missing age-related information. The most frequently reported serious events during this reporting period were headache, fatigue, and multiple sclerosis pseudo relapse. Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (elasomeran) During this reporting period, there was 1 non-serious case reported in a 16-year-old male. Fatal Cases in Individuals with MedHx AI/ID (elasomeran) During this reporting period, 5 cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran. Refer to Appendix 12.17 for further information. **Overview of MedHx AI/ID Cases Reported for elasomeran/imelasomeran:** During the reporting period, 22 cases (19 serious, 3 medically confirmed, 0 fatal) with 78 events (68 serious) reported in individuals with a known MedHx AI/ID after receiving elasomeran/imelasomeran. When gender was known, no important differences were noted in reports involving females (11 cases; 50.0%) and males (10 cases; 45.5%), with 1 case (4.5%) having no gender reported. The mean patient age was 56.9 years (SD:14.2) and median age was 62.0 years (range: 27.0 to76.0). Of note, 1 case (4.5%) was missing age-related information. The most frequently reported serious events were fatigue, diarrhoea, pain in extremity, syncope, and COVID-19 in individuals with known MedHx AI/ID who received elasomeran/imelasomeran. Subpopulation Analysis:

	Use in Children <18 years of Age with MedHx AI/ID (elasomeran/imelasomeran) During this reporting period, no cases were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (elasomeran/imelasomeran) During this reporting period, no cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran/imelasomeran. **Overview of MedHx AI/ID Cases Reported for elasomeran/davesomeran:** During the reporting period, 25 cases (6 serious, 21 medically confirmed, 0 fatal) with 72 events (9 serious) reported in individuals with known MedHx of AI/ID after receiving elasomeran/davesomeran. The majority of cases were reported in females (17 cases; 68.0%) compared to males (7 cases; 28.0%), with 1 case (4.0%) having no gender reported. The mean patient age was 64.8 years (SD:14.4) and median age was 68.0 years (range: 28.0 to 92.0 years). Of note, 3 cases (12.0%) did not report agerelated information. During this reporting period, anaphylactic reaction was reported in 2 cases, (22.2%), and all other serious events, each were reported once (11.1%) in individuals each with known MedHx AI/ID receiving elasomeran/davesomeran. Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (elasomeran/davesomeran) During this reporting period, no cases involving elasomeran/davesomeran were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (elasomeran/davesomeran) During this reporting period, no cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran/imelasomeran. **Overview of AI/ID Cases Reported for andusomeran:** During this reporting period, 62 cases (26 serious, 27 medically confirmed, 1 fatal case) with 248 events (84 serious) were reported in individuals with a known MedHx AI/ID after receiving andusomeran. The majority of cases (44; 71.0%) were reported in females compared to males (14 cases; 22.6%), with a small proportion of cases (4; 6.5%) having no gender reported. The mean patient age was 57.0 years (SD: 17.7) and median age was 57.0 years (range: 24.0 to 89.0 years). Of note, 8 cases (12.9%) did not provide age-related information. The most frequently reported serious events during this reporting period often reflected expected reactogenicity events, such as pyrexia, headache, and fatigue. These are consistent with cumulative reporting. Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (andusomeran) During this review period, no cases involving andusomeran were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (andusomeran)

	During this reporting period, 1 case with fatal outcome was reported in an individual with known MedHx AI/ID who received andusomeran. Refer to Appendix 12.17 for further information. **Overview of MedHx AI/ID Cases Reported for a vaccine under the SPIKEVAX (NOS) classification:** During this reporting period, 14 cases (3 serious, 9 medically confirmed, 0 fatal) with 33 events (9 serious) were reported in individuals with a known MedHx AI/ID after receiving a vaccine under the SPIKEVAX (NOS) classification. When gender was known, no important differences were noted in reports involving females (6 cases, 42.9%) and males (4 cases, 28.6%), and 4 cases (28.6%) had no gender information reported. The mean patient age was 57.5 years (SD: 10.6) and median age was 59.0 years (range: 37.0 to 74.0 years). Of note, 6 cases (42.9%) did not provide age-related information. During this reporting period, all serious events (haematuria, pyrexia, axillary mass, cardiogenic shock, diarrhoea, influenza, lymphadenopathy, stress cardiomyopathy and vomiting) each were reported once (11.1%). Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (SPIKEVAX [NOS]) During this review period, no cases involving a vaccine under the SPIKEVAX (NOS) classification. were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (SPIKEVAX [NOS]) During this reporting period, no cases with fatal outcome were reported in individual with known MedHx AI/ID who received a vaccine under the SPIKEVAX (NOS) classification.
Discussion	Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers the cases of MedHx AI/ID to be consistent with the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2 and the benefits for elasomeran far outweigh any possible vaccine-associated risks. No new safety concerns were identified in the literature review concerning marketed Moderna vaccines targeting SARS-CoV-2. The safety and benefit/risk profile of COVID vaccination in individuals with AI/ID remains acceptable. In AI/ID patients with disease flares, there is a natural waxing and waning course, and there are no reliable referenced data on the background rates of respective flares especially given the number of various AI/ID diseases and how to accurately measure a flare. The identified flare cases did not demonstrate a safety concern for this reporting period. 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 marketed Moderna vaccines targeting SARS-CoV-2. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving marketed Moderna vaccines targeting SARS-CoV-2. For the fatal AI/ID cases, common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, and hyperlipidemia, are similar to those reported in the general population fatal reports.
Conclusion	Evaluation of the data during this reporting period did not identify any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2. Information presented in those reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Autoimmune/ inflammatory Disorders reported in temporal association with the administration of marketed Moderna vaccine targeting SARS-CoV-2 did not raise any new safety concern. The MAH will continue to monitor events in individuals with known MedHx AI/ID using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Use in subjects with autoimmune or inflammatory disorders is a safety concern (missing information) in the PSUR only.

The MAH has presented information regarding use of marketed Moderna vaccines targeting SARS-CoV-2 in subjects with autoimmune or inflammatory disorders for the latest review period (18 Jun 2023 to 17 Dec 2023). Data were retrieved from the MAH's global safety database and from a literature search.

To date, clinical trials have not identified any specific safety risks in individuals with AI/AD. Because there was limited data from CTs on the use of elasomeran COVID-19 vaccines in individuals with AI/ID, the MAH has been closely monitoring the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in this population through routine pharmacovigilance.

Literature: 73 publications were retrieved by the MAH. No new and significant safety information was identified. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in AI/ID 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.

MAH's safety database: During the reporting interval, 490 cases (6 fatal cases) with 2,131 adverse events were reported for subjects with autoimmune or inflammatory disorders who received marketed Moderna vaccines targeting SARS-CoV-2. Most cases were observed for Elasomeran (367 cases of which 5 were fatal) and Andusomeran (62 cases of which 1 was fatal). The MAH's review of the six fatal cases

concluded that they were unassessable (n = 5) or unlikely (n = 1) due to limited information, negative TTO, and confounding by underlying disease. The Rapporteur agrees that based on the MAH's presentation of these fatal cases in PSUR appendix 12.17a, none of them provide significant new safety information.

Conclusion

The events in subjects with autoimmune or inflammatory disorders are consistent with the known safety profile for marketed Moderna vaccines targeting SARS-CoV-2.

The MAH will continue to monitor these events through routine surveillance.

2.3.2. Safety topics under monitoring including requests from Health Authorities or regulatory bodies

2.3.2.1. Requests from previous PSUSA (no 5)

2.3.2.1.1. ITEM 1 (Autoimmune hepatitis)

The MAH is requested to provide a cumulative review of autoimmune hepatitis with elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran or Andusomeran exposure in the next PSUR. Information from all relevant data sources including the literature, spontaneous case reports, randomised clinical trials (RCTs) and noninterventional studies should be considered. The MAH should also present and evaluate the literature case reports and observational studies related to Elasomeran mentioned in the article by Uzun et al. (PSUR page 7558). The MAH should ensure that all cases of autoimmune hepatitis are included and therefore any MedDRA preferred terms (PT) which could possibly overlap with AIH (i.e. acute hepatic failure, drug-induced liver injury, hepatitis acute, hepatitis fulminant, immunemediated hepatic disorder and immune-mediated hepatitis) should be checked.

The MAH should perform a causality assessment of all retrieved cases preferably using the WHO-UMC causality assessment criteria and provide a justification for the chosen causality category. Cases assessed by the MAH as "possible", "probable" or "certain" and all cases with positive re-challenge should be presented and discussed. Case narratives should be provided in an appendix. Eudravigilance case numbers should be provided when available. The MAH is kindly asked to present the cases in a table similar to the following:

Case ID	Consumer characteristics (gender, age)	Reaction PT	Rechallenge /dechallenge	Time to onset	Medical history	Concomitant medication	Causality assessment	WHO-UMC Causality Category

[...]

The MAH should also evaluate retrieved cases using the simplified diagnostic criteria of the International Autoimmune Hepatitis Group and present the cases according to the score they achieve by this set of criteria. However, otherwise well-documented cases that are not evaluated as "definite" or "probable" cases of autoimmune hepatitis according to these criteria should also be presented and discussed. Furthermore, the cumulative review should include a discussion of the potential mechanism of action. If the MAH considers an update of the product information warranted, a wording and frequency for inclusion

in the SmPC and package leaflet should be proposed with presentation of the used method for calculation of frequency.

MAH response

Following the review of PBRER#5, a request from a health authority was received to provide a cumulative review of autoimmune hepatitis (AIH) with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran exposure in the next PSUR.

Source of the AIH Review:

A Health Authority requested the following information on AIH as part of the final assessment report of PBRER #5:

- The MAH is requested to provide a cumulative review of AIH with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran exposure in the next PSUR.
- Information from all relevant data sources including the literature, spontaneous case reports, randomised clinical trials (RCTs) and non-interventional studies should be considered.
- The MAH should also present and evaluate the literature case reports and observational studies related to elasomeran mentioned in the article by Uzun (PSUR page 7,558) [9].
- The MAH should ensure that all cases of autoimmune hepatitis are included and therefore any MedDRA PT which could possibly overlap with AIH (i.e., acute hepatic failure, druginduced liver injury, hepatitis acute, hepatitis fulminant, immune-mediated hepatic disorder and immune-mediated hepatitis) should be checked.
- The MAH should perform a causality assessment of all retrieved cases preferably using the WHO-UMC causality assessment criteria and provide a justification for the chosen causality category.
- Cases assessed by the MAH as "possible", "probable" or "certain" and all cases with positive re-challenge should be presented and discussed. Case narratives should be provided in an appendix. Eudravigilance case numbers should be provided when available.
- The MAH should also evaluate retrieved cases using the simplified diagnostic criteria of the International AIH Group and present the cases according to the score they achieve by this set of criteria. However, otherwise well-documented cases that are not evaluated as "definite" or "probable" cases of AIH according to these criteria should also be presented and discussed.
- Furthermore, the cumulative review should include a discussion of the potential mechanism of action.
- If the MAH considers an update of the product information warranted, a wording and frequency for inclusion in the SmPC and package leaflet should be proposed with presentation of the used method for calculation of frequency.

Background of Information:

Autoimmune Hepatitis is a non-resolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinaemia even in the absence of cirrhosis, circulating autoantibodies, association with human leukocyte antigens (HLA) DR3 or DR4, interface hepatitis on liver histology, and a favourable response to immunosuppression (e.g., with corticosteroids). The disease, if untreated, often leads to cirrhosis, liver failure and death. It is well established that AIH is a clinically distinct syndrome characterized by a large heterogeneity of clinical, laboratory and histological manifestations. Therefore, AIH should be considered in any patient with acute or chronic liver disease, particularly if hypergammaglobulinemia is present, and if the patient has features of other autoimmune diseases. The

disease also affects males (25–30% of all AIH patients) and may present at any age and in all ethnic groups. In most studies, a bimodal age pattern at presentation has been reported with one peak during childhood/teenage years and another in middle age between the 4th and 6th decade of life. Recent studies have shown that an increasing number of patients are diagnosed also at older ages (above 65 years). Recently it has been shown that appropriate attention should also be paid to the health-related quality of life (HRQoL) parameters, since a high rate of previously unrecognised mental impairment with depression and anxiety symptoms are present in patients with AIH. Manifestations were reported in 31% cases at diagnosis.

The diagnosis of AIH is usually based on the presence of the typical phenotype of the disease along with the exclusion of other causes of chronic liver diseases. The diagnostic criteria for AIH and a diagnostic scoring system have been codified by a group of experts in the IAIHG in 1993, revised in 1999 and more recently proposed in a simplified manner for routine clinical use.

According to the PRAC final assessment report (**Procedure no.: EMEA/H/C/PSUSA/00010897/202206**) (Reporting Period 01 Jan 2022 to 18 Jun 2022) the following conclusions were discussed:

"*As of 18 Jun 2022, there has cumulatively been 10 reported cases classified as "definitive" or "probable" cases of AIH according to the European Association for the Study of the Liver (EASL) guidelines, while 201 cases were categorized as not cases of AIH according to the Simplified Classification Guidelines or that were unassessable based on missing information. The reporting rate of AIH is low being 0.01 per million doses administered, and there is not sufficient data to indicate a causal association between AIH and Elasomeran despite any temporal association. No new safety issue of concern was identified. AIH-related events are not presently a safety issue of concern, and the MAH will continue to evaluate events of "AIH-related events" using routine surveillance, which is supported."*

Methods:

The Company clinical database and the GSDB were queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 Dec 2020 to 17 Dec 2023, worldwide, reported for the mRNA-1273 vaccine (ModernaTx, Inc COVID-19 vaccine) using the following PTs: "*Autoimmune Hepatitis, Alloimmune hepatitis, Immunemediated hepatitis, Immune-mediated hepatic disorder, Liver injury, Drug-induced liver injury, Hepatitis acute, Hepatitis toxic, Hepatocellular injury, Hepatitis fulminant, Hepatotoxicity, Acute hepatic failure, and Hepatic failure*". The CT data is from the 3 adult CTs (mRNA-1273-P301, mRNA-1273-P205 and mRNA-1273-P205).

All retrieved cases were classified into two categories, following the Simplified diagnostic criteria of the International AIH Group: Definite AIH and not an AIH case (Table 15-2).

Case of AIH:

- Definite autoimmune hepatitis: 7 Points or more
- Probable autoimmune hepatitis: 6 Points

Not a Case of AIH: Those cases for which there were insufficient information to provide a diagnostic classification were classified as "Unassessable".

Table 29: Simplified diagnostic criteria of the International Autoimmune Hepatitis Group

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

ANA= antinuclear antibodies SMA= smooth muscle antibodies LKM= liver kidney microsomal antibodies

SLA= soluble liver antigens LP= liver pancreas

Addition of points achieved for all autoantibodies (maximum, two points).

Typical liver histology for AIH = each of the following features had to be present namely, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation.

Compatible liver histology for AIH = chronic hepatitis with lymphocytic infiltration without all the features considered typical.

Atypical = showing signs of another diagnosis, like steatohepatitis.

For those cases classified as definite and probable AIH, the Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

It is important to note that the MAH has conducted previous cumulative reviews of AIH as per request from a health authority from 18 Dec 2020 to 02 Feb 2022 (SPIKEVAX EPITT ref. No. 19,750), as well as in PBRER # 3 (Reporting Period 01 Jan 2022 to 18 Jun 2022).

The signal of AIH was triggered from PRAC signal assessment report (EPITT 19750) (dated 02 Dec 2021), based on the available evidence from case reports published in the literature and submitted to Eudravigilance (EV). Following assessment based on the review of all available sources, no cases of AIH were reported in the CT setting. Analysis from the Company global safety database retrieved 165 cases, 11 cases (7%) were suggestive of AIH, and of these, 8 cases were considered as related (including cases where only temporal association with elasomeran was reported). No disproportionate reporting of AIH was found in EVDAS or VAERS. The O/E analysis for PT AID did not provide observed counts higher-than-expected. In age-stratified O/E analysis interpretability of data was limited due to small numbers. Several articles described AIH and mRNA vaccine, but none showed a direct temporal association with mRNA vaccines against COVID-19 disease. No plausible pathognomonic findings were found to support a possible causal association between the administration of elasomeran and the occurrence of AIH. In conclusion MAH considered AIH in association with elasomeran as refuted.

Review of Data from All Sources:

Clinical Trial Data:

The topic of AIH was cumulatively reviewed in the Company clinical database from 3 adult CTs to identify unsolicited events (serious and non-serious), reported using the following MedDRA PT "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis

fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immunemediated hepatic disorder, Immune-mediated hepatitis, Liver injury".

The review performed in mRNA-1273-P301 (as of 04 May 2021); for mRNA-1273.222-P205-Part H (as of 23 Sep 2023), and mRNA-1273.815-P205- Part J (as of 25 May 2023), did not retrieve any cases for AIH related terms.

Review of the Global Safety Database

The MAH queried the GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 17 Dec 2023, for Marketed Moderna vaccines targeting SARS-CoV-2 and SPIKEVAX (NOS) for cases of AIH including the MedDRA PTs: "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury" (see Appendix 12.8).

Of note, throughout the document for simplicity reasons AIH is used in text or tables to describe the entire topic; it is inclusive of all the PTs from the search strategy i.e., "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury".

Results

Cumulatively, through 17 Dec 2023, the MAH received 315 cases (327 events) of AIH related PTs involving Moderna vaccines targeting SARS-CoV-2, of which 306 cases (317 events) involved elasomeran, six (6) cases involved elasomeran/imelasomeran, one (1) case involved elasomeran/davesomeran, and two (2) cases involved andusomeran. There were no cases of AIH reported for SPIKEVAX (NOS). There were 310 serious cases, and 232 cases were medically confirmed. There were 30 cases with a fatal outcome. A total of 133 cases (42.2%) involved males and 177 cases (56.2%) involved females and 5 (1.6%) cases missing gender. The mean age was 54.7 (SD: 17.9), with a median 56.0 years (range 0.0 to 96.0 years). Most of the events reported had an outcome of recovered/ recovering (121; 37.0%).

During the initial cumulative review of AIH as of 31 Dec 2021, a total of 165 cases (171 events) of AIH-related terms were retrieved, with 138 (74.3%) cases medically confirmed. Out of those, 163 were serious cases with 22 cases with a fatal outcome. The majority of the reports were in females 96 (58.2%) and in patients >50 years of age. Same demographic information as during this second updated cumulative review. Information on these cases and its initial evaluation is included in Appendix 12.8.

During this updated review of AIH (01 Jan 2022 to 17 Dec 2023), there were 152 cases (156 events) of AIH-related terms retrieved, with 94 (61.8%) cases medically confirmed. Out of those, 147 were serious cases with 8 cases with a fatal outcome. During this updated review there were no important differences between males (77; 50.56%) and females (81; 53.3%). Mean reporting age was 54.7 years. Information on these cases and its evaluation is included in Appendix 12.8.

Cases Classification by the Simplified diagnostic criteria of the International AIH Group

1. Cumulative review as of 31 Dec 2021

Out of the 165 case reports identified in the first cumulative evaluation, there were two cases that were considered duplicate and one case report that was miscoded [redacted] was as a cases of myocarditis injury that was mistakenly coded to liver injury).

After evaluation of the 165 cases, there were 155 cases that were classified as not cases of AIH or that were unassessable, based on missing information including clinical course, laboratory data, dose and/or

TTO. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history not reported, as well as concomitant medications. Of the 165 cases there was a follow-up information reported on two cases (and), rest of the cases, there is no change or updated information as of 17 Dec 2023.

There were 7 case reports that were considered confirmed AIH according to the EASL Simplified diagnostic criteria. All those reports were considered possible according to the WHO causality assessment by the MAH. Two reports were considered probable by the PRAC assessor. As mentioned above, the following case had follow-up information and upon internal review, it was identified that the case is duplicate of original case . All the information from case has been incorporated into case . Another case (which was assessed as not an AIH case in the initial review was assessed as AIH case due to follow-up information. both these cases are reviewed and commented in the updated review. Information on all these 163 cases is included in Appendix 12.8.

2. Updated review as of 17 Dec 2023

Out of the 152 new reports of AIH-related events identified during this updated review, there were 141 cases that were classified as not cases of AIH or that were unassessable, based on missing information including clinical course, laboratory data, dose and/or TTO. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history not reported, as well as concomitant medications.

Review of AIH Exacerbations

During the updated cumulative review, there were 5 cases and in which it was reported as having previous history of AIH or related- liver conditions (including HBV) that may have been considered as indicators of a possible pre-existing asymptomatic AIH. It has been reported that classical AIH takes an asymptomatic subclinical course in about half of cases [10].

Review of WHO Probable and Possible Cases:

During this updated review of cases with AIH-related events, there were 11 cases that were considered confirmed AIH according to the EASL Simplified diagnostic criteria. According to the WHO causality assessment, there were seven cases considered "Possible", and 4 cases considered "Unlikely" related to vaccination (Note: one case was re-assessed as AIH case from previous assessment due to the follow-up case details and another case had merged data from case . Information on all these 163 cases is included in Appendix 12.8.

Review of the 11 cases demonstrates that most are heavily confounded by the presence of multiple confounding factors such as, medical history, concurrent medications, drug hypersensitivity and underlying diseases, and pre-existing conditions making it difficult to establish a causal association. Additionally, several cases involved patients taking medications such as statins, hormonal therapies, and pain relievers like ibuprofen and paracetamol. These medications have known hepatotoxic potential and are important confounders for an appropriate causality assessment. Details of these cases are presented in Appendix 12.8.

Literature Review

Literature search review:

A focused cumulative search of published literature was conducted in PubMed, from 18 Dec 2020 through 17 Dec 2023. A total of 278 articles (See Appendix 13.4 for search criteria) were retrieved. Review of the

278 articles did not show any causal association between elasomeran vaccination and AIH. These articles encompassed different types of studies, including case reports (31), observational studies (7), and others were general literature reviews on importance of vaccination or other general AIH topic. There are not pathognomonic findings to link vaccine to these AIH adverse events.

Among these articles, the following article Uzun et al [9], was summarized in detailed as requested by health agency. There were six individual cases created based on this article [redacted] and [redacted] of these 6 cases 4 were considered as a true case of AIH and two case was categorized as not a case of AIH. All these cases were described in PBRER#5 and there are no changes from earlier assessment of this article.

Probable Mechanism(s) for Vaccine-associated AIH

During this updated cumulative review of AIH, no new information was identified related to probable mechanism associated with the reported cases of AIH after COVID-19 vaccination. Several hypotheses have been presented in several articles reporting cases of patients with AIH following COVID-19 mRNA vaccination. Among these it is postulated that COVID-19 mRNA vaccination, through activation of the innate immune system and subsequent non-specific activation of autoreactive lymphocytes, may lead to the development of autoimmune diseases including AIH or trigger a drug-induced liver injury with features of AIH [11]. The trigger, if any, may become more apparent over time, especially following withdrawal of immunosuppression.

Other authors have suggested that given that the COVID-19 mRNA vaccines lacks immune adjuvants, genetic susceptibility, exposure to foreign peptides homologous to human peptides (molecular mimicry), and immune system stimulation by vaccine adjuvant may not be part of the problem, but the homology between the SARS-CoV-2 spike protein and soluble liver antigen may be a clue: i) similar native or glycosylated amino acid epitopes shared between the protein expressed in the host after vaccination and soluble liver antigen, and ii) structural similarities between the proteins. It is also possible that other liver autoantigens (different from SLA) share sequence homology with the protein expressed by the host after SARS-CoV-2 vaccination with mRNA vaccines. In other words, the mechanism for the development of AIH is still not well understood. AIH has also been reported following immunization with other vaccines (not directed against SARS-CoV2, e.g., seasonal influenza, HPV). Causative mechanisms are similarly unclear for these cases. None of the hypotheses presented in the literature provide a clear mechanism for Vaccine-associated AIH.

Discussion

An updated cumulative search of GSDB as of 01 Jan 2022 to 17 Dec 2023, was performed. The search retrieved additional 152 cases (156 events) for a cumulative total of reported cases from 18 Dec 2020 to 17 Dec 2023 of 315 cases (327 events). After evaluation of all these cases, there were 297 cases that were classified as not cases of AIH based on missing information including clinical course, laboratory data, dose and/or TTO. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history is not reported, as well as concomitant medications. There were 18 cases confirmed as AIH according to the EASL Simplified diagnostic criteria.

For all reports identified cumulative, there were more women (177; 56.2%) than men (133; 42.2%) which is what have been described in the general population where AIH preferentially affects women more than men by a ratio of 3.6/1.05 [12]. As of 17 Dec2023, there have been 1,776,284,733 doses of elasomeran distributed worldwide, with 1,043,567,281 doses that are estimated to have been administered.

Based on the cumulative identification of 18 reported cases classified as confirmed cases of AIH, the reporting rate of AIH after administration of elasomeran is 0.02 per million doses administered. No unique or novel risk factors were identified from this aggregate sample. Insufficient information was present in the literature to suggest a relationship between Elasomeran administration and the event of AIH. Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of AIH to be consistent with the known safety profile of Moderna vaccines targeting SARS-CoV-2 and the benefits of vaccination far outweigh any possible vaccine-associated risks, including the risks of AIH. Based on this information the MAH does not consider necessary at this time that an update of the product information is warranted.

Conclusion

Overall, based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers that cases included under AIH, are heavily confounded, have alternative reasons for the reported events, and do not provide sufficient information to establish a causal relationship to the administration of any marketed Moderna vaccines targeting SARS-CoV-2. No new safety issue of concern was identified that would differ from the known safety profile of Moderna vaccines targeting SARS-CoV-2. The available data does not warrant an update to the product information. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has upon request provided a cumulative review for autoimmune hepatitis (AIH) for the period 18 December 2020 to 17 December 2023.

Unfortunately, the MAH has responded less detailed than requested which makes it difficult to analyze whether autoimmune hepatitis appears to be associated with administration of Moderna's mRNA vaccines targeting SARS-CoV-2 or not.

This rapporteur assessment will therefore describe elements included in the review as well as contribute with more assessor comments on what could be suggested as appropriate in order to meet the detailed request as well as to contribute to an understanding of whether Spikevax can be refuted, suspected or concluded as associated to AIH.

Sources of information for the review

The MAH's clinical trials safety database was queried, the global safety database was searched for AIH and AIH-suspected diagnoses, just as VAERS and EVDAS were reviewed as external databases. Additionally, a literature search was performed.

Clinical Trial Safety Database

The company clinical database from three adult clinical trials were reviewed for AIH and AIH-related terms; the review showed no cases of AIH or AIH-related terms. No CTs comprising children or adolescents were mentioned.

The information on CTs is not acknowledged as complete, please see below for assessor comment 2 regarding CTs.

Global Safety Database

The GSDB was searched cumulatively for the period 18 December 2020 through 17 December 2023. Search criteria were based on a customized MedDRA query with the PTs "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury".

Cumulatively, through 17 December 2023, a total of 315 cases (327 events) were reported, 232 cases were medically confirmed. Of the 315 cases, as many as 310 cases were assessed as serious. The outcome was fatal in 30 cases, while 121 were reported as recovering/recovered.

Listed by vaccine content, 306 cases were related to elasomeran, 6 cases to elasomeran/imelasomeran, 1 case to elasomeran/davesomeran, and 2 cases to andusomeran.

Gender and Age

Of the 315 cases, 133 cases (42.2%) involved males, 177 cases (56.2%) involved females, and 5 (1.6%) were of missing gender. The age range was 0.0-96.0 years, with the median being 56.0 years. No cases in infants or adolescents were reported in this cumulative review, although the age range of cases are reported to be 0.0-96.0 years of age.

There is a discrepancy between the reported age range and the fact that the MAH has not reported anything about patients < 18 years; please see assessor comment 3 regarding infants and adolescents.

Dose number and TTO:

In many cases, dose number and/or time to onset are unknown, and the MAH has defined all these cases as unassessable due to missing on information.

This categorization of data as unassessable in case of unknown dose is not acknowledged, and it unfortunately results in discarding a large amount of data; please see assessor comment 4 below regarding dose number.

Cases confirmed as AIH and WHO causality assessment

The MAH divided all retrieved cases into the two groups, namely a "Case of AIH" or "Not a case of AIH" based on the score each case achieved according to the Simplified Classification Guidelines by the International AIH Group.

All cases fulfilling the score for either probably AIH or for definite AIH were categorized as "a case"; all other cases were categorized as "not a case". This comprises cases that were considered unassessable due to lack of information. Cumulatively, only 18 of the 315 cases (5.7%) were considered "a case of AIH" according to the guidelines, while 297 cases were categorized as "not a case of AIH". The 18 cases fulfilling the criteria for being defined a case of AIH were also categorized according to the WHO causality assessment by the MAH. The MAH defined 14 cases as "possible" and 4 cases as "unlikely", but added that two of the cases categorized as "possible" previously were assessed as "probable" by the PRAC assessor.

External Databases

VAERS and EVDAS were reviewed for AIH and AIH-related PTs. No disproportionality was found.

Literature review

The MAH has reported that a focused literature search was performed as of 17 December 2023 using PubMed, and that the search gave 278 manuscripts. Repeating the search with the same search string and end date confirmed the number of manuscripts. However, many of these manuscripts seem to be unrelated to COVID-19 vaccines or COVID-19 and autoimmune hepatitis. It appears as if the MAH has omitted to report how literature was further selected from the primary search achieved with the reported search string. Please see assessor comment 5 regarding literature search.

The MAH was requested to comment upon a paper by Uzun et al. The MAH refers that 6 cases were identified based on this paper, and that all 6 cases were described in the previous PSUR (the 5th PSUR).

Possible Mechanism(s) for Vaccine-associated Autoimmune Hepatitis

AIH is an immune-mediated disorder. Known triggers include infection, medication, toxins, and dcreased tolerance to hepatocyte-specific autoantigens appears to a role. More hypotheses for the pathogenesis of AIH following COVID-19 mRNA vaccination have been presented in the literature, among these that COVID-19 vaccination by activation of the innate immune system and the following non-specific activation of autoreactive lymphocytes might lead to the development of autoimmune diseases, AIH included, or may trigger a drug-induced liver injury with features of AIH. Molecular mimicry may play a role as antibodies against spike proteins. But the etiology and exact pathophysiological mechanism for development of AIH is still unrevealed.

Conclusion

The MAH found that the provided review does not provide sufficient information to give rise to concern about causality. Nevertheless, the assessor found the review somewhat insufficient and that the provided information can neither support nor exclude causality. **The MAH is therefore requested to submit an updated cumulative review of autoimmune hepatitis, within this procedure** (please refer to section 6. "Rapporteur Request for supplementary information" of this assessment report for more details).

Assessor comment no. 1:

This cumulative review of AIH was done upon request. Unfortunately, the MAH has responded less detailed than requested which makes it difficult to analyze whether Spikevax can be refuted, suspected or concluded as associated to AIH.

It has also been somewhat difficult to compare to previous PSURs due to an overlap of time periods. The MAH has previously made a cumulative review from 18 December 2020 and to 17 June 2022; it is uncertain why the MAH has not just defined the latest time period as from 18 June 2022. The overlap in reported time periods has made it more difficult to compare numbers in the current and previous reviews of AIH following Spikevax.

Assessor comment no. 2 regarding Clinical Trials:

It is noted by the assessor that the MAH specified that the review of clinical trials comprised 3 CTs with adult participants. As the MAH has previously reported a clinical trial safety database review in which cases among children were reported, the assessor is concerned about whether all clinical trial databases were searched or if the three CTs with adult participants were selected among more trials without justification. Ensuring presentation of data from all clinical trials to which the MAH has access can be of relevance in the assessment, either as supporting a possible ADR suspicion or as supporting the refute of it. The request included information from all relevant data sources, and for this purpose all clinical trials for which there are reported cases of AIH or AIH-related PTs are considered relevant. It is recognized that the data has been presented last year, but a previous presentation does not make data irrelevant in a cumulative review.

The MAH states that it did not retrieve any cases from the three reviewed clinical trials. However, the assessors note that PSUR appendix 3a "Cumulative Summary Tabulations of Serious AEs from Clinical Trials for elasomeran" includes 2 cases of hepatic failure and 1 case of hepatitis acute in the category "investigational medicinal product". Within this procedure, the MAH is requested to present data on autoimmune hepatitis from all clinical trials including the 2 cases of hepatic failure and the 1 case of hepatitis acute. The data should also include paediatric cases.

For better overview and easier follow-up, it is suggested to tabulate clinical trials, both those mentioned earlier as well as new ones including CT number, age groups, review date, and results. For example, as

shown here:

CT	Age groups	Cumulatively as of *(date)*	AIH/AIH-related PTs	Classified AIH case
mRNA- 1273-P301	Adults	*as of 04 May 2021*	No cases	No cases
mRNA-1273-P203		*as of 27 Jan 2022*	One case (1 female adolescent)	No cases
mRNA-1273-P204		*as of 21 Feb 2022*	One case (1 female infant)	No cases
mRNA-1273.222-P205-Part H	Adults	*as of 23 Sep 2023*	No cases	
mRNA-1273.815-P205- Part J	Adults	*as of 25 May 2023*	No cases	

Assessor comment no. 3 regarding Infants, Children and Adolescents Aged 0-17 Years.

No cases in patients 0-17 years were reported in this cumulative review, although the age range of cases is reported to be 0.0-96.0 years which implies that cases in infants/children have been reported. Cases in infants, children and adolescents should at least be commented on.

Assessor comment no. 4, regarding dose number

The MAH was requested to present data including TTO and dechallenge/rechallenge. For this, dose number could be used as a proxy measure. This request was not sufficiently met, as all cases in which dose number or TTO was missing were discarded as unassessable. Cases should, according to request, be listed with information on dechallenge/rechallenge (dose) and TTO; lack of dose number should not be a reason for excluding a case from being assessed.

In the 3rd PSUR, data were presented tabulated by dose as well as by TTO. Within this procedure, the tables with AIH by dose and TTO as used by the MAH in the 3rd PSUR should be updated and presented.

Assessor comment no. 5 regarding the literature review

The literature search was checked by inserting the search string in PubMed. Overall, 278 manuscripts were confirmed but include papers that are not of relevance. The MAH has not reported how the further selection of manuscripts was done, and the MAH is therefore encouraged to improve the literature review, for example by simply describing what was done to include/exclude manuscripts for the final focused review, and with information of the number of stepwise excluded/included papers.

Assessor comment no. 6 regarding Uzun et al.

The MAH was requested to present and evaluate the literature case reports and observational studies related to elasomeran mentioned in the article by Uzun et al. However, the MAH has not presented and evaluated the literature case reports and observational studies mentioned in Supplementary Table 14 of this publication (page 7558 of PSUR no. 5) as requested. Within this procedure, the MAH is requested to present and evaluate these literature case reports and observational studies.

2.3.2.1.2. ITEM 2 (secondary Hemophagocytic lymphohistiocytosis)

After DLP of the present PSUR, a paper including a case report and a literature review on secondary Hemophagocytic lymphohistiocytosis (sHLH) and COVID-19 vaccination has been published (Premec H, Živko M, Mijić M, Jelić-Puškarić B, Lalovac M, Filipec Kanižaj T, Sobočan N. Acute Liver Failure Caused by Secondary Hemophagocytic Lymphohistiocytosis After COVID-19 Vaccination -Case Report and Literature Review. Int Med Case Rep J. 2023 Aug 7;16:449-455. doi: 10.2147/IMCRJ.S417347. PMID: 37577009; PMCID: PMC10416787.).

The MAH is requested to comment on this paper in the next PSUR and comply with appropriate measures based on the cumulative information including mechanism of actions concerning sHLH and elasomeran and andusomeran containing vaccines.

MAH Response

The article mentioned by the PRAC, relates to a case report and a literature review conducted by Premec et al (Premec et al. 2023). The case report is for a 61-years old Caucasian patient with a medical history of arterial hypertension and Warthin's right parotid gland tumour, who 10 days after receiving an unknown dose number of the Ad26.COV2.S vaccine (viral vector vaccine against COVID-19 - AstraZeneca-Oxford) experienced fever. Patient went to an outpatient clinic at an unknown date and was prescribed antibiotics. Fever persisted for an unknown time, and the patient was hospitalized at an unknown date with additional symptoms of algic syndrome and diarrhea. Laboratory findings included elevated liver enzymes, normal INR and renal function. Abdominal MSCT scan showed hepatosplenomegaly. The patient was treated empirically and given multiple intravenous antibiotics (cefuroxime, ciprofloxacin, metronidazole, piperacillin/tazobactam). Subsequently, Clostridium difficile toxin antigen was isolated from the stool and vancomycin was administered orally. Despite treatment, fever persisted, and although bone marrow aspirate revealed no signs of hemophagocytosis, HLH was suspected and Dexamethasone (20 mg IV) was introduced on the twelfth day of hospitalisation, after which the patient was afebrile. Liver enzymes continued to increase with, jaundice, coagulation disorder (INR 2.71) and portal systemic encephalopathy. A transjugular liver biopsy was performed, and submassive liver necrosis was found in the pathohistological sample. Bone marrow aspiration was repeated, and a high number of phagocytes was found in aspirate smears, along with individual cytophages. Twenty days after hospitalization the patient had encephalopathy and jaundice, with palpable hepatomegaly. At an unknown date a transjugular liver biopsy was performed, and submassive liver necrosis was found in the pathohistological sample. Bone marrow aspiration was repeated, and a high number of phagocytes was found in aspirate smears, along with individual cytophages. H-score value was 186 (75% probability of HLH diagnosis) with 6 out of 8 criteria of HLH-2004 (fever, splenomegaly, bicytopenia, low fibrinogen level, hemophagocytosis in bone marrow aspirate and high ferritin level), resulting in the diagnosis of HLH. Patient had intravenous immunoglobulins added to his treatment, but despite the treatment, the patient rapidly deteriorated, and the patient died 46 days after vaccination.

HLH presents as primary/familial or as a secondary/acquired form. It is described that the secondary form of the disease is most often provoked by chronic inflammation, immunosuppression, infections, malignancies, drugs and vaccines, and it is most common reported among adults. Hemophagocytic lymphohistiocytosis is characterised by blood cytopenias, hepatocellular injuries, coagulopathy, and in severe cases, signs of multiorgan system failure. High fever, arthralgia and lymphadenopathy persisting without a clear infectious focus and despite adequate antimicrobial therapy should arouse suspicion of HLH. There are no clinical or laboratory parameters that can unambiguously establish the diagnosis of HLH. Currently, the diagnosis of secondary forms of HLH is based on the HLH-2004 criteria. The sHLH can be sub-categorised as infection-related (e.g. viral, bacterial, fungal, parasitic) or non-infection-related (e.g. malignancy or autoimmune diseases); of the infection-related types, viral sHLH is the most common. Viral sHLH can further be divided into EBV-sHLH (Epstein Barr Virus-related secondary HLH)

and non-EBV-sHLH. The non-EBV-sHLH is triggered by some viruses, among which SARSCoV-2 is found associated to sHLH with uncontrolled immune system activation, but non-EBV-sHLH can also be triggered by other viruses that, similar to EBV, cause latent infection and can be reactivated.

Liver injury is a common complication of HLH and is reported in about 85% of patients with a secondary form of the disease. In most patients, only a slight increase in AST and ALT is present, although progression to acute liver failure is possible as a result of multiple-organ failure and lymphocytic infiltration of the periportal liver spaces with hepatic parenchyma necrosis.

In the case report presented in this article, no autoimmune or malignant provoking factors were found. Only a nosocomial Clostridium difficile infection was reported, which according to the authors rarely triggers secondary HLH. Additionally, a clinical and microbiological resolution of the C. difficile infection after vancomycin therapy, makes it unlikely C. difficile infection being the provoking factor. There are very important information missing in this report including any testing conducted on the patient for

SARS-CoV-2, as well as Epstein–Barr viremia, which according to the authors do constitute a limitation to this report. Epstein–Barr virus (EBV) is a commonly present provoking factor in setting of sHLH in adults. EBV is known to play a significant role in some cases of hemophagocytic lymphohistiocytosis (HLH), specifically in the context of secondary or reactive HLH (Filipovich 2009). EBV is linked to a greater proportion of HLH cases than any other pathogen. In the case of secondary HLH associated with EBV, the virus can be involved in the triggering of a hyperimmune response. The pathophysiological mechanism of HLH is related to defective function of NK cells and cytotoxic T lymphocytes (CTLs), resulting in uncontrolled activation of lymphocytes and macrophages that induce excessive production of cytokines, that cause the inflammatory response and characteristic inflammation seen in HLH (Park et al. 2019) and (Otrock and Eby 2015). The exact mechanisms by which EBV is associated with HLH are not fully understood. The vast majority of EBV infections do not lead to HLH; however, in individuals with a predisposition or underlying immune dysfunction, such as genetic susceptibility to HLH, EBV infection can be a triggering factor for the development of HLH (Janka and Lehmberg 2014).

In evaluation of the information presented in this report, according to the WHO causality assessment this report is considered possible related to vaccination with Ad26.COV2.S.

As of the DLP of this PBRER #6, no new cases of hemophagocytic lymphohistiocytosis have been received by the MAH, with the same 36 reported cases (36 events) of hemophagocytic lymphohistiocytosis (HLH) that were presented in PBRER #5. There were 35 cases involving elasomeran and 1 case involving elasomeran/imelasomeran. There were no reports for cases involving elasomeran/davesomeran or andusomeran. Out of the 36 cases all were considered serious (36 serious events) and 4 cases reported a fatal outcome. There were 34 medically confirmed cases.

The article by Premec et al, in addition to the case report mentioned above, includes references to additional 17 cases involving all COVID-19 vaccines, out of which 2 were after mRNA-1273 ((Rocco et al. 2021). The other 15 cases included nine reports after BNT162b2 vaccination ((Park et al. 2023); (Rocco et al. 2021); (Baek et al. 2022); (Sassi et al. 2021); (Caocci et al. 2021); (Hieber et al. 2022); and (Awan et al. 2023)), 5 reports after the ChAdOx1 nCoV-19 vaccine ((Cory et al. 2021); (Tang and Hu 2021); (Ai et al. 2022); (Baek et al. 2022); and (Attwell et al. 2022)), and one report after an inactivated vaccine (China inactivated SARS-CoV-2 vaccine)(Tang and Hu 2021). The report from Hieber et. al, includes information on all these cases (Table 1. Synopsis of clinical features of patients with hemophagocytic lymphohistiocytosis (HLH) after vaccination against SARS-CoV-2 infection). Out of these reports there were 15 reports after Dose 1 with a TTO ranging from right after vaccination (day 0) to 12 days after vaccination.

There was only one report after dose 2, 21 days after vaccination. Six reports did not include any previous medical history; the rest of the reports are heavily confounded by their past or concurrent

medical history, including viral syndrome, HIV, MAC, pulmonary aspergillosis, diabetes, cancer, among others. There were no differences related to sex, and the ages range from 20 to 85 years of age (mean: 52.7/ median 52.5). All patients met the diagnostic criteria for HLH using the online available H-score tool. The symptoms and clinical presentations were consistent with HLH, and the patients experienced various degrees of liver injury, with some cases progressing to acute liver failure. The report suggests that these cases of HLH may be triggered by an excessive immune response to the vaccine components, leading to a hyperinflammatory syndrome. The authors do not explain the exact pathophysiological mechanisms but propose a hyperinflammatory response leading to a cytokine storm.

- **Mechanisms of action:** There is no clear indication that vaccination with a COVID-19 vaccine produces secondary hemophagocytic lymphohistiocytosis (sHLH). There are some proposed hypotheses indicating that sHLH may be triggered by a hyperinflammatory response to the vaccine components. In the case of mRNA vaccines, it is suggested that the up-regulated secretion of interleukin 1 beta (IL-1-beta) from macrophages in response to the spike protein encoded by the vaccine could be responsible for the development of a hyperinflammatory syndrome. For DNA adenoviral vector vaccines, a similar hyperinflammatory syndrome might arise due to a hyperimmune response to the adenoviral components of the vaccine. This hyperinflammatory response is characterized by a positive feedback loop between macrophages, activated CD8+ T cells, and antigen-presenting cells, leading to a "cytokine storm" and persistent antigenic stimulation of T cells. However, none of these hypotheses could be clearly demonstrated.

Conclusion:

Evaluation of the Premec H et al, 2023 article does not suggest a plausible association with vaccination of a COVID-19 vaccine, including any authorized Moderna vaccine targeting SARS-CoV2, and it remains unclear on the exact pathophysiological mechanisms between the sHLH events and administration of a COVID-19 vaccine. Information presented in this article does not change the known safety profile of authorized Moderna vaccines targeting SARS-CoV-2. The MAH will continue to monitor events for HLH using routine surveillance. The benefit-risk evaluation remains positive.

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Rapporteur assessment comment:

Secondary haemophagocytic lymphohistiocytosis (sHLH)

The MAH was requested to comment on a paper published after DLP of the previous PSUR and comply with concerns based on cumulative information and to consider mechanisms of action for sHLH and COVID-19 mRNA vaccines from Moderna.

Article review

The specific paper (by Premec et al.) presented a case report about a patient who was vaccinated with a viral vector vaccine against COVID-19, and who acquired a nosocomial infection with *Clostridium difficile*, and without relevant information about tests for SARS-CoV-2 and EBV. This case is not relevant in relation to Spikevax: Information on SARS-CoV-2 and EBV should preferably have been given, as sHLH is most commonly infection-related, often viral, with EBV and SARS-CoV-2 being possible triggers. *Clostridium difficile* infection can also a be possible trigger of sHLH although more rarely. Further, the vaccine type was not an mRNA vaccine but a viral vector-based vaccine. The paper also referred to 17 other cases involving COVID-19 vaccines, of these 2 were mRNA-1273 (Spikevax). The two patients who had received mRNA-1273 developed hyperinflammatory responses after the 1st vaccine dose, but they were predisposed to hyperinflammation due to preexisting immune dysregulation, and causality cannot be ascertained.

Results from the Global Safety Database:

The MAH reported that no new cases of HLH had been received within the latest period. This information is therefore the same as presented in the previous PSUR, where it was reported that the GSDB showed cumulatively 36 cases of HLH.

Conclusion:

The MAH has met the request about commenting on the specific paper by Premec et al; this does not cause new concern about sHLH and Spikevax. The MAH has met the request about considering mechanisms of action in sHLH, which is an acquired hyperinflammatory and hypercytokinemic syndrome triggered by underlying disease. The MAH has also met the request about considering information based on cumulative data.

Overall, the review provided by the MAH does not cause new concern about sHLH. The MAH will continue monitoring of sHLH through routine surveillance. The Rapporteur agrees to this.

Assessor comment:

In the last PSUR, EBV-related sHLH was the focus of interest, and as part of the rapporteur assessment it was suggested that the focus of EBV-related sHLH was too limited and should be extended to viral-associated sHLH due to principle of parallelism in etiology. In this 6th PSUR, the overall diagnosis sHLH is used, and it could have been advantageous if the MAH had made the effort to present the 36 cases again but this time with sHLH in focus (in contrast to the narrow focus of EBV-related sHLH in the previous 5th PSUR).

2.3.2.1.3. ITEM 3 (Postural orthostatic tachycardia syndrome)

Two papers concerning POTS and the association with COVID-19 vaccination have been published after the DLP of the present PSUR. The MAH is requested to comment on these in the next PSUR and comply with appropriate measures based on the cumulative information concerning POTS and elasomeran and Andusomeran containing vaccines. The papers are the following:

- Tv P, Tran TT, Hao HT, Hau NTH, Jain N, Reinis A. Postural orthostatic tachycardia syndrome-like symptoms following COVID-19 vaccination: An overview of clinical literature. Hum Antibodies. 2023;31(1-2):9-17. doi: 10.3233/HAB-220013. PMID: 37248893; PMCID: PMC10357168.
- Gómez-Moyano E, Rodríguez-Capitán J, Gaitán Román D, Reyes Bueno JA, Villalobos Sánchez A, Espíldora Hernández F, González Angulo GE, Molina Mora MJ, Thurnhofer-Hemsi K, Molina-Ramos AI, Romero-Cuevas M, Jiménez-Navarro M, Pavón-Morón FJ. Postural orthostatic tachycardia syndrome and other related dysautonomic disorders after SARS-CoV-2 infection and after COVID-19 messenger RNA vaccination. Front Neurol. 2023 Aug 16;14:1221518. doi: 10.3389/fneur.2023.1221518. PMID: 37654428; PMCID: PMC10467287.

MAH response

Article 1:

Tv P, Tran TT, Hao HT, Hau NTH, Jain N, Reinis A. Postural orthostatic tachycardia syndrome-like symptoms following COVID-19 vaccination: An overview of clinical literature. Hum Antibodies. 2023;31(1-2):9-17. doi: 10.3233/HAB-220013. PMID: 37248893; PMCID: PMC10357168.

Company Comment:

This meta-analysis summarizes the findings from a literature review undertaken by the authors concerning cases with reported term of Postural Orthostatic Tachycardia syndrome (POTS) following the

use of different COVID-19 vaccines (Pfizer-BioNTech, Moderna and Ofxord-Astrazeneca COVID-19 vaccines).

The aetiology of POTS can be multifactorial. The authors noted that the diagnosis of POTS requires the fulfillment of the specific clinical-diagnostic criteria, including a thorough evaluation of the other potential contributory (risk) factors which can also mimic similar autonomic dysfunction(s). Also, given the slow evolution of the disorder (POTS), the lack of definitive testing and familiarity among the healthcare providers with POTS, there may be a tendency for misdiagnosis of POTS. There is no significant increase in the risk of mortality due to POTS.

For the purpose of the review, the authors retrieved a total of 18 cases of reported POTS following COVID-19 vaccination from eight published literature articles in English language. Of these 18 cases which reported 'POTS like symptoms', 6 cases were reported post vaccination with a marketed Moderna vaccine targeting SARS-CoV-2. The MAH has identified all six cases in the Moderna global safety database ([redacted]. All these cases were evaluated medically and in 3 of these cases ([redacted] and [redacted]), the diagnosis of POTS was not the reported term. The other 3 cases [redacted] and [redacted] contained the reported term of POTS and these cases were included in the cumulative safety review of POTS presented in PBRER #5. In these cases, while a temporal association was reported, other significant risk factors in the form of relevant medical history, and/or concurrent medical conditions and/or concomitant medications were noted which may have been contributory towards the reported adverse events or an unlikely short latency was noted. Overall, a causal association between POTS and SPIKEVAX vaccination cannot be determined based on the information presented in these cases.

This meta-analysis is not robust and has limitations in that this study doesn't provide original research data, but rather a summary of existing (published) literature and therefore no new information is provided. Similarly, the article postulates to reports of POTS following the HPV and Influenza (H1N1) vaccinations, probably attributable to a similar pathogenetic mechanism, however, the currently approved EU- labels for these vaccines do not contain the Adverse Drug Reaction (ADR) of POTS (SmPCs Section 4.8 for Gardasil 9 and the Quadrivalent Influenza Vaccine (split virion, inactivated)), consequently these do not constitute as substantive evidence. Overall, the MAH do not consider that the above literature article provides any new significant safety information for the topic of POTS with SPIKEVAX use. The benefitrisk profile of SPIKEVAX continues to remain unchanged.

Article: 2

Gómez-Moyano E, Rodríguez-Capitán J, Gaitán Román D, Reyes Bueno JA, Villalobos Sánchez A, Espíldora Hernández F, González Angulo GE, Molina Mora MJ, Thurnhofer-Hemsi K, Molina-Ramos AI, Romero-Cuevas M, Jiménez-Navarro M, Pavón-Morón FJ. Postural orthostatic tachycardia syndrome and other related dysautonomic disorders after SARS-CoV-2 infection and after COVID-19 messenger RNA vaccination. Front Neurol. 2023 Aug 16;14:1221518. doi: 10.3389/fneur.2023.1221518. PMID: 37654428; PMCID: PMC10467287

Company Comment:

This meta-analysis provides a review of POTS and related dysautonomic disorders following SARS-Cov-2 infection and COVID-19 mRNA vaccination, and covers the general overview regarding the etiopathogenic basis, epidemiology, clinical manifestations, diagnosis, treatment, prognosis, and socioeconomic impact of the SARSCoV-2 disease. It includes a general review of 89 articles identified from different databases (PubMed, Google Scholar, and Web of Science). Further, the authors have retrieved a total of 12 case reports from published literature involving patients diagnosed with new-onset POTS after 2-21 days of receiving a COVID-19 vaccine. The MAH has identified 2 of these cases reported after a Moderna vaccine;

both cases were already included in the Moderna global safety database. Of note, the 2 cases were also referred to and discussed in Article 1 above [redacted] **and** [redacted]. A causal association between POTS and SPIKEVAX vaccination cannot be determined based on the information presented in these cases.

The authors have emphasized on the pivotal role of vaccination in controlling the COVID-19 pandemic and that while the association between long COVID-19 symptoms and vaccination continues to remain unclear; they have referred to a UK study (n=6,030) which was indicative of the risk of long COVID-19 symptoms, including autonomic dysfunction, reduced by half following two doses of vaccination. Further, the authors have presented data that the risk of a POTS-related diagnosis was much higher (5.35 [5.05 – 5.68]) following a SARS-CoV-2 infection than after vaccination, as shown from a study in a cohort of 2,84,592 covid-19 vaccinated individuals. The authors have concluded that the potential for POTS following vaccination appears to be weaker than with the COVID-19 infection itself and that further research is needed. This meta-analysis has limitations in that this study doesn't provide original research data, but rather a summary of existing (published) literature and no new or significant safety information for SPIKEVAX is provided.

Conclusion:

A cumulative safety review of all cases with the reported term of POTS reported in the Moderna Global Safety database was presented in the previous Spikevax PBRER #5 had concluded that while some cases had a plausible temporal relationship from time of vaccine administration to development of reported POTS event, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of Moderna vaccines targeting SARS-CoV-2. The overall number of cases with the reported term of POTS for SPIKEVAX in the Moderna global safety database is considered to be low (178 cases total; reporting rate 0.2 cases per million doses administered; as off 17-December-2023) in the context of the significant number of all marketed Moderna vaccines targeting SARS-CoV-2 administered (1,043,567,281 of doses administered; as off 17 December 2023). POTS is considered an Adverse Event of Special Interest (AESI) for SPIKEVAX, and the event will continue to be monitored on an ongoing basis as part of ongoing routine safety surveillance activities at Moderna.

Overall, the MAH do not consider that the above literature article provides any new significant safety information for the topic of POTS with SPIKEVAX use. The benefitrisk profile of SPIKEVAX continues to remain unchanged.

Rapporteur assessment comment:

The MAH has reviewed the two meta-analyses by Tv P. (2023) and Gomez-Moyano E. (2023) concerning POTS and the potential association with COVID-19 vaccination.

Article 1: Tv P - Postural orthostatic tachycardia syndrome-like symptoms following COVID-19 vaccination: An overview of clinical literature.

TV P. et al conducted a meta-analysis to highlight the evidence that has been reported regarding POTS-like symptoms following COVID-19 vaccination. The authors identified 6 cases reporting POTS following vaccination with Moderna. The MAH reviewed all 6 cases in their global safety database and found that in 3 cases, the diagnosis of POTS was not the reported term. The remaining 3 cases were included in the safety review of POTS presented in PBRER #5. In these cases, while a temporal association was reported, other significant risk factors in the form of relevant medical history, and/or concurrent medical conditions and/or concomitant medications were noted which may have contributed to the reported adverse events, or an unlikely short latency was noted.

The authors use the principle of parallelism to compare POTS following COVID-19 vaccines to POTS following the vaccines against HPV and against influenza; however, the vaccines being compared have

not been causally linked to POTS, so the comparison does not support causality.

The MAH does not consider that the publication by Tv P. provides any new significant safety information on the topic of POTS with Spikevax use.

Article 2: Gómez-Moyano - Postural orthostatic tachycardia syndrome and other related dysautonomic disorders after SARS-CoV-2 infection and after COVID-19 messenger RNA vaccination.

Gómez-Moyano et al. conducted a meta-analysis concerning POTS and related dysautonomic disorders following SARS-Cov-2 infection and COVID-19 mRNA vaccination.

The authors identified 2 case reports from published literature involving patients diagnosed with new-onset POTS after receiving Spikevax; both cases were also referred to and discussed in Article 1 above.

The authors have presented data that the risk of a POTS-related diagnosis was higher (5.35 [5.05 – 5.68]) following a SARS-CoV-2 infection than after vaccination, concluding that the potential for POTS following vaccination appears to be weaker than with the COVID-19 infection itself and that further research is needed.

No new significant information was identified by the MAH from the publication.

Conclusion

Overall, the MAH does not consider that the above literature articles provide any new significant safety information for the topic of POTS with SPIKEVAX use.

The MAH's arguments for why the findings in the two publications do not rise new concern are acknowledged. Furthermore, it appears that relevant case reports mentioned in these two publications which reported POTS after exposure to Spikevax were included in the MAH's cumulative review presented in the previous PSUR. In the corresponding PSUSA procedure, the PRAC concluded that the available evidence was insufficient to establish a causal association. The cohort study by Kwan et al., which Gómez-Moyano et al. referenced, has also been assessed in previous PSUSA procedures. Therefore, the Rapporteur agrees that these two publications do not provide significant new safety information. POTS is considered an Adverse Event of Special Interest (AESI) for Spikevax, and the event will continue to be monitored on an ongoing basis as part of routine safety surveillance activities. Please refer to section 2.3.2.2.1 of this AR for an evaluation of interval data related to POTS.

2.3.2.1.4. ITEM 4 (Multisystem Inflammatory Syndrome)

In relation to the search strategy for MIS-related cases, the MAH states that the search terms used for PSUR #4 are the ones recommended by the Brighton Collaboration group. However, it is unclear which exact reference the MAH has used for these search terms. In the document "AESI Case Definition Companion Guide – Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A)" by the Brighton Collaboration group, the terms "multisystem inflammatory syndrome", "cytokine storm" and "cytokine release syndrome" do not appear in appendix 1 (diagnostic codes). On the other hand, this appendix lists the MedDRA PTs "sepsis syndrome", "haemophagocytic lymphohistiocytosis" and "toxic shock syndrome" which are not used by the MAH. Therefore, with the next PSUR the MAH is requested to provide the exact reference from the Brighton Collaboration group which the search terms have been based on. Furthermore, the MAH is requested to clarify why the MedDRA PTs "sepsis syndrome", "haemophagocytic lymphohistiocytosis" and "toxic shock syndrome" are not used.

MAH response

The MAH would like to clarify its previous response to the source of search strategy for reported cases under MIS-C/A. The current search strategy used to identify the observed cases of MIS-C/A in the Moderna global safety database (GSD) includes case reports with the MedDRA Preferred Terms (PT) of Multisystem inflammatory syndrome in children, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, Systemic inflammatory response syndrome, Multisystem inflammatory syndrome and Multisystem inflammatory syndrome in adults. The search strategy suggested by EMA on 03/Sep/2021 included the same PTs mentioned above plus: Multiple organ dysfunction syndrome, Toxic shock syndrome, Distributive shock, Hypotensive crisis, Vaccine associated enhanced disease, Vaccine associated enhanced respiratory disease, Haemophagocytic lymphohistiocytosis, Macrophage activation, Macrophages increased, Septic shock, and Autoinflammatory disease. This search strategy was used from MSSR8 (August 2021) through BSSR #3 (April-June 2022), when PRAC ended the requirement to submit MSSRs/BSSRs. This was also included in the review of MIS A/C for PBRER #2 and PBRER # 3. After PBRER #3 the Moderna internal search strategy for MIS A/C was used for (Multisystem inflammatory syndrome in children, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, Systemic inflammatory response syndrome, Multisystem inflammatory syndrome and Multisystem inflammatory syndrome in adults).

According to the case definition presented in the SPEAC – AESI Case Definition Companion Guide for MIS-C/A, the search strategy could include "Narrow" or "Broad" terms. Based on this, the MAH created the initial/ current search strategy, using a combination of MedDRA terms from both options, always looking for the better search strategy that could be used for spontaneous safety data avoiding the potential for masking any potential safety issue. Although, the Brighton collaboration definition of MIS A/C includes codes for sepsis syndrome and toxic shock syndrome, the MAH did not include these in the current search strategy due to significant difference in the background incidence of sepsis/ toxic shock syndrome and MIS. Furthermore, including cases of sepsis/toxic shock syndrome as mentioned before, might mask any potential safety issue associated with reported cases of MIS-C/A.

4.1 MIS-C/A Diagnostic Codes: ICD-9/10-CM and MedDRA

TABLE 1. NARROW TERMS FOR MIS-C/A

UMLS Concept	Diagnostic Coding System Term and Codes					
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C5391534	Multisystem inflammatory syndrome in children with COVID-19 infection	Multisystem inflammatory syndrome in children	10084767			895448002
C5439527	Multisystem inflammatory syndrome in adults	Multisystem inflammatory syndrome in adults MIS-A	10085850 10085855		M35.81	1119306006

TABLE 2. BROAD TERMS FOR MIS-C/A

UMLS Concept	Diagnostic Coding System Term and Codes					
CUI	Name	Term	MedDRA	ICD9CM	ICD10CM	SNOMEDCT
C5439525	Post-acute COVID-19*	Post-acute COVID-19				1193003
C5203670	COVID-19	COVID-19	100839006		U07.1	840539006
C0026691	Mucocutaneous lymph node syndrome	Mucocutaneous lymph node syndrome (Kawasaki) Acute febrile mucocutaneous lymph node syndrome Acute febrile mucocutaneous lymph node syndrome NOS Kawasaki's disease Kawasaki's disease	10028083 10000747 10023320	446.1	M30.3	75053002 195349001 155444003 195348009
C0242966	Systemic inflammatory response syndrome	Systemic inflammatory response syndrome (SIRS) Systemic inflammatory response syndrome (SIRS) NOS Systemic inflammatory response syndrome, unspecified Sepsis syndrome SIRS	10051379 10053879 10062357	995.9 995.90 995.90	R65.10	2381490007 238150007
C3697422	Non-infectious systemic inflammatory response syndrome					700049004
C0024291	Lymphohistiocytosis, Hemophagocytic	Haemophagocytic lymphohistiocytosis	10071580 10071583		D76.1	190958003 234437005
	Macrophage activation syndrome					
C0600327	Toxic shock syndrome	Toxic shock syndrome	10044248	040.82	A48.3	18504008

THIS PROJECT HAS BEEN FUNDED IN WHOLE BY CEPI.

For confirmation of the statement presented above, the MAH conducted observed to expected (O/E) analyses of MIS-C/A (as defined by MAH) and, separately for sepsis. Observed to expected analysis compares the observed number of cases of an adverse event occurring in vaccinated individuals and the

expected number of cases that would have naturally occurred in the same population without vaccination, estimated based on available incidence rates in a non-vaccinated population. In order to estimate observed reporting rates, person-time at risk was estimated by using the number of vaccine doses administered including elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and/or andusomeran doses, which was estimated as 58.5% of doses distributed globally as of data lock point of this PBRER. A risk window of 21 days was assigned after each administered vaccine dose. This window was selected for consistency with analyses that have been conducted by the US Vaccine Safety Datalink and represents a conservative estimate of person-time at risk given that observed cases were not required to occur within a specified time to onset. The sum of all person-time was then used as a denominator to calculate the reporting rate, which is expressed as reported cases per 100,000 person-years.

Appropriate expected background incidence was obtained from published literature. Expected rates were then multiplied by the same estimate of exposed person-years identify the count of expected cases. The observed reporting rate for each AESI was divided by the expected rate and presented alongside its associated 95% confidence interval (CI) calculated as: $e^{(\log(\text{incidence rate ratio}) \pm 1.96 * \text{standard error}(\log(\text{incidence rate ratio})))}$.

The age distribution of administered doses (0-<12, 12-<18, 18-<50, 50-<65 and ≥65 years) was estimated based on the demographic distribution of vaccine recipients as reported by the most updated data from CDC (May 11,2023[1]). Additionally, sensitivity analyses were conducted to assess the potential impact of under reporting and/or data lags in reporting. In these assessments observed to expected rate ratios were recalculated assuming that cases captured in the observed reporting rate represented 50% or 25% of the true exposed cases. Age and gender-specific incidence rates identified from published literature were then used to estimate expected cases within each category. Where age groups used in sources of background incidence did not align with the available grouping for population-based vaccine administration, the average of age-specific incidence was used, provided at least three years of overlap in the age bands as reported in the source data.

Limitations in comparing observed reporting rates and expected background rates include lack of direct visibility regarding patient-level data for administration, and limited availability of details on exposure in special risk groups who have received marketed Moderna COVID-19 vaccines targeting SARS CoV-2 (other than an expectation that governments distributed elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and/or andusomeran to the indicated population). Further, it should be noted that many AESI have highly variable estimates of incidence across sources. While the MAH has endeavored to select appropriate background rates on the basis of published literature and plausible care settings suitable to capture of relevant diagnoses, mischaracterization of the background rate has the potential to either exaggerate or mask a potential risk.

Because the proportion of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and/or andusomeran recipients with relevant comorbidities and other risk factors for the outcomes assessed is unknown, it is possible that estimates are confounded, and subgroup analyses of potential interest are infeasible.

All observed cases of sepsis were identified using the MedDRA preferred terms of "sepsis", any time after elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and/or andusomeran were included in the analysis. Overall, there were 503 cases of sepsis. Since, there was only one case of toxic shock syndrome it was not included in the analysis. The expected incidence for sepsis was obtained from a retrospective cohort study using National Inpatient Sample from 2004 to 2009 was conducted by Gaieski et al, 2013. The cases of sepsis were identified using ICD-19 code for sepsis (995.91), severe sepsis (995.92) or septic shock (785.52); a validated code list (Rhee et al. 2017). The authors estimated the

annual incidence of sepsis ranging from 300 per 100,000 population to 1,031 per 100,000 person-years[2] (Shankar-Hari et al. 2017).

[1] The federal COVID-19 public health emergency declaration ended on May 11, 2023, and with that CDC authorization to collect certain types of public health data expired. The last update of the publicly posted demographic distribution included data through May 11, 2023.

[2] The most common cause of toxic shock syndrome is release of toxins into bloodstream following Staphylococcus aureus, Streptococcus pyogenes, and Clostridium sordellii. The information on incidence of toxic shock syndrome in the general population is scare in the published literature, The estimated incidence of septic shock admissions was 20 per 100,000 person-years

In the observed-to-expected analyses, there were 503 sepsis cases cumulatively (reporting rate 1.13 per 100,000 person-years). Overall incidence described by Gaieski et al was 300 per 100,000 person-years, corresponding to an estimated 133,578 cases expected. The rate ratio was 0.0 (95% CI: 0.0, 0.0). The sensitivity analyses assuming 25% or 50% cases reported did not change the interpretation of the results. The product-specific analyses did not change the interpretation of the results. (Table 30)

Table 30: Age and gender stratified observed to expected analysis of Sepsis as of 17 December 2023

		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)
Sepsis								
Reference: US, Gaieski et al, 2013								
Overall								
Overall	59,999,762	503	0.84	179,999	300.00	0 (0, 0)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
Overall, by age								
<12 years	762,496	0	0.00	2,287	300.00	NA	NA	NA
12 - 17 years	1,287,126	2	0.16	3,861	300.00	0 (0, 0)	0 (0, 0)	0 (0, 0)
18 - 49 years	25,802,761	80	0.31	77,408	300.00	0 (0, 0)	0 (0, 0)	0 (0, 0)
50 - 64 years	15,430,150	109	0.71	46,290	300.00	0 (0, 0)	0 (0, 0.01)	0.01 (0.01, 0.01)
≥ 65 years	16,717,228	296	1.77	50,152	300.00	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.02 (0.02, 0.03)
By gender								
Male	28,193,307	262	0.93	84,580	300.00	0 (0, 0)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
Female	31,806,454	236	0.74	95,419	300.00	0 (0, 0)	0 (0, 0.01)	0.01 (0.01, 0.01)
Males, by age								
<12 years	358,156	0	0.00	1,074	300.00	NA	NA	NA
12 - 17 years	602,243	1	0.17	1,807	300.00	0 (0, 0)	0 (0, 0)	0 (0, 0.01)
18 - 49 years	12,169,535	44	0.36	36,509	300.00	0 (0, 0)	0 (0, 0)	0 (0, 0.01)
50 - 64 years	7,246,084	60	0.83	21,738	300.00	0 (0, 0)	0.01 (0, 0.01)	0.01 (0.01, 0.01)
≥ 65 years	7,817,289	149	1.91	23,452	300.00	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.03 (0.02, 0.03)
Females, by age								

		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)
<12 years	404,339	0	0.00	1,213	300.00	NA	NA	NA
12 - 17 years	684,883	1	0.15	2,055	300.00	0 (0, 0)	0 (0, 0)	0 (0, 0.01)
18 - 49 years	13,633,226	35	0.26	40,900	300.00	0 (0, 0)	0 (0, 0)	0 (0, 0)
50 - 64 years	8,184,067	48	0.59	24,552	300.00	0 (0, 0)	0 (0, 0)	0.01 (0.01, 0.01)
≥ 65 years	8,899,939	146	1.64	26,700	300.00	0.01 (0, 0.01)	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)
Elasomeran/imelasomeran and/or elasomeran/davesomeran								
Overall	11,851,982	6	0.05	35,556	300.00	0 (0, 0)	0 (0, 0)	0 (0, 0)
Andusomeran								
Overall	2,634,162	1	0.04	7902.486	300	0 (0, 0)	0 (0, 0)	0 (0, 0)

For the observed-to-expected analysis of MIS-C/A, all observed cases of MIS were identified as per MAH internal definition of MIS, any time after elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, and/or andusomeran were included in the analysis. The expected background incidence rate for MIS was obtained from the ACCESS (The vACCine covid-19 monitoring readinESS - https://vac4eu.org/covid-19- vaccine-monitoring/ last accessed 15 December 2023). ACCESS project was launched in May 2020 to prepare for real-world monitoring of COVID-19 vaccines. This project generated background incidence rates of 41 adverse events of special interest including MIS. This cohort study included distributed data network of 10 healthcare database from 7 European countries (Italy, Spain, Denmark, The Netherlands, Germany, France and United Kingdom) over the period 2017 to 2020. For MIS, the appropriate background incidence selected was from Spanish database. The estimated incidence of MIS was 2.03 per 100,000 person-years.

In the observed-to-expected analyses, there were 176 MIS cases cumulatively (reporting rate 0.29 per 100,000 person-years). Overall incidence described by Willame et al was 2.03 per 100,000 person-years, corresponding to an estimated 1,218 cases expected. The rate ratio was 0.14 (95% CI: 0.12, 0.17). The sensitivity analyses assuming 25% or 50% cases reported did not change the interpretation of the results. The product-specific analyses did not change the interpretation of the results. (Table 31)

Table 31: Age and gender stratified observed to expected analysis of multisystem inflammatory syndrome as of 17 December 2023

		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)
Multisystem inflammatory syndrome								
Reference: Spain (FISABIO) 2019[2]								
Overall								
Overall	59,999,762	176	0.29	1,218	2.03	0.14 (0.12, 0.17)	0.29 (0.26, 0.33)	0.58 (0.53, 0.63)
Overall, by age								
<12 years	762,496	1	0.13	50	6.51	0.02 (0, 0.15)	0.04 (0.01, 0.17)	0.08 (0.03, 0.22)
12 - 17 years	1,287,126	5	0.39	84	6.51	0.06 (0.02, 0.15)	0.12 (0.06, 0.23)	0.24 (0.15, 0.39)
18 - 49 years	25,802,761	57	0.22	233	0.90	0.24 (0.18, 0.33)	0.49 (0.39, 0.61)	0.98 (0.81, 1.17)
50 - 64 years	15,430,150	40	0.26	103	0.67	0.39 (0.27, 0.56)	0.78 (0.58, 1.04)	1.56 (1.22, 2)
≥ 65 years	16,717,228	63	0.38	225	1.34	0.28 (0.21, 0.37)	0.56 (0.45, 0.7)	1.12 (0.94, 1.34)
By gender								
Male	28,193,307	76	0.27	524	1.86	0.15 (0.11, 0.18)	0.29 (0.24, 0.35)	0.58 (0.5, 0.67)
Female	31,806,454	99	0.31	512	1.61	0.19 (0.16, 0.24)	0.39 (0.33, 0.46)	0.77 (0.68, 0.88)
Males, by age								
<12 years	358,156	1	0.28	27	7.47	0.04 (0.01, 0.28)	0.07 (0.02, 0.31)	0.15 (0.05, 0.43)
12 - 17 years	602,243	3	0.50	45	7.47	0.07 (0.02, 0.21)	0.13 (0.06, 0.31)	0.27 (0.14, 0.5)
18 - 49 years	12,169,535	21	0.17	86	0.71	0.24 (0.15, 0.39)	0.49 (0.34, 0.71)	0.98 (0.72, 1.32)
50 - 64 years	7,246,084	21	0.29	45	0.62	0.47 (0.28, 0.78)	0.93 (0.61, 1.42)	1.87 (1.3, 2.69)
≥ 65 years	7,817,289	28	0.36	124	1.58	0.23 (0.15, 0.34)	0.45 (0.33, 0.62)	0.91 (0.7, 1.17)
Females, by age								
<12 years	404,339	0	0.00	22	5.49	N/A	N/A	N/A
12 - 17 years	684,883	2	0.29	38	5.49	0.05 (0.01, 0.22)	0.11 (0.04, 0.3)	0.21 (0.1, 0.46)
18 - 49 years	13,633,226	35	0.26	150	1.10	0.23 (0.16, 0.34)	0.47 (0.35, 0.62)	0.93 (0.74, 1.18)
50 - 64 years	8,184,067	19	0.23	59	0.72	0.32 (0.19, 0.54)	0.65 (0.43, 0.98)	1.3 (0.92, 1.83)
≥ 65 years	8,899,939	35	0.39	98	1.10	0.36 (0.24, 0.52)	0.71 (0.52, 0.97)	1.43 (1.1, 1.85)
Elasomeran/imelasomeran and/or elasomeran/davesomeran								
Overall	11,851,982	3	0.03	241	2.03	0.01 (0, 0.04)	0.02 (0.01, 0.06)	0.05 (0.03, 0.09)
Andusomeran								

		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)
Overall	2,634,162	0	0.00	53	2.03	N/A	N/A	N/A

In conclusion, there is significant difference in the background incidence of sepsis and MIS. Given the high incidence of sepsis and number of observed cases, including both of these conditions in one analysis would have the potential for masking any safety issues associated with MIS-related reported events.

Rapporteur assessment comment:

In the previous PSUSA procedure, the assessors noted a discrepancy between the search terms used by the MAH for MIS-related cases and the search terms mentioned in the Brighton Collaboration Group's document: "AESI Case Definition Companion Guide – Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A)". Some of the search terms mentioned in this document were not used by the MAH even though the MAH stated that its search strategy was the one recommended by the Brighton Collaboration Group. Therefore, within the current PSUR, the MAH was requested to provide the exact reference from the Brighton Collaboration Group on which the search terms are based and to clarify why the MedDRA PTs "sepsis syndrome", "haemophagocytic lymphohistiocytosis" and "toxic shock syndrome"

are not used.

In the MAH's response, it references the same document from the Brighton Collaboration Group as the one identified by the assessors in the previous PSUSA procedure ("AESI Case Definition Companion Guide – Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A)"). The MAH clarifies that although the Brighton Collaboration Group's definition of MIS includes codes for sepsis syndrome and toxic shock syndrome, the MAH did not include these in the current search strategy due to significant differences in the background incidence of sepsis/toxic shock syndrome and MIS. However, it is noted that the MAH does not provide an incidence of toxic shock syndrome in the general population due to scarce information in the published literature and it is also noted that toxic shock syndrome was not included in the MAH's observed/expected analysis, as there was only one case. Even though toxic shock syndrome may share clinical characteristics with MIS, the Rapporteur endorses that the MAH does not include "toxic shock syndrome" as a search item when retrieving MIS cases, as this condition is caused by bacterial toxins, and it is deemed unlikely that well-documented MIS cases will be erroneously reported as toxic shock syndrome (without a co-reported MIS-related PT).

The MAH presents one publication that finds that the annual incidence of sepsis ranges from 300 to 1,031 per 100,000 persons. Furthermore, the MAH presents that based on a Spanish database, the estimated incidence of MIS is 2.03 per 100,000 person-years. Due to this significant difference in incidence, the MAH argues that inclusion of sepsis cases with MIS cases could mask any potential MIS safety issue. Furthermore, the MAH presents that there have been 176 MIS cases cumulatively and 503 sepsis cases cumulatively. Based on these data, the Rapporteur agrees that the inclusion of sepsis cases with MIS cases appears inappropriate, as it may obscure the qualitative and quantitative analyses of MIS cases. Furthermore, as also argued for "toxic shock syndrome", it is deemed unlikely that well-documented MIS cases will be erroneously reported as sepsis (without a co-reported MIS-related PT).

The MAH has not commented upon why the MedDRA PT "haemophagocytic lymphohistiocytosis" (HLH) mentioned in the document by the Brighton Collaboration Group has not been used as search term. However, the Rapporteur deems that even though HLH may share clinical features with MIS, these are distinctive disease entities, and it is deemed unlikely that well-documented MIS cases will be erroneously reported as HLH (without a co-reported MIS-related PT). Therefore, the MAH's decision to not use HLH as search term to retrieve cases of MIS is considered appropriate.

In order to ensure transparency, it would be appreciated, if the MAH in the future would clarify when and why it does not adhere completely to a referenced case definition, set of search criteria etc. In the matter at hand, the Rapporteur deems that the MAH's approach regarding the search terms "sepsis syndrome", "haemophagocytic lymphohistiocytosis" and "toxic shock syndrome" is sound. Issue resolved.

2.3.2.1.5. ITEM 5 (IgA Nephropathy)

In the previous PSUSA procedure (no. 4) and in relation to the important potential risk IgA Nephropathy (only included in PSUR Summary of safety concerns), the MAH was requested to include the publication by Ma and Xu in the risk characterisation presented in this PSUR. However, it appears that the MAH has only discussed the article in PSUR section 16.3 and not in PSUR section 16.4. The PRAC deems that this article adds value to the risk characterisation as it presents proposed mechanisms of action by which COVID-19 vaccination might induce IgA nephropathy. Therefore, the PRAC reiterates its request. The MAH is requested to include the following publication in the risk characterisation of IgA nephropathy in section 16.4 of the next PSUR with special focus on the proposed mechanisms of action:

- 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.

MAH Response

The MAH has included information from the Ma et al study in both sections of PSUR #6, sections 16.3 and 16.4.

Rapporteur assessment comment: The publication by Ma and Xu has been included in PSUR section 16.4. Issue resolved.

2.3.2.2. Other safety topics

2.3.2.2.1. Postural orthostatic tachycardia syndrome (POTS)

Source of New Information	• Moderna GSDB • Evaluation of cases of POTS is presented in this PBRER, cumulative as of 17 Dec 2023, given that the observed number of cases was higher than the expected number of cases. In the observed to expected analyses, the lower bound of 95% CI of rate ratio was > 1 for the 50-64 years subgroup. These were based on 2 case reports observed in this subgroup for the interval period. • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 25 articles o New and Significant Safety Information: None (0)
Background	Postural orthostatic tachycardia syndrome is a chronic and often disabling disorder characterized by orthostatic intolerance with excessive heart rate increase without hypotension during upright posture. Patients often experience a constellation of other typical symptoms including fatigue, exercise intolerance and gastrointestinal distress. A typical patient with POTS is a female of child-bearing age, who often first displays symptoms in adolescence. The onset of POTS may be precipitated by immunological stressors such as a viral infection. A variety of pathophysiologies are involved in the abnormal postural tachycardia response; however, the pathophysiology of the syndrome is incompletely understood and undoubtedly multifaceted [13]. The prevalence of POTS is based largely on clinical experience, ranging from 0.2% and 1% of the US population, which would suggest approximately 1–3 million affected persons [14-16]. Most patients present with POTS between the ages of 12 to 50 years old and more than 75% are female (F:M ratio > 4:1). POTS is also common in patients with chronic fatigue syndrome [16]. The cause of this condition remains unclear. Although there is a consensus clinical definition for POTS, misdiagnosis is common. The syndrome is heterogeneous in the sense that the spectrum of clinical features varies among patients, multiple etiologies may produce similar clinical phenotype and there is overlap with other clinically defined syndromes. The clinical evaluation of patients with suspected POTS is not standardized, nor are treatment approaches. There is a lack of

	familiarity with POTS in the medical community, and the epidemiology of the disorder and natural history are not known [17]. According to Sheldon et al., POTS is a clinical syndrome usually characterized by (1) frequent symptoms that occur with standing, such as light-headedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue; (2) an increase in heart rate of ≥30 beats per minute (bpm) when moving from a recumbent to a standing position (or ≥40 bpm in individuals 12 to 19 years of age); and (3) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure). The symptoms associated with POTS are those that occur with standing, such as light-headedness and palpitations; not associated with particular postures, such as bloating, nausea, diarrhoea, and abdominal pain; and systemic, such as fatigue, sleep disturbance, and migraine headaches. The standing (or orthostatic) heart rate of individuals with POTS is often ≥120 bpm and undergoes greater increases in the morning than in the evening. The increases in orthostatic heart rate gradually decrease with age and not abruptly at age 20. Many patients with POTS faint occasionally, although presyncope is much more common. It is important to note that the diagnoses of POTS and vasovagal syncope are not mutually exclusive. In addition, POTS has been found to overlap with or occur in certain conditions such as migraine, hypermobile Ehlers-Danlos syndrome (hEDS), mast cell activation syndrome (MCAS) or chronic fatigue syndrome (CFS), inappropriate tachycardia syndrome and some other forms of orthostatic intolerance such as neurocardiogenic syncope [18]. Amyloidosis, Sjogren's syndrome, multiple sclerosis, mast cell activation disorders and hypermobility syndrome (Ehlers-Danlos syndrome type III) are other diseases associated with or thought to cause POTS. This subset of POTS patients commonly reports episodes of flushing, urticaria, dyspnoea, headache, excessive diuresis, and gastrointestinal symptoms such as diarrhoea, nausea, and vomiting, which may be accompanied by elevated urine methylhistamine or 11-ß-Prostaglandin F2 excretion or elevation of other mast cell mediators [19]. Some researchers have suggested that there is a neuropathic basis underlying at least half of patients with POTS and found that about 1:7 of patients studied had ganglionic acetylcholine receptor antibodies suggesting an autoimmune etiology for this proportion of patients with POTS. Several mechanisms have been described in patients with POTS, including autonomic denervation, hypovolemia, hyperadrenergic stimulation, deconditioning, and hypervigilance, which is a careful and at times unusual focus on bodily sensations. These mechanisms often appear to co-exist in patients with POTS. The onset of POTS may be precipitated by a typical immunological stressor such as viral syndrome (often upper respiratory or gastrointestinal and for example, with Epstein–Barr virus (EBV)), physical trauma (such as concussion), menarche, pregnancy, or surgery and autoimmunity as with paraneoplastic conditions in small cell lung and pancreatic cancers as well as with autoimmune autonomic neuropathy. An antecedent history of suspected viral infection is reported in 20–50% of patients [20]. The presentation seems to have two patterns – acute onset after one of the above triggers or with slowly progressive symptoms over a longer period of time [21]. Significant symptomatic recovery has been reported by a

	subset of patients, but a majority report chronic symptoms with recurrent exacerbations. POTS is now known as one of many possible features of post-acute COVID-19 syndromes that can develop after SARS-CoV-2 infection. While the acute impacts of COVID-19 were the initial focus of concern, it is becoming clear that in the wake of COVID-19, many patients are developing chronic symptoms that have been called Long-COVID. Some of the symptoms and signs include those of POTS [22]. Commonly described symptoms of Long-COVID include some combination of breathlessness, palpitation, chest discomfort, fatigue, pain, cognitive impairment ("brain fog"), sleep disturbance, orthostatic intolerance, peripheral neuropathy symptoms (pins and needles, and numbness), abdominal discomfort, nausea, diarrhea, joint and muscle pains, symptoms of anxiety or depression, skin rashes, sore throat, headache, earache, and tinnitus. These symptoms, when combined with excessive orthostatic tachycardia, can lead to a diagnosis of POTS post-COVID-19 [22]. The UK National Institute for Health and Care Excellence (NICE) has defined various symptomatic phases of COVID-19 [23]. These include: • "Acute COVID-19" which includes signs and symptoms up to 4 weeks following onset of illness. • "Ongoing symptomatic COVID-19" for signs and symptoms of COVID-19 from 4 to 12 weeks after the onset of illness • "Post-COVID-19 syndrome" for signs and symptoms that develop during or after an infection consistent with COVID-19, continue for > 12 weeks and are not explained by an alternative diagnosis. • "Long-COVID" that includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Given that SARS-CoV-2 infection can trigger POTS and other cardiovascular dysautonomia's, it has been hypothesized that COVID-19 infection might be a potent immune trigger that evokes an autoimmune response in susceptible individuals [24]. The post-COVID-19 cardiovascular autonomic dysfunction can affect global circulatory control, producing not only a POTS-like pattern but also tachycardia at rest, blood pressure instability with both hypotension and hypertension, and local circulatory disorders such as migraine, coronary microvascular dysfunction, or Raynaud-like symptoms. Microvascular dysfunction with inadequate regional microvascular and macrovascular responses, such as vasospasm and circulatory mismatch between local oxygen demands and supply, and venous retention leading to pooling and reduced venous return after standing, might explain the plethora of symptoms that are frequently observed in POTS. There are sparse reports suggesting that microvascular dysfunction is an important mechanism of post-COVID-19 complications. All these dysautonomic phenotypes might coexist, and, more importantly, they preferentially affect young and middle-aged women, possibly suggesting a genetic predisposition and/or a mechanistic role for sex hormones. Of note, POTS is extremely rare among either prepubertal girls or postmenopausal women. There have been reports of POTS in the medical literature, from Japan, Korea, and the US, about new onset POTS in previously

	healthy people who had recently received a messenger RNA (mRNA) COVID-19 vaccine. A large cohort study [25] identified a possible association between COVID-19 vaccination and POTS as well as a much stronger link between SARS-CoV-2 infection and POTS. Kwan AC et al.used a retrospective cohort of patients 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 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 authors found the post-Dose 1 odds of new POTS -associated diagnoses (1.33, 95% CI=1.25–1.41) was slightly higher than for CPC diagnoses (OR=1.21, 95% CI=1.18–1.23) in the vaccinated cohort, and post-infection odds 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. Although this single medical center study identified a slightly elevated risk of receiving a POTS diagnosis after COVID-19 vaccination, the interpretation of the results requires caution given the following limitations, and additional studies are required to verify the association as the authors recommended. First, the primary analysis was restricted to vaccinated persons and consequently may have had bias away from the null because people who experienced POTS may have delayed or may not have received a COVID-19 vaccine, violating a key assumption of the SSA analytic methodology (i.e., the event of interest [POTS] does not alter the probability of subsequent exposure [vaccination]). No distribution of POTS diagnoses pre- and post-vaccination was 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, the authors acknowledged that "the lack of a standard single ICD code for capturing a formal diagnosis of POTS can lead to overlap with other medical conditions and variation in the application of available ICD codes". Moreover, 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 ICD codes". The degree of misclassification pre- and post-vaccination may not necessarily be non-differential because diagnostic vigilance of POTS may be intensified after vaccination, biasing the association away from the null; moreover, symptoms associated with common vaccine reactogenicity such as fever and fatigue might lead to patient complaints that overlap some POTS criteria. 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 that occurred pre and post vaccination. Fourth, diagnosis of POTS, as noted above, requires a three-month duration of symptoms; however, the authors did not confirm this important

	temporal aspect, relying instead on ICD codes that are not specific for POTS and may only represent acute diagnoses. In summary, POTS is a chronic multi-system disorder involving the autonomic nervous system that is characterized by an exaggerated sinus tachycardia, and symptoms upon standing. POTS primarily affects females starting around puberty and through their child-bearing age and is associated with significant functional disability, such as decreased ability to participate in education, limited ability to work and generate an income, and decreased quality of life. The pathophysiology is incompletely understood, which is likely responsible for limited data on effective treatments. Postural tachycardia syndrome cases associated with COVID-19 infection have been reported, as well as cases occurring after COVID-1 vaccination.
Methods of Evaluation	The ModernaTx, Inc. GSDB was queried cumulatively to 17 Dec 2023 for valid case reports received from HCPs, HAs, consumers, and literature worldwide, for marketed Moderna vaccines targeting SARS-CoV-2 using the MedDRA PT of "Postural orthostatic tachycardia syndrome". Identified cases were evaluated according to the latest case definition presented by Vernino et al [13] as part of the National Institute of Health Expert Consensus meeting of 2019, based on the different previous definitions by major international neurologic, autonomic, cardiac and pediatric societies [16,22,26] as requiring: • **Confirmed**: o A sustained HR increment of not less than 30 beats/minute within 10 min of standing or head-up tilt. For individuals who are 12 to 19 years old, the required HR increment is at least 40 beats/minute; and o An absence of orthostatic hypotension (i.e., no sustained systolic blood pressure drop of 20 mm Hg or more); and o Frequent symptoms of orthostatic intolerance during standing, with rapid improvement upon return to a supine position. Symptoms may include light-headedness, palpitations, tremulousness, generalized weakness, blurred vision, and fatigue; and o Duration of symptoms for at least 3 months; and o Absence of other conditions explaining sinus tachycardia such as anorexia nervosa, primary anxiety disorders, hyperventilation, anaemia, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, use of cardioactive drugs (e.g., sympathomimetics, anticholinergics) or severe deconditioning caused by prolonged bed rest. • Unassessable: A reported event of POTS with insufficient evidence to meet the case definition. • Not a Case: Alternative diagnosis for the described events. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

Results:

Refer to PSUR Appendix 12.9 for additional information, on case evaluations, and assessments.

During the reporting period, a total of 22 cases (21 serious, 5 medically confirmed), with 22 events (17 serious) with the reported term of POTS have been received for marketed Moderna vaccines targeting SARS-CoV-2. No case report noted a fatal outcome. The majority of cases were reported in females (15 cases; 68.2%) compared to males (7 cases; 31.8 %). The mean patient age was 35.1 years of age (SD: 10.4) and median age of 35.0 years of age (range: 22.0 to 61.0 years). Of note, 4 cases (18.2%) did not provide information on age. The majority of the events (13; 59.1%) did not report sufficient information to determine dose number, and 9 events (40.9%) did not report TTO.

Case Evaluation was performed according to the case definition described above in the Methods of Evaluation section. Causality assessment was conducted based on the WHO-UMC causality assessment.

Out of the 22 cases reported:

- Elasomeran (20 cases):
    - One case reported in literature described a non-serious event of POTS in a 32-year-old female patient in the post-acute/long COVID-19 setting. The initial symptoms of POTS reportedly appeared 3-months after she had received her 2nd dose of elasomeran, following a concurrent severe COVID-19 infection requiring hospitalisation. It was reported that the symptoms worsened three months later following a recurrence of another episode of severe COVID-19 infection requiring another hospitalisation. The patient was treated with propranolol, event outcome was unknown. Patient's medical history is unknown. The authors postulated "Long COVID" to be related to a virus- or immune-mediated disruption of the autonomic nervous system resulting in orthostatic intolerance syndromes. The causality was deemed as unlikely in this case as a long latency was noted and the concurrent severe COVID-19 infection provided a more likely explanation for the reported POTS event.
    - There was one case involving a potential flare-up of pre-existing POTS which occurred >12 months after receiving elasomeran. The patient had a concurrent relevant medical condition of CFS and was noted to be on prolong bed rest (>15 months), which together provide a more plausible explanation of the reported event of POTS. Accordingly, the WHO-UMC causality was assessed as unlikely.
    - The remaining 18 cases were deemed unassessable as these lacked vital information including: detailed clinical course of events including relevant signs/symptoms for the reported condition of POTS, any supportive testing (laboratory or diagnostic) conducted to establish the diagnosis of POTS, patients' medical history and in some instances the COVID-19 vaccine dose number and the TTO of the POTS event in relation to elasomeran administration (latency), important to establish causal association with the vaccine.
- Elasomeran/imelasomeran (2 cases)
    - There were 2 reports, one involving a potential flare-up of pre-existing POTS, for both cases the causality was unassessable, as these contained insufficient information for a complete assessment (lacking vital information on the clinical course of events, latency, dose numbers, details of any supportive diagnostic investigations and any treatment given for POTS including the event outcome).

No cases with the reported term of POTS were received for elasomeran/davesomeran and andusomeran during the interval period.

Discussion

Evaluation of cases of reported POTS is presented, given that the observed number of cases were higher than the expected number of cases. In the observed to expected analyzes, the lower bound of the 95% CI of the rate ratio was > 1 for the 50-64 years subgroup. These were based on 2 case reports observed in this subgroup for the interval period.

During the reporting period, there were a total of 22 cases reports with the reported term of POTS for individuals that had been vaccinated with one or more doses of elasomeran (20 cases; 90.9%) and elasomeran/imelasomeran (2 cases; 9.1%). No cases were reported for elasomeran/davesomeran and andusomeran for the interval period. Overall, no new significant safety information was identified following a review of these cases for marketed Moderna vaccines targeting SARS-CoV-2.

As evident from published literature, POTS has been found to overlap with or occur in certain conditions such as migraine, hypermobile Ehlers-Danlos syndrome, MCAS or CFS, inappropriate tachycardia syndrome and some other forms of orthostatic intolerance such as neurocardiogenic syncope. In addition, the onset of POTS may be precipitated by a typical immunological stressor such as viral syndrome (often upper respiratory or gastrointestinal and for example, with EBV), physical trauma (such as concussion), menarche, haemorrhage, pregnancy, or surgery, prolong bed rest and autoimmunity as with paraneoplastic conditions in small cell lung and pancreatic cancers as well as with autoimmune autonomic neuropathy. Commonly described symptoms of Long-COVID include some combination of breathlessness, palpitation, chest discomfort, fatigue, pain, cognitive impairment ("brain fog"), sleep disturbance, orthostatic intolerance, peripheral neuropathy symptoms (pins and needles, and numbness), abdominal discomfort, nausea, diarrhea, joint and muscle pains, symptoms of anxiety or depression, skin rashes, sore throat, headache, earache, and tinnitus. These symptoms, when combined with excessive orthostatic tachycardia, can lead to a diagnosis of POTS post-COVID-19.

Cumulatively, based on the total number of doses administered, estimated (as of 17 Dec 2023), the reporting rates for cases reported as POTS in the GSDB per million doses administered of elasomeran is 0.2 cases; for elasomeran/imelasomeran is 0.07 cases and elasomeran/davsesomeran is 0.01 cases. There have been no cases reported for andusomeran. There have been no reports with a fatal outcome.

Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported POTS event, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of marketed Moderna vaccines targeting SARS-CoV-2.

The MAH reviewed two articles concerning POTS and COVID-19 vaccination as per request from a health authority [27,28]. Review of the Tv P. et al article showed that this meta-analysis does not provide robust data nor adequate information on the possible association of COVID-19 vaccines and POTS, including as an important limitation the lack of original research data, but rather a summary of existing (published) literature and therefore no new information is provided. Similarly, the article postulates to reports of POTS following the HPV and Influenza (H1N1) vaccinations, probably attributable to a similar pathogenetic mechanism, however, the currently approved EU- labels for these vaccines do not contain the ADR of POTS (SmPCs Section 4.8 for Gardasil 9 and the Quadrivalent Influenza Vaccine (split virion, inactivated)), consequently these do not constitute as substantive evidence.

The article by Gomez-Moyano et al [28], is a meta-analysis that provides a review of POTS and related dysautonomic disorders following SARS-Cov-2 infection and COVID-19 mRNA vaccination and covers the general overview regarding the etiopathogenic basis, epidemiology, clinical manifestations, diagnosis, treatment, prognosis, and socioeconomic impact of the SARS-CoV-2 disease. The authors concluded that the potential for POTS following vaccination appears to be weaker than with the COVID-19 infection itself and that further research is needed. Overall, the MAH do not consider that the above literature article

provides any new significant safety information for the topic of POTS with elasomeran use. The benefit-risk profile of elasomeran continues to remain unchanged.

Conclusion

Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2. Information presented in those reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important safety information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of POTS, reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any new safety issue of concern and the information provided does not support evidence of causality between marketed Moderna vaccines targeting SARS-CoV-2 exposure. The MAH will continue to monitor events for POTS events using routine pharmacovigilance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Postural orthostatic tachycardia syndrome (POTS)

The MAH has provided a review regarding POTS following use of Spikevax vaccines, the latest review period being 18 June 2023 through 17 December 2023. Data presented are from the MAH's global safety database, observed/expected number, and from the literature in form of a review of two articles according to health authority request and a literature search.

POTS is a chronic multi-system disorder involving the autonomic nervous system that is characterized by an exaggerated sinus tachycardia, and symptoms upon standing. POTS primarily affect females starting around puberty and through their child-bearing age and is associated with significant functional disability. POTS is characterized as a syndrome with heterogeneous clinical presentations, often overlapping with other syndromes, and is diagnostically somewhat a challenge. Neither the clinical evaluation of patients nor the treatment approaches are standardized in cases of (suspected) POTS. Cases associated with COVID-19 infection have been reported, as well as cases occurring after COVID-19 vaccination. However, the pathophysiology is not fully understood.

Results

Results from the Global Safety Database

In the review period 18 Jun to 17 Dec 2023 there were 22 cases (22 events) reported after receiving a Spikevax vaccine against COVID-19. Of these, 20 cases were reported for elasomeran, 2 cases for elasomeran/imelasomeran, none for elasomeran/davesomeran, and none for andusomeran. Neither in the review period nor cumulatively were there any fatal cases.

Cases were retrieved by searching the PT 'Postural orthostatic tachycardia syndrome'. Identified cases were evaluated according to the latest case definition presented as part of the National Institute of Health Expert Consensus meeting of 2019, according to these criteria the cases were categorized as 'confirmed', 'unassessable', or 'not a case'.

For the review period, POTS occurred in patients aged 22 to 61 years, median age being 35 years; grouped by gender, 68.2% (15 cases) were females vs. 31.8% (7 cases) in males. This is quite in accordance with the observation that generally most patients with POTS are aged 12 to 50 years old and the female to male ratio is > 4:1. No pattern in TTO or dose number was identified as the majority of the

events (13; 59.1%) did not report sufficient information to determine dose number, and 9 events (40.9) did not report TTO.

Observed vs. Expected ratio

According to table 15-3, the 22 cases reported for the review period approximately equaled the expected average rate. Cumulatively, in total 178 cases were reported, and for the cumulative period the observed ratio was 0.3, and below the expected rates.

Literature review

The MAH has performed a literature review based on a literature search in PubMed. The search string for PubMed is listed in appendix 13.4. The MAH reported having retrieved 25 articles. Of these, none had new and significant safety information.

Assessor comment: Applying the search string in PubMed, the assessor identified 69 cases. A proper description of a literature search should also comprise how papers were filtered by exclusion criteria or by selection criteria.

The MAH also reviewed two articles upon request (see section 2.3.2.1.3 of this assessment report); arguments for why these do not raise new concern are acknowledged. In particular, concerning the paper by Tv P et al., which uses the principle of parallelism to compare POTS following COVID-19 vaccines with POTS following vaccines against HPV and influenza; the vaccines to which Spikevax is compared have not been found causally associated with POTS, and therefore, the comparison does not support causality.

Conclusion

POTS is a chronic, multi-system disorder that overlaps with other conditions, presenting a challenge for diagnostic certainty. Furthermore, its pathophysiology is not fully understood. POTS occurs mostly in females and mainly within the age range 12 to 50 years of age.

In the review period 18 June to 17 December 2023 there were 22 cases of POTS; cumulatively since 18 December 2020, 178 cases have been reported after receiving a Spikevax vaccine. For the entire period, no cases have been fatal. Cumulatively, the observed/expected ratios do not give rise to concern. The reported cases do not reveal a pattern regarding TTO or dose number. Findings for age and gender are approximately as described as background data, with a majority of incidents among females aged 12-50.

Overall, no new significant safety information was identified based on the review of POTS cases, nor from the literature.

It is suggested that POTS will continue to be monitored by routine surveillance.

2.4. Characterisation of risks

[Please see PSUR section 16.4 for the MAH's Characterisation of Risks.]

Rapporteur assessment comment:

In the MAH's characterisations of the important identified risks "myocarditis" and "pericarditis", the Rapporteur notes that the MAH states that the product information was revised during the PSUR reporting period regarding these safety concerns. Specifically, the MAH states that the product information was updated with the following information: "*Post-authorisation data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than viral infectious myocarditis or pericarditis.*" The Rapporteur deems that this information is valuable to the clinician, however, the information is not included in the currently available version of the EU SmPC from EMA's

website.

Within this procedure, the MAH is requested to clarify which procedure this PI revision originates from, and provide, if relevant, the anticipated timeline for its implementation in the EU SmPC.

The safety concerns remain unchanged.

3. Risk management plan

3.1. RMP v8.3 (provided in initial submission of the PSUR)

The MAH submitted an updated RMP version 8.3 with data lock point of 30 November 2023 and final sign off date of 16 February 2024 with this PSUR.

The proposed RMP changes were the following:

- To update the myocarditis / pericarditis follow-up questionnaire (FUQ) in Annex 4

3.1.1. Annexes

Proposed to update the myocarditis/pericarditis follow-up questionnaire in Annex 4.

Rapporteur assessment comment:

The MAH stated in the cover letter that the effectiveness of FUQs were periodically reviewed with PSURs. By evaluating response rates, the MAH identified limitations of the myocarditis/ pericarditis FUQ, and therefore proposed the above-reflected update.

To the best of the assessor's knowledge, no effectiveness data were provided by the MAH, so the underlying limitations of the FUQ warranting an update are unclear. Moreover, the MAH is reminded that RMP updates can be submitted with a PSUR only when the changes to the RMP are a direct result of data presented in the PSUR.

In addition, process indicators such as a response rate cannot provide evidence on whether the FUQ is effective. The changes proposed by the MAH seem to increase the complexity of the FUQ, and it is therefore considered unlikely that such changes will increase response rates. However, without further elaboration, it is unclear whether low response rates are the primary issue. The MAH is requested to further clarify this and to provide the effectiveness results. However, if these are data outside the scope of the PSUR, the MAH is asked to submit an updated RMP (and the data supporting the proposed updates) in a separate type II variation. **RSI**

There are several additional PhV activities addressing the important identified risks myocarditis and pericarditis. Particularly PAS studies p910 (EU) and p911 (US) will provide systematic data on the clinical course, long-term outcomes and risk factors to further characterise these risks. In view of these studies, the additional value of the FUQ to obtain further data on individual cases which have been spontaneously reported is questioned. Without a denominator, any information from single cases collected with the FUQ will be challenging to contextualise. This limitation is overcome with the above-mentioned studies. Therefore, the MAH is requested to justify the continued need for a myocarditis/pericarditis FUQ, i.e. discuss if there is a reasonable expectation that the FUQ still is expected to facilitate a further characterisation of the risks which may change the current information on myocarditis and pericarditis in the SmPC. Applicable sections of the RMP may need to be amended accordingly. **RSI**

Pending the MAH's response to the questions above, in case a FUQ still is considered warranted by the MAH and the PRAC Rapporteur, the following issues with the proposed FUQ warrant amendments:

- A preface explaining the added value of the FUQ is lacking. This may help to increase the willingness of reporters to complete the FUQ. The MAH may consider to add the following *"You have reported an adverse reaction(s) of XXXX for "medicinal product name". This questionnaire is being sent to you for obtaining valuable additional information about the reported case to thoroughly evaluate the relation to "medicinal product name" exposure. The questionnaire is already prefilled with all the available information collected at the time of the initial report, only additional information should be filled in. By providing as detailed information as possible, you can make a useful contribution to the safety of "medicinal product name".*
- In line with the preface above, the MAH is reminded that the FUQ should be prefilled by the MAH with all the available information collected at the time of the initial report, to limit the burden on the reporters. Therefore, the following statement may be deleted: *"Please only provide information that has not been previously reported."*

In response to the RSI within this procedure, the MAH submitted an updated RMP version 8.3 with data lock point of 30 November 2023 and final sign off date of 11 June 2024 with this PSUR proposing removal of the myocarditis/pericarditis follow-up questionnaire upon EMA feedback.

As discussed previously, in view of several additional PhV activities aiming to further characterise the risks myocarditis and pericarditis, the additional value of the FUQ to obtain further data on individual cases which have been spontaneously reported is questioned. Considering also the lack of effectiveness of these FUQs, as demonstrated by the MAH (see section 2.3.1.1.2.), the PRAC Rapporteur agrees that there is no reasonable expectation that the FUQ will contribute to a better characterisation of these risks. Deletion of the FUQs as proposed by the MAH is therefore accepted.

Applicable sections of the RMP (III.1, V.3 and Annex 4) have been amended accordingly.

3.2. Overall conclusion on the RMP

In view of several additional PhV activities aiming to further characterise the risks myocarditis and pericarditis, the additional value of the FUQ to obtain further data on individual cases which have been spontaneously reported is questioned. Therefore, the removal of the myocarditis/pericarditis follow-up questionnaire upon EMA feedback is accepted. Applicable sections of the RMP (III.1, V.3 and Annex 4) have been amended accordingly.

The changes to the RMP (version 8.3 with sign off date 11 June 2024) are considered acceptable.

4. Benefit evaluation

The vaccines are indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 months of age and older.

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 1.7 billion doses of elasomeran distributed, and more than 774 million doses estimated to have been administered globally as of 17 Dec 2023. Further, safety for bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran), as well with the 2023-2024 monovalent variant vaccine (andusomeran), has been demonstrated in adults including young adults (18 to < 25 years) in clinical studies and post authorization settings, where approximately more than 251 million doses have been administered.

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.

Rapporteur assessment comment:

In PSUR section 17.2, the MAH presents new data that shows that elasomeran can be co-administered with herpes zoster or influenza vaccine. The MAH also presents efficacy data for vaccination of immunocompromised individuals. As noted in section 1.3.2 of this AR, these data appear to have been submitted via a Type II variation and are currently under review. Therefore, this will not be discussed further here. Please refer to section 1.3.2 of this AR or section 17.2 of the PSUR for more information.

There are no new data on efficacy that alters previous assessments which are described in the approved product information of Spikevax.

5. Benefit-risk balance

Elasomeran is approved and/or authorised 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 authorisations for third doses in special populations (e.g., immunocompromised) and/or as a booster dose, including authorisation for two bivalent vaccines (elasomeran/imelasomeran, and elasomeran/davesomeran) and andusomeran continue to expand.

On 06 Jun 2023, the ECDC and the EMA issued a statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants. Similar to the WHO TAG-CO-VAC statement, ECDC/EMA recommended a monovalent vaccine composition as suitable to ensure adequate immunogenicity against circulating SARS-CoV-2 variants in both primed and naïve individuals, and XBB.1.5 was considered a reasonable choice to increase the breadth of immunity also against XBB descendent lineages.

On 15 Jun 2023, the FDA VRBPAC voted unanimously in favor of recommending an update of the COVID-19 vaccines to a monovalent XBB-lineage for the andusomeran. Based on the totality of evidence, ModernaTx, Inc developed a vaccine with a monovalent XBB.1.5 composition.

No new significant information that would impact the benefit-risk balance was identified during the assessment of the data in this PSUSA.

No new important identified or potential risks were identified in the presented data from the reporting interval. No new and significant data were presented for the important risks and missing information already included in the summary of safety concerns.

Based on the presented data in the PSUR, the PRAC Rapporteur concludes that the benefit-risk balance remains unchanged for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran in the approved indications.

6. Rapporteur Request for supplementary information

1. **Regarding the proposed updates of the RMP, the MAH is requested to address the following points:**

- The MAH is requested to clarify which limitations of the myocarditis/ pericarditis FUQ are intended to be solved with an update of the FUQ and to provide the effectiveness results referred to in the cover letter. However, the MAH is reminded that RMP updates can be submitted with a PSUR only when the changes to the RMP are a direct result of data presented in the PSUR. If these are data outside the scope of the PSUR, the MAH is asked to submit an updated RMP (and the data supporting the proposed updates) in a separate type II variation.
- In view of several additional PhV activities with the aim to further characterise the important identified risks myocarditis and pericarditis, the MAH is requested to justify the continued need for a myocarditis/ pericarditis FUQ, i.e. discuss if there is a reasonable expectation that the FUQ still is expected to facilitate a further characterisation of the risks which may change the current information on myocarditis and pericarditis in the SmPC. Applicable sections of the RMP may need to be amended accordingly.
- Pending the MAH's response to the questions above, in case a FUQ still is considered warranted by the MAH and the PRAC Rapporteur, the following issues with the proposed FUQ warrant amendments:
    - A preface explaining the added value of the FUQ is lacking. This may help to increase the willingness of reporters to complete the FUQ. The MAH may consider to add the following "*You have reported an adverse reaction(s) of XXXX for "medicinal product name". This questionnaire is being sent to you for obtaining valuable additional information about the reported case to thoroughly evaluate the relation to "medicinal product name" exposure. The questionnaire is already prefilled with all the available information collected at the time of the initial report, only additional information should be filled in. By providing as detailed information as possible, you can make a useful contribution to the safety of "medicinal product name*".
    - In line with the preface above, the MAH is reminded that the FUQ should be prefilled by the MAH with all the available information collected at the time of the initial report, to limit the burden on the reporters. Therefore, the following statement may be deleted: "*Please only provide information that has not been previously reported*."

2. Literature

- The assessors identified one publication with potentially new and significant safety information that was published during the reporting interval. Marchand et al. found an increased risk of cardiac-related mortality after COVID-19 vaccination (HR = 1.06, 95% CI [1.02, 1.11], p = .007). In relation to this, it is noted that myocarditis and pericarditis are very rare adverse reactions listed in section 4.8 of the SmPC and that SmPC section 4.4 informs that fatal cases of myocarditis/pericarditis have been observed. As this publication has not been mentioned by the MAH and as it potentially includes new and significant safety information, the MAH is requested to comment upon it within this procedure.

  Reference: *Marchand G, Masoud AT, Medi S. Risk of all-cause and cardiac-related mortality after vaccination against COVID-19: A meta-analysis of self-controlled case series studies. Hum Vaccin Immunother. 2023 Aug 1;19(2):2230828. doi: 10.1080/21645515.2023.2230828. PMID: 37534766; PMCID: PMC10402862.*

3. Autoimmune hepatitis

- The assessor found the review somewhat insufficient and that the provided information

can neither support nor exclude causality. The MAH is therefore requested to submit an updated cumulative review of autoimmune hepatitis, within this procedure. Specifically, an update and improvement of the following topics of the cumulative review are suggested as appropriate in order to meet the detailed request as well as to contribute to an understanding of whether Spikevax is causally associated to AIH:

- Clinical trial database: It is noted by the assessor, that the MAH specified that the review of clinical trials comprised 3 CTs with adult participants. As the MAH has previously reported a clinical trial safety database review in which cases among children were reported, the assessor is concerned about whether all clinical trial databases were searched or if the three CTs with adult participants were selected among more trials without justification. Ensuring presentation of data from all clinical trials to which the MAH has access can be of relevance in the assessment, either as supporting a possible ADR suspicion or as supporting the refute of it. The original request included information from all relevant data sources, and for this purpose all clinical trials for which there are reported cases of AIH or AIH-related PTs are considered relevant.

  The MAH states that it did not retrieve any cases from the three reviewed clinical trials. However, the assessors note that PSUR appendix 3a "Cumulative Summary Tabulations of Serious AEs from Clinical Trials for elasomeran" includes 2 cases of hepatic failure and 1 case of hepatitis acute in the category "investigational medicinal product". Within this procedure, the MAH is requested to present data on autoimmune hepatitis from all clinical trials including the 2 cases of hepatic failure and the 1 case of hepatitis acute. The data should also include paediatric cases.

  For better overview and easier follow-up, it is suggested to tabulate clinical trials, both those mentioned earlier as well as new ones including CT number, age groups, review date, and results. For example, as shown here:

CT	**Age groups**	**Cumulatively as of *(date)***	**AIH/AIH-related PTs**	**Classified AIH case**
mRNA- 1273-P301	Adults	*as of 04 May 2021*	No cases	No cases
mRNA-1273-P203		*as of 27 Jan 2022*	One case (1 female adolescent)	No cases
mRNA-1273-P204		*as of 21 Feb 2022*	One case (1 female infant)	No cases
mRNA-1273.222-P205-Part H	Adults	*as of 23 Sep 2023*	No cases	
mRNA-1273.815-P205- Part J	Adults	*as of 25 May 2023*	No cases	

- Age: There is a discrepancy between the reported age range of cases and the fact that the MAH has not reported anything about patients < 18 years. No cases in patients 0-17 years were reported in this cumulative review, although the age range of cases is reported to be 0.0-96.0 years which implies that cases in infants/children have been reported. Cases in infants,

children and adolescents should at least be commented on.

- Dose number and TTO: In many cases dose number and/or time to onset are unknown, and the MAH has defined all these cases as unassessable due to missing information. This categorization of data as unassessable in case of unknown dose is not acknowledged, and it unfortunately results in discarding a large amount of data. The MAH was requested to present data including TTO and dechallenge/rechallenge. For this, dose number could be used as a proxy measure. This was not sufficiently met, as all cases in which dose number or TTO was missing were discarded as unassessable. Cases should, according to request, be listed with information on dechallenge/rechallenge (dose) and TTO; lack of dose number should not be a reason for excluding a case from being assessed.

  In the 3rd PSUR, data were presented tabulated by dose as well as by TTO. Within this procedure, the tables with AIH by dose and TTO as used by the MAH in the 3rd PSUR should be updated and presented.

- Uzun et al: The MAH was requested to present and evaluate the literature case reports and observational studies related to elasomeran mentioned in the article by Uzun et al. However, the MAH has not presented and evaluated the literature case reports and observational studies mentioned in Supplementary Table 14 of this publication (page 7558 of PSUR no. 5) as requested. Within this procedure, the MAH is requested to present and evaluate these literature case reports and observational studies.

  Reference: *Uzun S, Zinner CP, Beenen AC, Alborelli I, Bartoszek EM, Yeung J, Calgua B, Reinscheid M, Bronsert P, Stalder AK, Haslbauer JD, Vosbeck J, Mazzucchelli L, Hoffmann T, Terracciano LM, Hutter G, Manz M, Panne I, Boettler T, Hofmann M, Bengsch B, Heim MH, Bernsmeier C, Jiang S, Tzankov A, Terziroli Beretta-Piccoli B, Matter MS. Morphologic and molecular analysis of liver injury after SARS-CoV-2 vaccination reveals distinct characteristics. J Hepatol. 2023 Sep;79(3):666-676. doi: 10.1016/j.jhep.2023.05.020. Epub 2023 Jun 7. PMID: 37290592; PMCID: PMC10245467.*

4. **Characterisation of risks**

   - In the MAH´s characterisations of the important identified risks "myocarditis" and "pericarditis", the Rapporteur notes that the MAH states that the product information was revised during the PSUR reporting period regarding these safety concerns. Specifically, the MAH states that the product information was updated with the following information: *"Post-authorization data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than viral infectious myocarditis and pericarditis"*. The Rapporteur deems that this information is valuable to the clinician, however, the information is not included in the currently available version of the EU SmPC from EMA´s website.

     Within this procedure, the MAH is requested to clarify which procedure this PI revision originates from, and provide, if relevant, the anticipated timeline for its implementation in the EU SmPC.

7. MAH responses to Request for supplementary information

7.1. Item 1 – RMP

MAH response

- The MAH would like to clarify that the proposal for an updated myocarditis and pericarditis Follow-Up Questionnaire (FUQ) was to simplify the questionnaire by removing unnecessary questions and reducing the number of pages by half in order to decrease the burden on reporters, with the ultimate goal of increasing the reporting rate.
- The MAH would like to clarify that the changes to the RMP are a direct result of data presented in the PSUR. In addition, submission of EU RMP v8.3 along with the PSUR was discussed and endorsed by the PRAC Risk manager.
- Based on the feedback from the PRAC, the MAH has re-evaluated the necessity of maintaining a FUQ for the characterization of the important identified risks myocarditis and pericarditis and decided to discontinue its use. This decision is supported by the FUQ's poor effectiveness, evidenced by a near-zero response rate, and the existence of several additional pharmacovigilance activities already included in the EU-RMP. These activities are designed to further characterize the important identified risks of myocarditis and pericarditis. Therefore, there is no reasonable expectation that the FUQ will contribute to a better characterization of these risks in the Summary of Product Characteristics (SmPC).
- The MAH considers the myocarditis/pericarditis FUQ is no longer warranted and acknowledges the advice from PRAC for future FUQ preparation. The FUQ is removed from the updated EU RMP v8.3 that is submitted with this response.

Rapporteur assessment comment:

The MAH clarified that the changes to the RMP are a direct result of data presented in the PSUR. This is acknowledged and relevant section has now been identified by the assessor:

ModernaTx, Inc. Supplemental Follow-up Questionnaire for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of a marketed Moderna vaccine targeting SARS-CoV-2

During the reporting period of this PBRER a total of 165 follow-up questionnaires (FUQs) for collecting supplementary information on cases of potential/confirmed Myocarditis/Pericarditis were sent by the MAH to the reporters, of which 0 FUQ responses were received. The response rate to this questionnaire was 0%. Cumulatively, a total of 730 Myocarditis/ Pericarditis FUQs have been sent to reporters, of which only 25 FUQs were received, for a response rate of 3%.

This very low response rate may be an indicator of the reporter's difficulties to address all the requested follow-up information. The length of the questionnaire and the redundancy of certain information already provided by the reporter may also discourage reporting. In addition, reporters may not understand the importance of documenting cases to inform and further characterize these already known risks.

Since its implementation in Jul 2021, the cumulative review of FUQs experience, shows an extremely low reporting rate. Hence, ModernaTx, Inc. concludes that the current format of the FUQ included in Annex 4 of the SPIKEVAX RMP is not adequate. In order to improve data collection for these 2 important identified risks, ModernaTx, Inc. proposes an updated version of the FUQ streamlining the information requested in the form and avoiding duplication of the information related to patients' demographic.

The proposed updated questionnaire is included in Annex 4 of the updated EU-RMP version 8.3 submitted

with this PBRER.

As discussed in section 3, in view of several additional PhV activities aiming to further characterise the risks myocarditis and pericarditis, the additional value of the FUQ to obtain further data on individual cases which have been spontaneously reported is questioned. Considering also the lack of effectiveness of these FUQs, as demonstrated by the MAH, the PRAC Rapporteur agrees that there is no reasonable expectation that the FUQ will contribute to a better characterisation of these risks. Deletion of the FUQs as proposed by the MAH is therefore accepted.

Conclusion

The updated RMP version 8.3 is acceptable (for details, refer to section 3.2).

7.2. Item 2 - Literature

MAH response

The study conducted by Marchand et al. (Marchand et al. 2023) was a systematic review and meta-analysis in which they included a self-controlled case series (SCCS) for the purpose of investigating the safety of COVID-19 vaccination and to evaluate the risk of cardiac-related mortality following COVID-19 vaccination.

According to the authors the following were the main findings of their study:

a. **All-Cause Mortality**:

- The pooled hazard ratio (HR) revealed no significant association between COVID-19 vaccination and all-cause mortality (HR = 0.89, 95% CI [0.71, 1.10], p = .28).
- Subgroup analysis by age indicated no increased risk in the 18–24 age group (HR = 1.04, 95% CI [0.81, 1.35], p = .74).
- Heterogeneity in data was noted (I^2 = 94%) and excluding one study (Stivanello et al. 2022) resolved this, but the results remained non-significant.

b. Cardiac-Related Mortality:

- The analysis suggests a small but statistically significant increase in cardiac-related mortality following COVID-19 vaccination (HR = 1.06, 95% CI [1.02, 1.11], p = .007).
- Subgroup analysis identified male gender as a significant risk factor for increased cardiac-related mortality (HR = 1.09, 95% CI [1.02, 1.15], p = .006).
- No significant associations were found in subgroups of females and the 18–24 age group.
- The authors mentioned other studies (Xu et al. 2021) in which those authors did not found an association with increased cardiac risk.
- Another study conducted by (Bardenheier et al) showed that the risk of mortality was significantly higher in unvaccinated residents than those who received vaccines.
- One of the important limitations of this study, especially related to cardiac-related mortality is that the above 60 age group may lead to confounding in cardiac-related mortality.
- In the Ladapo et al. (Ladapo et al.) study the >60 years age group was the majority of all cardiac-related death rates, and when the authors removed this group from the analysis, the

pooled risk incidence (RI) reported no significant association between mortality and COVID-19 post-vaccination (RI = 1.15, 95% CI = 0.99–1.34), mRNA vaccination (RI = 1.17, 95% CI = 1.00–1.37), and males with mRNA vaccination (RI = 1.09, 95% CI = 0.89–1.34).

Strengths of the Study:

- Use of SCCS design which may controls for fixed-time confounders, such as underlying health conditions, by comparing the incidence of events in the same individuals during different time periods. According to the authors this design is particularly effective in vaccine safety studies as it uses individuals as their own controls, thus minimizing between-person confounding.
- Large Sample Size, given that the study includes data from approximately 750,000 patients, providing a robust sample size that enhances the reliability of the findings.
- The meta-analysis specifically targets the immediate post-vaccination period, which is considered the highest risk period for adverse events. This focus allows for a more precise assessment of the risks associated with vaccination.
- According to the authors the findings of the study are consistent with previous studies that identified an increased risk of myocarditis, particularly following mRNA vaccinations, but that does not necessarily equate to a higher risk of mortality due to cardiac-related events.

Limitations of the Study:

- Significant heterogeneity was found among the included studies, which complicates the interpretation of pooled results. Although this was partially resolved by excluding one study, it remains a concern.
- Different definitions of the risk period and follow-up durations across studies might contribute to this heterogeneity.
- Only three SCCS studies were included, limiting the generalizability of the findings. More studies would be needed to confirm these results across diverse populations and settings.
- The SCCS design assumes that the occurrence of an event does not affect subsequent exposure. In the context of COVID-19 vaccines, this assumption might not hold true, especially for mRNA vaccines, potentially introducing bias.
- The studies did not provide specific data on the timing of events post-vaccination or on which vaccines were associated with the events, limiting deeper important analysis and probably introducing additional confounder to the study.
- There was also a lack of detailed demographic data, which could have provided more insights into risk factors.
- The inclusion of a very politically driven study (Ladapo et al - published through the Florida Department of Health) may have introduce important bias to the findings of this study, especially those associated with cardiac-related mortality. Several authors have express concerns related to the inclusion of the Ladapo study in the Marchand et al. paper given some reported data issues especially in previous version of the Ladapo report in which the authors acknowledges that "the primary analysis did not use the correct self-controlled case series method as it did not account for multiple exposures, and that"[the primary analysis] violates the assumption that an event does not affect subsequent exposure (for mRNA vaccines),which may introduce bias upwards.." (Black et al). After the author reportedly performed a sensitivity analysis using the correct event-dependent exposures method to look at the risk following each dose. They concluded "[the association of COVID-19 vaccination and cardiac-related mortality at 28 days] was attenuated

and no longer significant when applying the more appropriate event-dependent exposures model utilized for multidose vaccines. Thus, there is little suggestion of any effect immediately following vaccination."

Conclusion:

The MAH considers that information included in the study by Marchand et al., does not provide new and significant safety information that would have required inclusion in the Literature section of PBRER #6. Information provided in this metanalysis includes safety data that have already been published and evaluated by the MAH. As per reference, please refer to the PRAC PSUR assessment report for PBRER #4 (Procedure no.: EMEA/H/C/PSUSA/00010897/202212) in which the PRAC requested an amendment of the SmPC, Section 4.4 for the warning and precautions for Myocarditis and Pericarditis, adding a sentence informing providers that "*fatal cases have been observed*." Additionally, the MAH updated the Company Core Data Sheet (version 18.0), to include information that "*Although causality has not been established, fatal events have been very rarely reported*".

This meta-analysis provides insights into the safety profile of COVID-19 vaccines but does not provide safety information that could be considered new, hence the fact that the article was review but it was not considered to be relevant for inclusion in the literature section of PBRER #6.

Information provided in the article by Marchand et al., does not change the known safety profile of the marketed Moderna vaccines targeting SARS-CoV-2, not the benefit risk balance of the vaccines, which continues to be positive.

References:

Marchand G, Masoud AT, Medi S. Risk of all-cause and cardiac-related mortality after vaccination against COVID-19: A meta-analysis of self-controlled case series studies. Hum Vaccines Immunother. 2023;19(2):2230828.

Stivanello E, Beghelli C, Cardoni F, Giansante C, Marzaroli P, Musti MA, et al. Shortterm mortality following COVID-19 vaccination in Bologna, Italy: a one-year study. Vaccine. 2022;40(39):5709–15.

Xu S, Huang R, Sy LS, Glenn SC, Ryan DS, Morrissette K, et al. COVID-19 Vaccination and Non–COVID-19 Mortality Risk — Seven Integrated Health Care Organizations, United States, December 14, 2020–July 31, 2021. Morb Mortal Wkly Rep. 2021;70(43):1520–4.

Rapporteur assessment comment:

The MAH has commented on the publication by Marchand et al. as requested.

Marchand et al. conducted a meta-analysis including approximately 750,000 patients, which identified a small but statistically significant increase in cardiac-related mortality following COVID-19 vaccination (HR = 1.06, 95% CI [1.02, 1.11], p = .007). Male gender was identified as a significant risk factor for increased cardiac-related mortality (HR = 1.09, 95% CI [1.02, 1.15], p = .006)

Several critical issues are highlighted by Somovilla, and Black T. and colleagues, suggesting that the conclusions drawn by Marchand et al. are not robust and may be fundamentally flawed:

Inclusion of Non-Peer-Reviewed Study: Marchand et al. justify including the non-peer-reviewed Ladapo paper by claiming it meets the definition of "published and peer reviewed" as it was produced by a U.S. Department of Health. However, no evidence shows approval of the final version by anyone other than Ladapo, despite the report being referred to as Ladapo et al. Previous versions of the publication by Ladapo obtained through a freedom of information request indicate disagreement with the final version. These versions acknowledge that the primary analysis used an incorrect self-controlled case series method, not accounting for multiple exposures and thereby introducing bias. Correct sensitivity analyses

found no significant association between COVID-19 vaccination and cardiac-related mortality at 28 days, and another version using a 42-day exposure period also failed to replicate the findings.

Data Extraction Errors: Numerous inaccuracies in extracted data, such as incorrect hazard ratios and mislabeling incidence rate ratios, raise concerns about the authors' understanding and representation of the cited studies.

Methodological Concerns: The authors' methodology states they use a fixed-effects model for homogeneous data and a random-effects model for heterogeneous data ($I^2 > 50\%$ or $P < .1$). However, in model 1.2.1 [cardiac-related mortality in all patients], with an I^2 of 61%, they incorrectly used a fixed-effects model. Correctly using a random-effects model would yield an IRR of 1.03 (0.91–1.16), overturning their conclusions.

Additionally, the fixed-effects model over-weights a single study (Ladapo et al.) with > 99% weight, making it less a meta-analysis. According to Cochrane principles, these analyses should have used random-effects due to study differences, such as populations and age ranges, violating the requirement for homogeneity.

The MAH considers that information included in the study by Marchand et al., does not provide new and significant safety information. Due to the critical methodological shortcomings of this study as pointed out by Somovilla and Black et al., the Rapporteur agrees. No further action is considered warranted.

Issue resolved.

Reference:

Somovilla Del Saz B. Questionable robustness in the findings of a meta-analysis. Hum Vaccin Immunother. 2023 Aug;19(2):2253959. doi: 10.1080/21645515.2023.2253959. Epub 2023 Oct 6. PMID: 37799069; PMCID: PMC10578341.

Marchand GJ, Masoud A. Response to Dr. Somovilla del Saz's letter to the editor regarding "Risk of all-cause and cardiac-related mortality after vaccination against COVID-19: A meta-analysis of self-controlled case series studies". Hum Vaccin Immunother. 2023 Dec 15;19(3):2264599. doi: 10.1080/21645515.2023.2264599. Epub 2023 Oct 8. PMID: 37806668; PMCID: PMC10791150.

Somovilla Del Saz B. Reconsidering the inclusion of Ladapo's work in the meta-analysis: Validity concerns and implications. Hum Vaccin Immunother. 2024 Dec 31;20(1):2315711. doi: 10.1080/21645515.2024.2315711. Epub 2024 Feb 15. PMID: 38359841; PMCID: PMC10880802.

Black, T., Meyerowitz-Katz, G., Owusu-Boaitey, N., & Oliver, S. (2023). Errors and issues in risk of all-cause and cardiac-related mortality after vaccination against COVID-19: A meta-analysis of self-controlled case series studies. *Human Vaccines & Immunotherapeutics*, *19*(3). https://doi.org/10.1080/21645515.2023.2290173

7.3. Item 3 – Autoimmune hepatitis

MAH response

As per request from the PRAC, an updated cumulative review as of 17 Dec 2023, of Autoimmune hepatitis (AIH) in association with the use of mRNA-1273 in all patients exposed was performed using several data sources, including:

- Clinical trial data review with additional mRNA-1273 studies.
- Review of children and adolescent data below 18-Years of age

- Review of all Post marketed safety data with Autoimmune hepatitis specific terms
- Review of literature article by Unzu et al, 2023 including the supplemental data

Important to note that the number of spontaneous reports, including published literature has gradually decreased in number, with no new reports of AIH-related terms received after 17-Dec-2023, including valid published literature.

Clinical trial Section

As presented before, the topic of AIH was review in the mRNA-1273 clinical trials presented in the PBRER #6, using the Preferred Terms (PT) of: "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immunemediated hepatic disorder, Immune-mediated hepatitis, Liver injury". As per request from the PRAC additional clinical studies were reviewed and are included in the table below. Six new cases were identified in those studies, of which none were AIH cases.

CT	Age groups	Cumulatively as of (date)	AIH/AIH related PTs	Classified AIH case
Previously presented				
mRNA-1273-P301	Adults	*04 May 2021*	No cases	No cases
mRNA-1273.222-P205-Part H	Adults	*23 Sep 2023*	No cases	
mRNA-1273.815-P205- Part J	Adults	*25 May 2023*	No cases	
Newly reviewed as requested by PRAC				
mRNA-1273-P203	Healthy adolescents. Age group: 12 to < 18	*27 Jan 2022*	One case (1 female adolescent; information provided in PBRER#3)	No cases
mRNA-1273-P204	6 months to < 12 years	*21 Feb 2022*	One case (1 female infant; information provided in PBRER#3)	No cases
mRNA-1273-P205	18 to 55 years of age	*25 May 2023*	No cases	No cases
mRNA-1273-P206	Vaccine naïve Healthy participants aged 12 weeks to < 6 months	*25 Apr 2024*	No cases	No cases

mRNA-1273-P304	IC individuals who had a Solid Organ Transplant (SOT) and were aged ≥18 years	*17 Dec 2023*	One case of Autoimmune hepatitis in 24-Y-[redacted] One case of Liver injury in 57-Y-[redacted] Both these events were considered not related by investigation	No cases
mRNA-1273-P305	Age group: ≥ 16 years	*15 Jan 2024*	Two cases of Liver injury. Considered not related by the Investigator.	No cases
mRNA-1273-P306	aged 6 months to < 6 years	*21 Mar 2023*	No cases	No cases

Summary of cases from mRNA-1273-P304

Participant [redacted]: This case concerns a 57-Year-old, [redacted] subject with no reported medical history who experienced the non-serious unexpected adverse event of special interest (AESI) of acute liver injury. The event occurred 219 days after the third dose of mRNA-1273 administration and the following few days after the third dose. The subject was asymptomatic at the time of the event, and liver function tests were obtained due to routine monitoring. The subject received all scheduled doses of study drug prior to the event; therefore, no action taken with study vaccine in response to the event. The event, acute liver injury, which was apparent due to asymptomatic transaminitis, was reported as resolved. The report was confounded due to subject´s new supplements and missing a dose of immunosuppressant medications. The investigator causality was reported as not related to the study treatment.

Participant [redacted] This case concerns a 24-Year-old, [redacted] subject with no reported medical history who experienced the non-serious unexpected adverse event of special interest (AESI) of Autoimmune hepatitis. The event occurred 44 days after the third dose of mRNA-1273 administration. The subject received all scheduled doses of study drug prior to the event; therefore, no action taken with study vaccine in response to the event. The event, acute liver injury, which was apparent due to asymptomatic transaminitis, was reported as resolved. The investigator causality was reported as not related to the study treatment. No other information was available to review the case.

Summary of cases from mRNA-1273-P305

Participant [redacted]**:** This case concerns a 50-year-old 'Asian or Asian British', male subject with no reported medical history. The subject, categorized within the age group of >=16 and <65 years and received his 4th dose of the vaccine, experienced a non-serious adverse event of special interest (AESI) identified as acute liver injury with raised ALT levels. The adverse event reported on May 30, 2022, and resolved by August 30, 2022. Medically reviewed findings indicated the adverse event occurred 90 days following the administration of the first vaccination, with no prior indications of autoimmune hepatitis or immune-mediated hepatitis. This event was reported as not related to the study treatment and concluded as recovered/resolved. The subject's management included medical attention without changes to the

vaccine dose. The investigators causality was assessed as not related to the vaccine, based on the available information.

Participant [redacted] This narrative concerns a 66-year-old White female from the mRNA-1273-P305. The subject was undergoing her 4th dose regimen. The subject reported an adverse event of acute liver injury which began on December 12, 2022, and was still ongoing as of the last follow-up. This event occurred significantly post-vaccination, with an onset 278 days after the first vaccination, with no evidence linking the event directly to autoimmune or immunemediated hepatitis. The injury was medically attended, though it has not resolved or recovered yet. The investigators causality for this event was adjudicated as not related to the vaccine. Also considered the liver injury events as not directly associated with vaccine administration.

Summary: Review of data from clinical trials did not identify any true case of Autoimmune hepatitis. After a detailed review of the adverse events reported in the clinical trials for the mRNA-1273 vaccine, specifically concerning cases of acute Autoimmune Hepatitis (AIH), it is evident that there were no true cases of AIH. The adverse events reported were either linked to external factors or other medical conditions unrelated to the vaccine. Furthermore, the investigator causality assessments consistently indicated that the vaccine was not related to the reported Autoimmune Hepatitis related events.

Review of Post marketed Data in Patients < 18 years of Age

The MAH acknowledges the assessor's comments regarding Infants, Children, and Adolescents Aged 0-7 Years (Comment no. 3). Review of the GSDB identified 4 reports of AIH-related terms (one newborn, two 13-year-olds, and a 15-year-old). None of these 4 reports had the reported term of autoimmune hepatitis or Immune mediated hepatitis (reported PT: Acute hepatic Failure, Hepatitis acute, Hepatic failure, and Liver injury).

Each report was medically reviewed, and it was confirmed that none of them represented true AIH cases. None had any evidence of AIH or related disorders. They all had an AIH score of 0. There was no mention of AIH, or any speculation of an immune mediated source and all 4 reports had other events explaining the hepatic events. These 4 reports are summarized below:

Case ID	Age/gender	PTs	Case Summary	MAH Comment
[redacted] (Regulatory Report)	0/Unknown	**Acute hepatic failure,** Foetal hypokinesia, Foetal movement disorder, Low birth weight baby	Neonate (gender not provided), whose mother received first dose of mRNA-1273 15 days prior to initiation of infant's events, when it was first diagnosed with fetal hypokinesia. The baby was born prematurely (roughly 33 weeks gestation) via caesarian section 70 days after vaccination of the mother and was diagnosed with acute hepatic failure leading to DIC. The neonate was noted to have a calcified liver, but there were no signs of AIC, and per EASL this report had no elements of AIC. Of note, the mother	This report described a neonate whose mother was exposed to vaccine. The neonate appeared to suffer liver damage of another source in utero, given the noted calcified liver, not consistent with AIH. No diagnostic aspects of autoimmune hepatitis were described.

			was of advanced maternal age (42 year) and suffered from Thrombophilia A1 deficiency.	
[redacted] (Regulatory Report)	13/Female	**Hepatitis acute**	Thirteen-year-old female patient who experienced hepatitis acute 19 days after her first dose of mRNA-1273. The report provided very little information, not providing medical history, concomitant medications, treatment details or course of events. No diagnostics were provided. The acute hepatitis was reported to be resolving at the time of the report. Reportedly, the patient did receive a second dose of mRNA-1273 but no adverse events or details of the rechallenge were reported.	This report provided very little information for an assessment. However, there was no suggestion of autoimmune hepatitis, and no diagnostic criteria were provided.
[redacted] (Consumer Report)	13/Male	Brain injury, Cardiac arrest, Cerebrovascular accident, Endocarditis, **Hepatic failure,** Immunodeficiency, Myocarditis, Renal failure, Sepsis	Thirteen-year-old male experienced myocarditis on the day of his 2nd dose of mRNA-1273. Myocarditis led to endocarditis with sepsis/immunodeficiency 61 days after the initial diagnosis of myocarditis. On an unknown date experienced cerebrovascular accident, renal failure, brain injury, hepatic failure, and cardiac arrest leading to death. The patient had significant past medical history including neonatal cardiac surgery, with a diagnosis of truncus arteriosis type 1 and interrupted aortic arch. As well, patient had a liver transplantation at 6 months of age.	Patient with a history of liver transplant. The event of hepatic failure occurred in the setting of myocarditis, CVA, renal failure, cardiac arrest, and brain injury, and was likely part of multiorgan failure. No evidenced of AIH provided.

[redacted] (Literature Report)	15/Female	Anorexia nervosa, Condition aggravated, Dehydration, Epistaxis, Gelatinous transformation of the bone marrow, Hyponatraemia, **Liver injury,** Normocytic anaemia, Osteoporosis, Osteoporotic fracture, Renal failure	This is a literature report: "When refeeding is not enough: severe and prolonged pancytopenia in an adolescent with anorexia nervosa". It describes a 15-year-old female with a 2-year history of anorexia nervosa and amenorrhea. On an unknown date the patient received her first dose of mRNA-1273 and her second dose, on an unknown date, and an unknown time afterwards experienced worsening of anorexia nervosa, gelatinous transformation of the bone marrow, epistaxis, osteoporosis, hyponatremia, dehydration, liver injury, renal failure, normocytic anemia, and osteoporotic fracture. No suggestion or diagnostics consistent with AIH were reported which was focused on the patient's end stage cachexia.	This report described a patient with end stage cachexia related to her longstanding anorexia nervosa. The event of liver injury is most likely related to her worsening anorexia nervosa, and no data or diagnostics were provided suggesting AIH.

Updated Review of Post-marketed Data:

The MAH queried the global safety database for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 17 December 2023, for Spikevax marketed products. Search criteria used the PTs of "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury". Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches were described for cumulative cases.

The search retrieved 315 reports with 326 events. The following were the counts for each of the search terms used in the search strategy.

Table-3: Events Retrieved from Global Safety Database Search as of 17 Dec 2023

PT from Search Strategy	Number of Reports
Autoimmune hepatitis	114
Liver injury	61

Hepatic failure	44
Hepatitis acute	35
Acute hepatic failure	22
Drug-induced liver injury	19
Hepatocellular injury	18
Hepatotoxicity	5
Hepatitis fulminant	4
Immune-mediated hepatitis	3
Immune-mediated hepatic disorder	1
Hepatitis toxic	0

11 reports included 2 of these PTs.

Out of the 315 reports retrieved from the GSDB, a total of 211 reports were already included and evaluated in PBRER #3. That assessment stands as those reports were evaluated by the PRAC.

Reports were reviewed in case any new additional follow up information was provided that may had changed the previous evaluation of that report. No cases fulfill this requirement. As per the PRAC assessment report of PBRER #3 (Procedure no.: EMEA/H/C/PSUSA/00010897/202206) final comments on AIH: "As of 18 June 2022, there has cumulatively been 10 reported cases classified as "definitive" or "probable" cases of AIH according to the EASL guidelines, while 201 cases were categorized as not cases of AIH according to the Simplified Classification Guidelines or that were unassessable based on missing information. The reporting rate of AIH is low being 0.01 per million doses administered, and there is not sufficient data to indicate a causal association between AIH and Elasomeran despite any temporal association. No new safety issue of concern was identified. AIH-related events are not presently a safety issue of concern, and the MAH will continue to evaluate events of "AIH related events" using routine surveillance, which is supported."

The rest of the 315 reports (104 case reports) were carefully re-evaluated and reviewed by a clinician for any evidence of autoimmune hepatitis. Each report, regardless of the reported hepatic term, or amount of data provided, was scored using the simplified diagnostic criteria of the International Autoimmune Hepatitis Group paradigm, as previously conducted in both PBRER #3 and PBRER #6. Special attention was paid to any report in which the reported event term was "Autoimmune hepatitis" (n=114) or "Immune mediated hepatitis" (IMH) (n=5).

Diagnostic Criteria for Autoimmune Hepatitis

The International autoimmune hepatitis Group's simplified diagnostic criteria is summarized in the following Figure-1.

Figure-1: Simplified diagnostic criteria of the International Autoimmune Hepatitis Group

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

ANA= antinuclear antibodies SMA= smooth muscle antibodies LKM= liver kidney microsomal antibodies SLA= soluble liver antigens LP= liver pancreas. Addition of points achieved for all autoantibodies (maximum, two points). Typical liver histology for autoimmune hepatitis = each of the following features had to be present namely, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation. Compatible liver histology for autoimmune hepatitis = chronic hepatitis with lymphocytic infiltration without all the features considered typical. Atypical = showing signs of another diagnosis, like steatohepatitis.

As noted in Figure-1, the cases were classified into two categories including autoimmune hepatitis (including definite and probable) and unassessable, following the Simplified diagnostic criteria of the International Autoimmune Hepatitis Group:

- Definite autoimmune hepatitis: 7 -8 Points
- Probable autoimmune hepatitis: 6 Points
- Unassessable: 5 to 1 Points - Those cases for which there were insufficient information to provide a diagnostic classification.
- Not a Case of AIH: 0 Points

Of these 315 cases, most of the cases were not an AIH case. Detailed counts of these cases are presented in Table-4.

Table-4: Cumulative Reports with EASL Score Category

#	EASL Score Category	EASL Category of AIH cases	Count of Cases/Reports
1	Score of 0 (Zero)	Not AIH	237
2	Score of 1 to 2	Unassessable	29
3	Score of 3 to 4	Unassessable	20
4	Score of 5	Unassessable	9
5	Score of 6	Probable AIH	3
6	Score by 7 to 8	Definitive AIH	17
Total			**315**

Cases Not Meeting AIH Case Definition

Reports with an AIH Score of Zero

There were 237 (75%) reports that had an AIH score of zero, meaning no elements of autoimmune hepatitis were provided by the reporter.

- Of these, 170 reports did not report a term of interest (autoimmune hepatitis or immune mediated hepatitis). It was clear that these reports did not describe autoimmune hepatitis following vaccination but were describing other hepatic adverse events.
- Sixty-six (67) reported a term of potential interest (AIH, n=64, IMH, n=3). These reports were reviewed in detail to determine if there was any information confirming a diagnosis of autoimmune hepatitis. None of these reports were identified to have any information other than the reporting term to suggest an actual case of AIH.

While none of these 241 reports demonstrated evidence of AIH, these cases are described in the Appendix-1a and full narratives are presented in Appendix 1b.

Two reports, both with extremely limited information, and neither medically confirmed (consumer reports), did describe a *potential* **rechallenge** and are presented in more detail here:

[redacted]**:** A regulatory report which originated from a consumer, not medically confirmed. A 59-year-old female reported greatly elevated liver test, "autoimmune liver disease triggered". Occurred 11 days after first dose. No other details were provided. Information on treatment, past medical history, concomitant medications, information on any diagnostics to support diagnosis, etc. was missing. Patient stated that after the second dose "the values increased even more". Six months after vaccination "values dropped slightly. No medical history, concomitant medications, or treatment t details were provided. WHO UMC Causality: Unassessable.

MAH Comment: Consumer report with no medical confirmation. No details or diagnostics for autoimmune hepatitis were provided. Patient reported a potential rechallenge positive but provided no details. Lack of medical history and concomitant medications makes assessment difficult.

[redacted]**:** A spontaneous reports from a consumer, not medically confirmed. A male patient, of unknown age, reported events on Facebook. On unknown dates, he received his first and second doses of mRNA-1273. On an unknown date, he experienced "hepatitis with rapid onset of liver injury". The social media post stated that the rapid onset of liver injury occurred after the first dose of mRNA-1273. Patient stated re-exposure led to acute severe autoimmune hepatitis. Not other details were provided, and the reporter did not allow further contact. No medical history, concomitant medications, or treatment details were provided. WHO UMC Causality: Unassessable.

MAH Comment: Consumer report with no medical confirmation. No diagnostics indicative of a diagnosis of AIH were provided. The patients did not provide any medical history, concomitant medications, or clinical course of the events. Patient's age was not even available. Lack of all critical data points make an assessment of AIH or causality impossible.

Unassessable Cases with an AIH Score of 5 points to 1 point

a. Reports with a AIH Score of One or Two

There were 29 reports with AIH Scores of just 1 (n=6) or 2 (n=23) points, clearly not providing enough information to allow for a complete evaluation of the cases as per the definition of autoimmune hepatitis.

Twenty-seven reports contained only than 1 of the 4 key elements to define a case as AIH. Two reports included 2 key elements, receiving score of 1 of 2 possible points in each those categories.

- Eleven reported some form of autoantibodies, with no other elements of AIH provided.
- Two reported an increase in IgG or hypergammaglobulinemia, a key aspect of AIH. Both only partially met these criteria.
- Eight reported liver histology at least suggestive of autoimmune hepatitis. Only 4 of these reports had liver histology fully compatible with AIH.
- Ten described patients testing negative for viral hepatitis, with no other elements of AIH provided.

Twenty-one of these reports did contain a term of interest (AIH, n=20 and IMH, n=1). Careful review of all available data failed to identify any further information to confirm them as a true case of autoimmune hepatitis. These cases are described in the Appendix-1a.

b. Reports with AIH Score of Three (3) or Four (4)

There are 16 reports in 3 to 4 categories, of which 5 reports received a score of 3, and 11 reports received a score of 4. Eleven out of the 16 reports were from the literature. Fourteen of these reports only described 2 of the 4 elements of autoimmune hepatitis, while 2 reported three elements, but only partially met 2 of them. These reports were carefully reviewed for any additional information that would suggest they represent a true case autoimmune hepatitis. These reports are described in Appendix-1a. According to the WHO causality assessment, 4 cases were considered unassessable, and 7 were unlikely due to confounders that provided a more plausible explanation for the reported events. There 5 reports deemed possible. See Appendix-1a.

c. Reports with AIH Score of Five (5)

There were 9 reports with an AIH score of 5. All these reports included at least 3 elements of the 4 used to define autoimmune hepatitis but failed to have a finding fully aligned with AIH in one of the 3 elements. After medical review of the cases no additional information was available for further evaluation of the reported terms of AIH. Of note, 4 of these 8 cases were reported from one literature reports, Uzun et al., which is presented below. (See Appendix-1a). According to the WHO causality assessment 2 reports were unassessable, as they provided very limited information related to the patient's history, medical course, treatment, etc. The rest of the reports (7) were deemed possibly related. All of these 7 were from the literature, with four of these 7 from the article by Uzun et al.

Cases Meeting AIH Case Definition

a. Reports with AIH Score of Six, Seven or Eight (Definite or Probable Cases of AIH)

Twenty-one (21), reports had a score of 6 or more for autoimmune hepatitis. Detailed information is provided in Appendix 1a.

Summary of reports with 6 points (Probable AIH)

- There were 3 reports that had 6 out of 8 points for AIH.
- All three (3) were from the literature.
- All three (3) reported the hepatic event as autoimmune hepatitis.
- All three (3) were determined to have a WHO UMC causality of possible.

Summary of reports with 7 or 8 points (Definite AIH)

- Eighteen reports had an AIH score of 7 or 8 points (Definite AIH)
- 5 had 7 points, and 13 had 8 points.
- Fifteen of the 18 were from the literature, 2 were regulatory reports, and only 1 was spontaneous.
- Fifteen of 18 had a reported term of autoimmune hepatitis, and one had a reported term of immune mediated hepatitis.
- Five of the 18 reports either provided a clear confounder, or did not provide enough information for a causal assessment, making a causal association with mRNA-1273 either unlikely (n=4) or unassessable (n=1)
- 13 of these reports had a WHO UMC causality assessment of either possible or probable, with 11 of the reports had a causality of "possible" due to the presence of other confounders/ risk factors that could provide a more plausible explanation for the reported events or failed to provide significant data to make a firm causal assessment. The rest, 2 reports, had a causality of "probable."

Cases from the Literature in Which Individual Patient Data Could Not be Completely Determined

Four reports were included in the article by Codoni et al ([redacted] and [redacted]. While there was limited information for those reports, much of the key data for AIH scoring and past medical history, etc., was only provided at the aggregate level amongst a larger case series. Therefore, the information for the individual Moderna cases is very limited, making all of these reports unassessable and making case definition scoring impossible.

Citation: Codoni G, Kirchner T, Engel B, Villlamil AM, Efe C, Sattermayer AF, et al. Histological and serological features of acute liver injury after SARS-CoV-2 vaccination. JHEP Rep. 2022;5 (1):1-12

Article summary: The authors investigated a large international cohort of individuals with acute hepatitis arising after SARS-CoV-2 vaccination, focusing on histological features. Individuals without known pre-existing liver diseases and transaminase level greater than or equal to 5X upper limit of normal within 3 months after vaccination, available liver biopsy was included.

There were no individual patient data presented. Concomitant and treatment medications were not provided. Patients were diagnosed acute hepatitis within 2 months from last vaccine dose. It was reported that clinical data at diagnosis and outcome after a follow-up of 6 months were collected. Histology and autoimmune serology are centrally tested. Locally tested serology was positive for anti-nuclear antibody (ANA) in 31 cases; anti-smooth muscle antibody (ASMA) in 14, anti mitochondrial antibody (AMA) in 3; 12 were ANA and ASMA-positive; none was anti-soluble liver antigen or anti-liver kidney microsomal antibody positive; 11 were seronegative while histological review showed isolated central perivenulitis (n = 2) or mixed portal and lobular hepatitis with interface injury and confluent necrosis (n = 5; Figure). Aggregates of plasma cells and eosinophils (>5 cells/hpf). However, no specific information was provided for the specific patient described in this report. It was also reported that one patient died of extrahepatic cause 7 months after the diagnosis of hepatitis. Interchange of vaccine product and Revaccination with different COVID-19 vaccine was also noted in this article. The present study could not prove or refute a causal relationship between SARS-CoV-2 vaccines and liver injury with autoimmune features. As most patients received other drugs during the 3 months preceding liver injury, other DILI triggers could not be excluded.

Authors concluded that acute liver injury with autoimmune features that showed a temporal association with SARS-CoV-2 vaccination was likely to be a heterogeneous condition requiring a thorough work-up and careful follow-up. Patients were often treated with immunosuppression, with a good short-term response, though firm indications on when to start immunosuppression are needed, to avoid adverse effects. This study did not justify withholding SARS-CoV-2 vaccination, which had prevented severe COVID-19 disease and death in millions of people.

Review of Literature Data from Uzun et al, Article

As requested by PRAC, literature data from Uzun et al, 2023 article was re-evaluated including the data from supplemental table-14. Overall, there were 40 articles cited in the supplemental table, of which 15 describe Moderna vaccination and remaining 25 citations refer non-Moderna covid-19 vaccine. The Uzun article describe 6 patients had Moderna vaccine which were presented in (**Appendix-1**).

Review of Modern Covid-19 Vaccine Related Citations in Supplemental Table-14 of Uzun article:

Based on a comprehensive analysis of 15 articles from Uzun et al, supplemental table discussing liver injuries following COVID-19 vaccination with SPIKEVAX (Moderna), a differentiation was made between cases classified as autoimmune hepatitis (AIH) and those not classified as AIH. Among these studies, 9 cases were categorized as AIH, while 6 were determined not to be AIH (details of these articles are provided in Appendix-2).

Key Observations:

AIH Classification: The articles reporting AIH presented cases with typical and atypical presentations of autoimmune hepatitis. These cases often included clinical features such as jaundice, fatigue, and significantly elevated liver enzymes shortly after vaccination.

Most of these cases also exhibited positive autoantibodies and elevated IgG levels, with liver biopsies supporting the diagnosis of AIH based on interface hepatitis and other histological features.

Non-AIH Cases: The cases not classified as AIH generally presented with acute liver injury where the clinical and histological patterns did not fully meet the criteria for AIH. These included liver injuries with different etiological explanations or those that resolved without the typical treatment regimen for AIH.

Confounding Factors:

A significant concern across the AIH classified cases is the presence of confounding factors that complicate the establishment of a direct causal relationship between the liver injuries and the SPIKEVAX vaccination. These confounding factors include:

- **Pre-existing Autoimmune or Liver Conditions**: Several patients had a history of autoimmune diseases or were on medications that could predispose them to liver injuries.
- **Concomitant Medication**: Use of other medications capable of inducing liver injury.
- **Multiple Vaccinations**: Receiving different types of COVID-19 vaccines, which could influence immune responses variably.
- **Therapeutic Interventions**: The initiation of treatments such as corticosteroids before a definitive diagnosis could mask or alter the natural progression of liver injury.

Review summary and Safety Consideration:

The analyzed articles suggest that while there is a temporal association between SPIKEVAX administration and the onset of liver injuries classified as AIH, the presence of multiple confounders and the lack of

consistent causal evidence across cases mean that a definitive link remains unestablished. The Marketing Authorization Holder (MAH) considers that the reported AIH cases, although clinically significant, are heavily confounded. These reports do not conclusively establish causality with the administration of SPIKEVAX. From a safety surveillance perspective, no new safety issue of concern was identified in relation to SPIKEVAX inducing AIH.

Review of Citations Related Non Moderna Covid-19 Vaccine in Supplemental

Table-14 of Uzun article:

All the citations included in the Uzun et al article were reviewed and the analysis in included in **Appendix 2.**

Conclusion

Overall, based on the analysis of all the safety data available as of 17 December 2023, the MAH considers that cases including AIH-related events, do not provide sufficient information to establish a causal relationship to the administration of SPIKEVAX. The majority of the cases are heavily confounded. No new safety issue of concern was identified. The available data does not warrant an update change to the label/SmPC and/or the RMPs. The MAH will continue to monitor events for AIH using routine pharmacovigilance surveillance.

Rapporteur assessment comment:

Autoimmune hepatitis
The MAH has upon request provided a cumulative review for autoimmune hepatitis (AIH) for the period 18 December 2020 to 17 December 2023.

Sources of information
The clinical trials safety database was queried, the global safety database was searched, and a specific article was reviewed according to request. Additionally, the MAH evaluated the literature case reports and observational studies related to vaccines from MODERNA presented in the article by Uzun et al.

Clinical trials
Information for AIH/AIH-related cases was presented in a table giving an overview of findings from the three CTs which were previously presented, all with adults, and another seven CTs which were presented according to request, of which five included children or adolescents < 18 years of age, and one included immunocompromised adult solid organ transplant recipients.
In the ten CTs there were in total 6 cases, among these 1 infant, 1 adolescent, and 4 adults of which 2 were organ transplant recipients. These cases were presented in more details in the text, and according to the review none were true cases of AIH, and there were other potential causes for the AIH-suspected events.

Global Safety Database
The GSDB was searched cumulatively for the period 18 December 2020 through 17 December 2023. Search criteria were based on a customized MedDRA query with the PTs "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury".
Cumulatively, through 17 December 2023, a total of 315 cases (326 events) were reported. Of these, as many as 114 were reported with the PT autoimmune hepatitis. The MAH has reported that 211 cases were previously reviewed and presented for PBRER#3, and that the remaining 104 cases were re-

evaluated for this updated review. Of note, the MAH states that there were no new reports of AIH-related terms received after 17-Dec-2023, including valid published literature.

Gender and Age
According to the 4th PSUR, 133 cases (42.2%) involved males, 177 cases (56.2%) involved females, and 5 (1.6%) were of missing gender, and the age range was 0.0-96.0 years, the median being 56.0 years. The MAH has upon request added information regarding infants, children and adolescents. In total four cases with hepatic events were found in the age group < 18 years. Among these, one neonate, two 13-year-olds and one 15-year-old. None of these cases were AIH, and there were other potential causes for the hepatic events.

Dose number and TTO:
The MAH has presented all cases in a table in Appendix 1A of the MAH's response. In the request, it was suggested to use dose number as a proxy measure for dechallenge/rechallenge. In the table there is, however, a column presenting information about dechallenge/rechallenge, but all are listed as "Not Applicable" or "Unknown" and is therefore less information than dose number would be. Dose number has to be searched in the case summary for each case. The TTO is clearly listed.

Cases confirmed as AIH and WHO causality assessment
The MAH sorted all retrieved cases based on the score each case achieved according to the Simplified Classification Guidelines by the International AIH Group. All cases meeting the score for either probable AIH (6 points) or definite AIH (7-8 points) were categorized as "Case of AIH." Cases scoring 1-5 points were categorized as "Unassessable" (i.e., insufficient information to provide a diagnostic classification), and cases scoring 0 points were categorized as "Not a Case of AIH".

The results regarding cases being a case or not a case of AIH have been updated since the presentation in the 4th PSUR. It is now reported that cumulatively, 20 cases (6.3%) were "a case of AIH" according to the guidelines, while 237 cases were categorized as "not a case of AIH". The remaining 58 cases scored between 1-5 points rendering them "unassessable" regarding AIH according to the classification by the International AIH Group.

The cases fulfilling the criteria for being defined a case of AIH were also categorized according to the WHO causality assessment by the MAH. There were 3 cases with "probable AIH", these were all WHO-UMC "possible". There were 17 cases with "definite AIH", of these 2 were WHO-UMC "probable", 11 were "possible", 4 were "unlikely", and 1 "unassessable".

Literature review
Upon request the MAH has made a review of the cases in the paper by Uzun et al, of which 15 cases included patients who had received COVID-19-vaccines from MODERNA of which 9 were AIH, and 6 were not AIH. The cases represent events with a temporal association to vaccination, but have confounding factors.

Conclusion
The MAH has upon request provided an updated review regarding AIH. Results have been updated according to this. The updated number includes the results from clinical trials, from the global safety database regarding cases being defined as "A case of AIH" and "Not a case of AIH", and specifically results regarding cases in 0-17 years of age. Furthermore, the cases from the paper by Uzun et al. have been reviewed as requested.
Overall, the MAH has met the requests regarding the updated review.
Most cases are confounded, but 2 cases were categorized as "definite AIH" and assessed as probably

causally associated to the vaccine (Spikevax). In total, only 20 cases with a high level of diagnostic certainty have been identified (i.e. probable/definite AIH categories). Of these, just 15 were deemed by the MAH to be of "possible" or higher causality. Even if underreporting may be a concern, the total number of well-documented cases is deemed low in light of the enormous exposure (estimated 1 billion doses administered). For perspective, according to UpToDate and based on European studies, the incidence of AIH in the general population is 0.9 to 2 per 100,000 population per year, with a prevalence of 11 to 25 per 100,000 population. I.e. with an exposure with the magnitude of Spikevax, a certain amount of AIH cases with temporal relationship with vaccination will occur – even well-documented cases.
The MAH has concluded that no new safety issue of concern was identified, that available data does not warrant an update to label/SmPC and/or the RMPs, and that the MAH will continue to monitor events for AIH using routine pharmacovigilance surveillance. The Rapporteur agrees to this conclusion.

7.4. Item 4 – Characterisation of risks

MAH response

The myocarditis/pericarditis text was revised in section 4.4 (Warnings and Precautions) of the Company Core Data Sheet (CCDS) v17.0, effective 1 September 2023. That CCDS text now reads as:

Myocarditis and pericarditis

Post-marketing safety data with Moderna COVID-19 Vaccine (original) are relevant to the bivalent Moderna COVID-19 Vaccines because these vaccines are manufactured using the same process.

There is an increased risk for myocarditis and pericarditis following vaccination with Moderna COVID-19 Vaccine. The majority of the cases have been reported in young males, 18 through 24 years of age.

Onset has primarily occurred within 14 days. These events have been observed more often after the second dose compared to the first dose and less often after subsequent doses (see section 4.8).

Available data indicate that most cases are typically mild and individuals tend to recover within a short time following standard treatment and rest. Some cases required intensive care support. Although causality has not been established, fatal events have been very rarely reported. Post-authorisation data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than infectious myocarditis or pericarditis. Information is not yet available about potential long-term sequelae.

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.

The MAH was not planning to revise the EU SmPC as it considered it already in line with the outcome of EMEA/H/C/005791/II/57:

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 (see section 4.8).

Available data indicate that most cases recover. Some cases required intensive care support and fatal cases have been observed.

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.

However, if EMA would prefer that we match the CCDS text verbatim, we can file it in a future variation.

Rapporteur assessment comment:

As noted in the PAR of this procedure, the MAH stated that the product information was updated with the following information regarding myocarditis and pericarditis: "*Post-authorization data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than viral infectious myocarditis and pericarditis*". The Rapporteur noted that this information was not included in the currently available version of the EU SmPC and therefore, requested that the MAH clarified this discrepancy within this procedure.

In its response, the MAH states that section 4.4 (Warnings and Precautions) of its CCDS was updated on 1st September 2023 and the MAH presents the current wording in its CCDS regarding myocarditis/pericarditis (including the sentence regarding "shorter duration and less severe than infectious myocarditis or pericarditis"). The MAH then argues that it was not planning to revise the EU SmPC as it considered it already in line with the outcome of EMEA/H/C/005791/II/57 (it appears that the correct procedure number is EMEA/H/C/005791/II/0057). The MAH then presents the current warning in section 4.4 of the SmPC (which does not include the sentence regarding "shorter duration and less severe than infectious myocarditis or pericarditis"). Finally, the MAH proposes that it can match the CCDS text verbatim in a future variation, if preferred by the EMA.

From the MAH's response it is unclear whether the aspects "shorter duration" and "lower severity" of vaccine-induced myocarditis/pericarditis compared with viral infectious myocarditis/pericarditis and the data supporting this statement have been evaluated in another procedure. However, after investigation, the assessors found out that the issue was evaluated in the 4th PSUSA procedure for Spikevax (EMEA/H/C/PSUSA/00010897/202212). In the UAR of this procedure, the PRAC Rapporteur proposed updates to section 4.4 of the SmPC regarding myocarditis/pericarditis including addition of the following sentences: "*Available data indicate that most cases tend to recover within a short time. Some cases required 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.*" In the final recommendation of the PRAC AR, the first sentence was edited (omitting the part about recovery in short time) and the last sentence about severity was omitted suggesting that the issue was evaluated by the PRAC and inclusion in the SmPC deemed unwarranted.

It appears that the rationale and/or data behind the MAH's CCDS text about "shorter duration" and "lower severity" of vaccine-induced myocarditis/pericarditis compared with viral infectious myocarditis/pericarditis have previously been evaluated by the PRAC, and therefore the Rapporteur considers that no further action regarding this issue is currently warranted. Issue resolved.

However, if the MAH has identified new and significant information regarding duration, severity or other relevant aspects of the clinical course of vaccine-induced myocarditis/pericarditis, which warrant an amendment of the product information and which have not previously been evaluated by EU regulatory authorities, the MAH should provide the relevant data via an appropriate procedure. The same applies if

the MAH identifies such information in the future.

8. Comments from Member States

8.1. MS1

We fully endorse the CHMP/CAT/PRAC Rapp assessment, and have no further comments.

8.2. MS2

We fully endorse the PRAC Rapp assessment, and have no further comments.

Member states' comments: The endorsement received from MS1 and MS2 is appreciated.

SIXTH 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), Elasomeran/davesomeran (SPIKEVAX Bivalent.222 Original/BA.4/5, mRNA-1273.222) and Andusomeran (SPIKEVAX XBB.1.5, mRNA-1273.815, SPIKEVAX 2023-2024 Formula)

ATC CODE: J07BN01 (previously J07BX03)
MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Products	Dates of Worldwide Authorisation	Marketing Authorization Holder
Spikevax (elasomeran and COVID-19 mRNA Vaccine [nucleoside-modified])	06 Jan 2021	Moderna Biotech Spain S.L.
Spikevax bivalent Original/Omicron BA.1 (elasomeran/imelasomeran)	12 Aug 2022	
Spikevax bivalent Original/Omicron BA.4-5 (elasomeran/davesomeran)	31 Aug 2022	
Spikevax XBB.1.5 (andusomeran)	11 Sep 2023	

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 18 Jun 2023 to 17 Dec 2023
DATE OF THIS REPORT:
16 Feb 2024

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EXECUTIVE SUMMARY

This sixth Periodic Safety Update Report (PSUR) (referred to as Periodic Benefit-Risk Evaluation Report [PBRER] throughout the report) 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), SPIKEVAX Bivalent.222 Original/BA.4/5® (elasomeran/davesomeran; mRNA-1273.222) and SPIKEVAX XBB.1.5® (andusomeran; mRNA-1273.815, SPIKEVAX 2023-2024 Formula) was compiled for regulatory authorities in the 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]). Throughout the PBRER, the term "SPIKEVAX NOS" is used to categorize the case reports received by ModernaTx, Inc when insufficient details were reported to determine the exact SPIKEVAX product that was utilized. Also, throughout the PBRER, "marketed Moderna vaccines targeting SARS-CoV-2" is used where appropriate instead of listing all currently approved/authorized mRNA-1273 vaccines (elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of marketed Moderna vaccines targeting SARS-CoV-2 based on the review of cumulative and reporting period safety information, received worldwide, during this PBRER reporting period. The reporting period for this PBRER#6 is 18 Jun 2023 to 17 Dec 2023. Currently, the marketed Moderna vaccines targeting SARS-CoV-2 PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates (EURD). In order to stay aligned with the EURD this 6-monthly PBRER (with data lock point [DLP] 17 Dec 2023) will be the last 6-monthly PBRER to be submitted, then the PBRER frequency will change to annual. The first yearly PBRER to be submitted will be PBRER #7 (DLP of 17 Dec 2024). The first three PBRERs (PBRER #1, PBRER #2 and PBRER #3) that were previously submitted included the single International Nonproprietary Name (INN) elasomeran. Beginning with PBRER#4, bivalent vaccines elasomeran/imelasomeran, and elasomeran/davesomeran were included; with this PBRER#6, andusomeran is also included.

Marketed Moderna vaccines targeting SARS-CoV-2 belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has Anatomical Therapeutic Chemical (ATC) code: J07BN01 (previously 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) (v18.0, dated 12 Oct 2023), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARSCoV2 in individuals six 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. Andusomeran is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

Elasomeran is Single-stranded, 5'-capped messenger Ribonucleic acid (RNA) (mRNA) produced using a cell-free in vitro transcription from the corresponding Deoxyribonucleic acid templates, encoding the full-length Spike protein of SARS-CoV-2, modified to introduce two proline residues to stabilize the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: heptadecan-9-yl 8((2hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and one monomethoxypolyethyleneglycol 2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG-2000DMG). Imelasomeran contains mRNA, 5'-capped, encoding a full length, codon optimized prefusion stabilized conformation variant (K983P and V984P) of the SARSCoV-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 Deoxyribonucleic acid templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). The S-protein of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical. Andusomeran 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 XBB.1.5).

During this reporting period, ModernaTx, Inc. was in Pharmacovigilance (PV) agreement with the following co-sponsors: 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), and University of Southampton. The agreements began on 21 Feb 2020 (Sanofi and DMID/NIAID), May 2020 (NCI), 15 Mar 2022 (UCLA), 14 Apr 2022 (SAMRC), 02 Dec 2021 (MSD), and 08 Feb 2022 (University of Southampton). The entities agreed to share

all the relevant safety data from trials 20-0003, 21-0002, 210012, 22-0004 (DMID/NIAID sponsored), 000115 (NCI Sponsored), COVID-19 Version 2.0 (UCLA sponsored), mRNA-1273-P508 (SAMRC sponsored), Vl 10-911-00 and V503-076-00 (MSD sponsored), and RHM MED1781 (University of Southampton 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 is formulated as a dispersion for injection to be supplied in single dose vial, multidose vial and single use pre-filled syringe. Elasomeran/davesomeran is formulated as a dispersion for injection to be supplied in multidose vial. Andusomeran is formulated as a dispersion for injection to be supplied in single dose vial, multidose vial and single use pre-filled syringe.

- Elasomeran 0.20 mg/mL dispersion for injection

Elasomeran is supplied as a multidose vial that contains ten 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

Elasomeran is supplied as a multidose vial that contains five doses of 0.5 mL each or a maximum of ten 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 LNPs).

- Elasomeran 50 ug dispersion for injection in pre-filled syringe

It has also been supplied as single use pre-filled syringe that contains one 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 in pre-filled syringe

Elasomeran/imelasomeran is supplied as a single dose vial which contains one 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 one 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).

- Andusomeran 0.1 mg/mL dispersion for injection

Andusomeran is supplied as a multi-dose 2.5 mL vial (blue flip-off cap). It contains 5 doses of 0.5 mL each or 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles) or one dose (0.25 mL) contains 25 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Andusomeran 50 μg dispersion for injection and in pre-filled syringe

Andusomeran is supplied as a single-dose 0.5 mL vial (blue flip-off cap) containing 1 dose of 0.5 mL for single use only. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). It is also supplied pre-filled syringe containing 1 dose of 0.5 mL for single use only. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Posology for primary series, a third dose in severely immunocompromised and booster doses for elasomeran and elasomeran/imelasomeran is provided in below Table 1-1 and posology for primary series and for immunocompromised doses for elasomeran/davesomeran and andusomeran is provided in Table 1-2 and Table 1-3 below.

Table 1-1 Dosages and description for elasomeran and elasomeran/imelasomeran

Strength	Vaccination Type	Age and Dose	Recommendations
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	It is recommended to administer the second dose 28 days after the first dose.

Strength	Vaccination Type	Age and Dose	Recommendations
		(0.5 mL each).	
		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 a 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	

Strength	Vaccination Type	Age and Dose	Recommendations
		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. *Children 6 years through 11 years of age* One dose (0.25 mL each, containing 25 ug mRNA)*	Moderna COVID-19 Vaccine may be used to boost individuals 6 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 imelasomeran.	

*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.

Table 1-2 Elasomeran/davesomeran and andusomeran posology

Age	Dose	Additional Recommendations
Children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL each, given intramuscularly*	Administer the second dose, 28 days after the first dose. If a child has received one prior dose of elasomeran, one dose of elasomeran/davesomeran should be administered to complete the two-dose series. If a child has received one prior dose of any elasomeran vaccine, one dose of andusomeran should be administered to complete the two-dose series.
Children 6 months through 4 years of age, with prior vaccination	One dose of 0.25 mL, given intramuscularly*	Elasomeran/davesomeran or andusomeran should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.
Children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly*	
Individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	
Individuals 65 years of age and older	One dose of 0.5 mL, given intramuscularly	One additional dose may be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

*Do not use the single-dose vial or pre-filled syringe to deliver a partial volume of 0.25 mL.

Table 1-3 Elasomeran/davesomeran and andusomeran posology for immunocompromised individuals

Age	Dose	Additional Recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly*	An additional dose in severely immunocompromised may be given at least 28 days after the second dose.
Immunocompromised children 6 months through 4 years of age, with prior vaccination	One dose of 0.25 mL, given intramuscularly*	Additional age-appropriate dose(s) may be administered in severely immunocompromised at least 2 months following the most recent dose of a COVID-19 vaccine at the discretion of the healthcare provider, taking into
Immunocompromised children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly*	

Age	Dose	Additional Recommendations
Immunocompromised individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	consideration the individual's clinical circumstances.

*Do not use the single-dose vial or pre-filled syringe to deliver a partial volume of 0.25 mL.

Marketed Moderna vaccines targeting SARS-CoV-2 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.

During the reporting period, ModernaTx, Inc. sponsored clinical trial mRNA-1273-P301 was completed and there were a total of 16 ModernaTx, Inc. sponsored clinical trials (CTs) ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P206, mRNA-1273-P304, mRNA-1273-P305, mRNA-1273-P306, mRNA-1283-P101, mRNA-1283-P201, mRNA-1283-P301, mRNA-CRID-001, mRNA-1083-P101, mRNA-1083-P301, mRNA-1273-1073-P101, mRNA-1230-P101, and mRNA-1345-P302).

Cumulatively, 59,907 subjects have been exposed in CTs 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, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 (including its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administered with mRNA-1010 or co-administered with mRNA-1345, or co-administered active licensed sFLU vaccines (Fluzone High dose [HD] or Fluarix) in the mRNA-1083 clinical development program sponsored by ModernaTx, Inc. The total count of 59,907 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).

During the reporting period, 6,203 subjects were estimated to be exposed to either mRNA-1273.214, mRNA-1273.222, or mRNA-1273.815 co-administered active licensed sFLU vaccines (Fluzone HD or Fluarix) in the mRNA-1083 clinical development program sponsored by ModernaTx, Inc.

As of DLP, 14,848 subjects were exposed to mRNA-1273 and its variants from ongoing CTs sponsored by licensing partners. Out of 14,848 subjects, 1,160 subjects were exposed to mRNA-1273 in CTs sponsored by DMID, 19 subjects from a CT sponsored by NCI, 19 subjects from a CT sponsored by UCLA, 12,340 subjects from a CT sponsored by SAMRC, 1,005 subjects from CTs sponsored by MSD, and 305 subjects from a CT sponsored by University of Southampton. Cumulatively, 1,573 subjects were enrolled in ongoing investigator-initiated trials.

The International Birth date of elasomeran is 18 Dec 2020. The product is currently authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelasomeran 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 the US Food & Drug Administration (FDA) on 31 Aug 2022. Andusomeran was granted authorization for individuals >18 years of age and EUA status for individuals 6 months to 11 years of age by US FDA on 11 Sep 2023.

Elasomeran and its variants are 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) and andusomeran continue to expand.

Cumulatively, at the end of the reporting period, 17 Dec 2023, a total of 1,776,284,733 doses of marketed Moderna vaccines targeting SARS-CoV-2 were delivered to 92 countries and an estimated total of 1,043,567,281 doses of Moderna vaccines targeting SARS-CoV-2 had been administered. Out of 1,776,284,733 doses, a total of 129,007,543 booster doses of elasomeran/imelasomeran had been delivered to 42 countries and an estimated total of 70,954,149 doses had been administered. A total of 245,792,144 booster doses of elasomeran/davesomeran had been delivered to 43 countries and an estimated total of 135,185,679 doses had been administered and 1,187,637,396 doses of original elasomeran had been delivered to 61 countries and an estimated total of 653,200,568 doses had been administered. As of 17 Dec 2023, 83,301,090 doses of andusomeran had been delivered to 19 countries and an estimated total of 45,815,600 doses were administered.

In this PBRER reporting period (18 Jun 2023 to 17 Dec 2023), a total of 111,594,410 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered and an estimated total of 65,561,716 doses had been administered. North America, Europe, and Latin America accounted for approximately 91% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed. Given that elasomeran distribution was discontinued worldwide after Jun 2023, no new doses were distributed during this PBRER reporting period.

The cumulative evidence on the safety and efficacy for marketed Moderna vaccines targeting SARS-CoV-2 fully supports the indication as described in the CCDS, authorized as a suspension for injection for active immunizations to prevent COVID-19 caused by SARS-CoV-2 in individuals six 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.

During the reporting period, the following safety-related actions were taken:

- Since Oct 2023, reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age, were received from various sources, including spontaneous reports, quality complaints and HCP inquiries. This issue was restricted to the US and is limited to the US EUA of ModernaTx, Inc COVID-19 vaccine (andusomeran) for individuals 6 months through 11 years of age. The pediatric SDV contains notably more than 0.25 mL of vaccine, which has led to provider confusion or administration errors, including overdose. Several risk minimization activities were conducted, including the creation and distribution of a Dear Healthcare Provider Letter (DHCP) for clarification on the dosage and administration instructions for the US pediatric presentation of the ModernaTx, Inc COVID-19 Vaccine (2023-2024 Formula)/andusomeran. The US Fact Sheet for Providers and for Consumers were updated providing correct dosage administration of the vaccine for the pediatric age group, specifically within the context of the US presentation. The US FDA and CDC distributed a notification to health care providers advising them to ensure appropriate dosing was provided to pediatric patients. No patient safety or quality issue were found to be associated with this incident. This medication error issue does not impact andusomeran approved in other countries.

The Reference Safety Information (RSI) for marketed Moderna vaccines targeting SARS-CoV-2 in effect at the end of the reporting period (DLP 17 Dec 2023) and used for this report is the CCDS v18.0 (dated 12 Oct 2023). During this reporting period, the RSI (CCDS) was updated from v16.0 (dated 03 Jan 2023) to CCDS v17.0 (dated 01 Sep 2023) to include updates to anaphylaxis and urticaria frequencies per latest data, addition of andusomeran (mRNA-1273.815) safety data per P205, Part J addition of P203 Part 3 single dose data (12 to 17 years), and addition of solid organ transplant safety data per P304. Further CCDS v17.0 was updated to v18.0 (dated 12 Oct 2023) to add co-administration data for flu vaccine and herpes zoster (shingles) vaccine

and Section 4.4 Warnings and precautions was updated to add information related to myocarditis and pericarditis, as well as to update information related to immunocompromised.

During the reporting period, six signals were closed by the ModernaTx, Inc. Of these, five closed signals were refuted by the MAH [Immunoglobulin A-nephropathy flare-up, Sensorineural hearing loss, Breast swelling, Mastitis, and Postmenopausal haemorrhage]. Additionally, one signal restricted to the US and limited to the US EUA of ModernaTx, Inc COVID-19 vaccine (andusomeran) was confirmed as an important potential risk regarding "Overdose in children in the context of overfill of the SDV indicated for individuals 6 months through 11 years of age in the US".

The important identified and potential risks valid at the end of the PBRER/PSUR reporting period and applicable for the PBRER/PSUR are as follow:

Important identified risks:

- Anaphylaxis
- Myocarditis
- Pericarditis

Important potential risk:

- IgA Nephropathy.

Examination of the data contained within this report supports the conclusion that the overall benefit-risk balance for marketed Moderna vaccines targeting SARS-CoV-2 continues to be positive and remains unchanged.

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LIST OF ABBREVIATIONS

Acronym	Definition
ACOG	American College of Obstetricians and Gynecologists
ADR	Adverse Drug Reaction
AE	Adverse Event
AEMS	Adverse Event Management System
AESI	Adverse Events of Special Interest
AHE	Adverse Health Event
AI/ID	Autoimmune and Inflammatory Disorder
AIH	Autoimmune Hepatitis
ANCOVA	Analysis of Covariance
ANSM	Agence nationale de sécurité du médicament et des produits de santé
AntiENA	Anti-Extractable Nuclear Antigens
AR	Adverse Reactions
ARDS	Acute Respiratory Distress Syndrome
ARTG	Australian Register of Therapeutic Goods
ATC	Anatomical Therapeutic Chemical
BCT	Breast-Conserving Therapy
BD	Booster Dose
BLA	Biologics License Application
BPM	Beats Per Minute
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control and Prevention
CEAC	Cardiovascular EndpointsAdjudication Committee
CFS	Chronic Fatigue Syndrome
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMQ	Certified in Medical Quality
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
COVAIL	COVID-19 Variant Immunologic Landscape Trial

Acronym	Definition
COVE	Corona Virus Efficacy
COVID-19	Coronavirus Disease-19
CPC	Common primary care
CSR	Clinical Study Report
CT	Clinical Trial
CU	Chronic Urticaria
D&C	Dilation and Curettage
DART	Developmental and Reproductive Toxicity
DCM	Dilated Cardiomyopathy
DHCP	Dear Healthcare Provider
DLP	Data Lock Point
DM	Diabetes Mellitus
DMID	Division of Microbiology and Infectious Diseases
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
DSUR	Development Safety Update Reports
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr Virus
ECDC	European Center for Disease Prevention and Control
ECG	Electrocardiogram
ED	Emergency Department
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	European Medicine Evaluation Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
ERR	Event Rate Ratio
ESRD	End-Stage Renal Disease
EU	European Union
EUA	Emergency Use Authorization
EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
EURD	European Union Reference Date
EVDAS	EudraVigilance Data Analysis System

Acronym	Definition
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
FUQ	Follow-up Questionnaire
FVFP	First Visit First Patient
GA	Gestational Age
GBS	Guillain-Barré Syndrome
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
HA	Health Authority
HBV	Hepatitis B Virus
HCP	Healthcare Care Professional
HCW	Health Care Workers
HD	High Dose
HHS	Health and Human Services
HHV	Human Herpesvirus
HI	Hemagglutination inhibition
HIRD	HealthCare Integrated Research Database
HIV	Human Immunodeficiency Virus
HL	Hearing Loss
HLA	Human Leukocyte Antigen
HLH	Hemophagocytic Lymphohistiocytosis
HLT	High Level Term
HMB	Heavy Menstrual Bleeding
HNL	Histiocytic Necrotizing Lymphadenitis
HPV	Human Papillomavirus
HR	Hazard Ratio

Acronym	Definition
HRQoL	Health-Related Quality of Life
HRT	Hormone Replacement Therapy
IAIHG	International Autoimmune Hepatitis Group
IBD	International Birth Date
ICD	International Classification of Diseases
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
IgAN	Immunoglobulin A Nephropathy
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
INN	International Nonproprietary Name
IP	Investigational product
IPTW	Inverse Probability Treatment Weights
IR	Incidence Rate
IRR	Incidence Rate Ratio
ISSNHL	Idiopathic Sudden Sensorineural Hearing Loss
IST	Internal Safety Team
IUD	Intrauterine Device
JMDC	Japan Medical Data Center
KSA	Kingdom of Saudi Arabia
LE	Lupus Erythematosus
LGE	Late Gadolinium Enhancement
LH	Luteinizing Hormone
LKM	Liver Kidney Microsomal
LLOQ	Lower Limit of Quantification

Acronym	Definition
LMIC	Low to Mid Income Countries
LNP	Lipid Nanoparticle
LP	Lumbar Puncture
LS	Lichen Sclerosus
LV	Left Ventricular
MAH	Marketing Authorization Holder
MC	Medically Confirmed
MCAS	Mast Cell Activation Syndrome
ME	Medication error
MedDRA	Medical Dictionary for Regulatory Activities
MedHX	Medical History
MERS	Middle East Respiratory Syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MIS-C	Multisystem Inflammatory Syndrome in Children
MM	Multiple Myeloma
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MSD	Merck, Sharp and Dohme
MSSR	Monthly Safety Summary Report
NCI	National Cancer Institute
NHIS	National Health Insurance Services
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NIS	Non-Interventional Study
NK	Natural Killer
NLIM	Non-Puerperal Infectious Mastitis
NOC	Notice of Compliance
NOS	Not Otherwise Specified

Acronym	Definition
NP	Nasopharyngeal
NSAID	Nonsteroidal Anti-inflammatory Drug
O/E	Observed Expected
OR	Odds Ratio
PAN	Polyarteritis Nodosa
PASC	Post-Acute Sequelae of SARS-CoV-2 Infection
PASS	Post-Authorization Safety Study
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
PHEIC	Public Health Emergency of International Concern
PHS	Public Health Service
PI	Product Information
PIL	Patient Information Leaflet
PL	Product Leaflet
PMB	Postmenopausal Bleeding
PMDA	Pharmaceutical and Medical Devices Agency
PMH	Postmenopausal Hemorrhage
PMS	Post-Marketing Surveillance
POTS	Postural orthostatic tachycardia syndrome
PPIs	Proton-Pump Inhibitor
PQC	Product Quality Compliance
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSF	Product Signaling Strategy Form
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
PsVNA	Pseudo virion Neutralization Assay
PT	Preferred Term

Acronym	Definition
PV	Pemphigus Vulgaris
PY	Person Year
QR	Quick Response
RA	Regulatory Authority
RCT	Randomized Clinical Trial
RF	Renal Failure
RLU	Relative Luminescence Unit
RMP	Risk Management Plan
RMST	Restricted Mean Survival Time
RNA	Ribonucleic Acid
ROR	Rate of Return
RP	Reporting Period
RR	Risk Ratio
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
RTQ	Response to Query
rVE	Relative Vaccine Effectiveness
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
SC	Subcutaneous
SCQM	Supply Chain Quality Management
SCRI	Self-controlled risk interval
SD	Standard Deviation
SDV	Single-Dose Vial
SER	Signal Evaluation Report
SLA	Soluble Liver Antigen
SLE	Systemic Lupus Erythematosus
SMA	Smooth Muscle Antibodies

Acronym	Definition
SmPC	Summary of Product Characteristics
SMQ	Standardizes MedDRA Query
SMT	Signal Management Team
SNHL	Sensorineural Hearing Loss
SOC	System Organ Class
SOCV	Single Organ Cutaneous Vasculitis
SOT	Solid Organ Transplant
SRMT	Safety and Risk Management Team
SRR	Sero Response Rate
SSA	Sequence Symmetry Analysis
SSNHL	Sudden Sensorineural Hearing Loss
SSR	Summary Safety Reports
SSRI	Selective Serotonin Reuptake Inhibitors
TEAE	Treatment-Emergent Adverse Event
TGA	Therapeutic Goods Administration
TTO	Time to Onset
UCLA	University of California, Los Angeles
UK	United Kingdom
ULOQ	Upper Limit of Quantification
UMC	Uppsala Monitoring Center
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
VOC	Variants of Concern
VOI	Variant of Interest
WHO	World Health Organization
WHO-UMC	World Health Organization-Uppsala Monitoring Center

1. INTRODUCTION

This sixth Periodic Safety Update Report (PSUR) (referred to as Periodic Benefit-Risk Evaluation Report [PBRER] throughout the report) 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), SPIKEVAX Bivalent.222 Original/BA.4/5® (elasomeran/davesomeran; mRNA-1273.222) and SPIKEVAX XBB.1.5® (andusomeran; mRNA-1273.815, SPIKEVAX 2023-2024 Formula) was compiled for regulatory authorities in the 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]). Throughout the PBRER, the term "SPIKEVAX NOS" is used to categorize the case reports received by ModernaTx, Inc when insufficient details were reported to determine the exact SPIKEVAX product that was utilized. Also, throughout the PBRER, "Marketed Moderna vaccines targeting SARS-CoV-2" is used where appropriate instead of listing all currently approved/authorized mRNA-1273 vaccines (elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of marketed Moderna vaccines targeting SARS-CoV-2 based on the review of cumulative and reporting period safety information, received worldwide, during this PBRER reporting period. The reporting period for this PBRER#6 is 18 Jun 2023 to 17 Dec 2023. Currently, the marketed Moderna vaccines targeting SARS-CoV-2 PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates (EURD). In order to stay aligned with the EURD this 6-monthly PBRER (with data lock point [DLP] 17 Dec 2023) will be the last 6-monthly PBRER to be submitted, then the PBRER frequency will change to annual. The first yearly PBRER to be submitted will be PBRER #7 (DLP of 17 Dec 2024). The first three PBRERs (PBRER #1, PBRER #2 and PBRER #3) that were previously submitted included the single International Nonproprietary Name (INN) elasomeran. Beginning with PBRER#4, bivalent vaccines elasomeran/imelasomeran, and elasomeran/davesomeran were included; with this PBRER#6, andusomeran is also included.

The international birth date (IBD) of elasomeran is 18 Dec 2020, the date of the first marketing approval in any country. The product is currently authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome (SARS)-CoV-2. First authorization approval for elasomeran/imelasomeran was granted

by the Medicines and Healthcare products Regulatory Agency (MHRA) for the United Kingdom (UK) on 12 Aug 2022, elasomeran/davesomeran was granted Emergency Use Authorization (EUA) status by US Food and Drug Administration (US FDA) on 31 Aug 2022 and andusomeran was granted authorization for individuals >18 years of age and EUA status for individuals 6 months to 11 years of age by US FDA on 11 Sep 2023.

Marketed Moderna vaccines targeting SARS-CoV-2 belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has Anatomical Therapeutic Chemical (ATC) code: J07BN01 (previously 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) (v18.0, dated 12 Oct 2023), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARSCoV2 in individuals six 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 6 years of age and older and 6 months of age and older respectively, who have previously received at least a primary vaccination course against COVID-19. Andusomeran is indicated for active immunization to prevent COVID-19 caused by SARS-CoV2 in individuals 6 months of age and older.

Elasomeran is Single-stranded, 5'-capped messenger Ribonucleic acid (RNA) (mRNA) produced using a cell-free in vitro transcription from the corresponding Deoxyribonucleic acid templates, encoding the full-length Spike protein of SARSCoV2, modified to introduce two proline residues to stabilize the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: heptadecane-9-yl-8-(2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and one mono-methoxy-polyethyleneglycol 2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG-2000DMG). Imelasomeran contains mRNA, 5'-capped, encoding a full length, codon optimized prefusion stabilized conformation variant (K983P and V984P) of the SARSCoV-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 Deoxyribonucleic acid templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). The S-protein of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical. Andusomeran 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 XBB.1.5).

During this reporting period, ModernaTx, Inc. was in Pharmacovigilance (PV) agreement with the following co-sponsors: 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), and University of Southampton. The agreements began on 21 Feb 2020 (Sanofi and DMID/NIAID), May 2020 (NCI), 15 Mar 2022 (UCLA), 14 Apr 2022 (SAMRC), 02 Dec 2021 (MSD), and 08 Feb 2022 (University of Southampton). The entities agreed to share all the relevant safety data from trials 20-0003, 21-0002, 210012, 22-0004 (DMID/NIAID sponsored), 000115 (NCI Sponsored), COVID-19 Version 2.0 (UCLA sponsored), mRNA-1273-P508 (SAMRC sponsored), Vl 10-911-00 and V503-076-00 (MSD sponsored), and RHM MED1781 (University of Southampton sponsored).

mRNA-1273.815 contains CX-038839, the monovalent mRNA that encodes for the S-2P of the SARS-CoV-2 Omicron subvariants XBB.1.5/XBB.1.9.1. mRNA-1273.231 contains CX-034476, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 Omicron subvariants BA.4/BA.5, and CX-038839, the mRNA that encodes for the S-2P of the SARS-CoV-2 subvariants XBB.1.5/XBB.1.9.1. The formulated mRNA in mRNA-1273.231 are mixed in a 1:1 ratio. Both mRNA-1273.815 and mRNA-1273.231 consist of mRNA formulated in a mixture of four lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG-2000-DMG.

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 is formulated as a dispersion for injection to be supplied in single dose vial, multidose vial and single use pre-filled syringe. Elasomeran/davesomeran is formulated as a dispersion for injection to be supplied in multidose vial. Andusomeran is formulated as a dispersion for injection to be supplied in SDV, multidose vial and single use pre-filled syringe.

- Elasomeran 0.20 mg/mL dispersion for injection

Elasomeran is supplied as a multidose vial that contains ten 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

Elasomeran is supplied as a multidose vial that contains five doses of 0.5 mL each or a maximum of ten 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 LNPs).

- Elasomeran 50 ug dispersion for injection in pre-filled syringe

It has also been supplied as single use pre-filled syringe that contains one 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 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 in pre-filled syringe

Elasomeran/imelasomeran is supplied as a single-dose 0.5 mL vial (blue flip-off cap). One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of imelasomeran, 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, 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 or 10 doses of 0.25 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) or one dose (0.25 mL) contains 12.5 ug of elasomeran and 12.5 ug of davesomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Elasomeran/davesomeran 25 µg/25 µg dispersion for injection and in pre-filled syringe

Elasomeran/davesomeran is supplied as a single-dose 0.5 mL vial (blue flip-off cap). One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of davesomeran, 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, for single use only. One dose (0.5 mL) contains 25 ug of elasomeran and 25 ug of davesomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Andusomeran 0.1 mg/mL dispersion for injection

Andusomeran is supplied as a multi-dose 2.5 mL vial (blue flip-off cap). It contains 5 doses of 0.5 mL each or 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles) or one dose (0.25 mL) contains 25 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Andusomeran (50 µg/50 µg)/mL dispersion for injection and pre-filled syringe

Andusomeran is supplied as a single-dose 0.5 mL vial (blue flip-off cap) containing 1 dose of 0.5 mL for single use only. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). It is also supplied pre-filled syringe containing 1 dose of 0.5 mL for single use only. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Posology for primary series, a third dose in severely immunocompromised and booster doses for elasomeran and elasomeran/imelasomeran is provided in below Table 1-1, posology for primary series and for immunocompromised doses for elasomeran/davesomeran and andusomeran is provided in Table 1-2 and Table 1-3.

Table 1-1 Dosages and description for elasomeran and elasomeran/imelasomeran

Strength	Vaccination Type	Age and Dose	Recommendations
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	

Strength	Vaccination Type	Age and Dose	Recommendations
		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 a 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.

Strength	Vaccination Type	Age and Dose	Recommendations
		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. *Children 6 years through 11 years of age* One dose (0.25 mL each, containing 25 ug mRNA)*	Moderna COVID-19 Vaccine may be used to boost individuals 6 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 imelasomeran.	

*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.

Table 1-2 Elasomeran/davesomeran and Andusomeran posology

Age	Dose	Additional Recommendations
Children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL each, given intramuscularly*	Administer the second dose, 28 days after the first dose. If a child has received one prior dose of elasomeran, one dose of elasomeran/davesomeran should be administered to complete the two-dose series. If a child has received one prior dose of any elasomeran vaccine, one dose of andusomeran

Age	Dose	Additional Recommendations
		should be administered to complete the two-dose series.
Children 6 months through 4 years of age, with prior vaccination	One dose of 0.25 mL, given intramuscularly*	Elasomeran/davesomeran or andusomeran should be administered at least 3 months after the most recent dose of a COVID-19 vaccine.
Children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly*	
Individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	
Individuals 65 years of age and older	One dose of 0.5 mL, given intramuscularly	One additional dose may be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

*Do not use the SDV or pre-filled syringe to deliver a partial volume of 0.25 mL.

Table 1-3 Elasomeran/davesomeran and Andusomeran posology for immunocompromised individuals

Age	Dose	Additional Recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly*	An additional dose in severely immunocompromised may be given at least 28 days after the second dose.
Immunocompromised children 6 months through 4 years of age, with prior vaccination	One dose of 0.25 mL, given intramuscularly*	Additional age-appropriate dose(s) may be administered in severely immunocompromised at least 2 months following the most recent dose of a COVID-19 vaccine at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances.
Immunocompromised children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly*	
Immunocompromised individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	

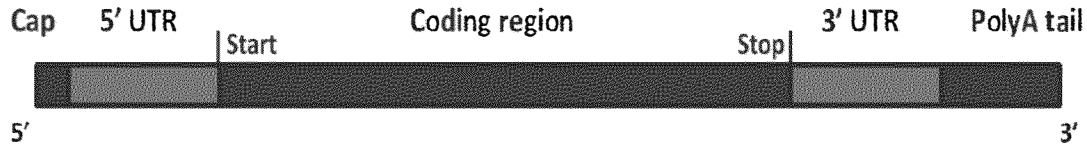
*Do not use the SDV or pre-filled syringe to deliver a partial volume of 0.25 mL.

Moderna vaccines targeting SARS-CoV-2 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.

Marketed Moderna vaccines targeting SARS-CoV-2, contain mRNA encapsulated in LNPs. The mRNA encodes for the full length SARS-CoV-2 spike protein modified with two proline substitutions within the heptad repeat one 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). Andusomeran contains nucleoside-modified messenger RNA (mRNA) encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5. 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.

Modified, variant-matched bivalent COVID-19 mRNA vaccine were developed containing 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 [BA.1], and elasomeran/davesomeran [BA.4-5]), each encapsulated into individual LNPs, and co-formulated into a single drug product (elasomeran 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. A modified variant-monovalent COVID-19 mRNA vaccine was developed encoding the pre-fusion stabilized Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5 (andusomeran). The nucleoside-modified mRNA in these vaccines, is formulated in lipid particles, which enable delivery of the nucleoside-modified mRNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits an immune response to the S antigen, which protects against COVID-19.

Below are the target variants for the various mRNA-1273 vaccines used in the clinical development program (See Table 1-4).

Table 1-4 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, BA.4/5
mRNA-1273.529	Omicron BA.1
mRNA-1273.815	Omicron XBB.1.5
mRNA-1273.231	Bivalent: 1:1 ratio of prototype and omicron XBB.1.5 (0.815)

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 Moderna vaccines targeting SARS-CoV-2 (current v18 dated 12 Oct 2023) in Appendix 1.

2. WORLDWIDE MARKETING APPROVAL STATUS

The IBD of elasomeran is 18 Dec 2020. Till DLP, marketed Moderna vaccines targeting SARS-CoV-2 are authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelasomeran was granted by the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by US FDA on 31 Aug 2022. Andusomeran was granted authorization for individuals >18 years of age and EUA status for individuals 6 months to 11 years of age by US FDA on 11 Sep 2023.

Marketed Moderna vaccines targeting SARS-CoV are 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 three bivalent vaccines (elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran) continue to expand.

Cumulative information on marketing authorizations in all countries and approval dates are provided in Appendix 2.

Table 2-1 Worldwide Marketing Authorizations

List of Authorizations	Link to Table
Use in adults aged 18 years and older (primary series)	Table 20-1
Use in adolescents aged 12 to < 18 years (primary series),	Table 20-2
Use in for age 6 to <12-year-old pediatrics indication (primary series)	Table 20-3
Use in 6 months to < 6-year-old indication (pediatrics)	Table 20-4
Use as a booster indication in adults (50 ug)	Table 20-5
Use as a booster indication in adolescents (50 ug)	Table 20-6
Third dose in immunocompromised patients	Table 20-7
Elasomeran/imelasomeran booster indication for adults aged 18 years and older	Table 20-8
Elasomeran/imelasomeran booster indication for adolescents aged 12 to <18 years	Table 20-9
Elasomeran/imelasomeran booster indication for the 6 years to <12-year-old (pediatrics)	Table 20-10
Elasomeran/davesomeran Primary Series Adults 18+	Table 20-11

List of Authorizations	Link to Table
Elasomeran/davesomeran Primary Series for use in adolescents aged 12 to <18 years of age	Table 20-12
Elasomeran/davesomeran Primary Series for the 6 years to <12-year-old (pediatrics)	Table 20-13
Elasomeran/davesomeran Primary Series for the 6 months to <6-year-old	Table 20-14
Elasomeran/davesomeran Booster Adults 18+	Table 20-15
Elasomeran/davesomeran Booster Adults 18+ Booster 12 to <18-Years of Age (Adolescents)	Table 20-16
Elasomeran/davesomeran Booster 6 to < 12-Year-Old Indication (Pediatrics)	Table 20-17
Elasomeran/davesomeran Booster Indication 6 months to < 6-Year-Old	Table 20-18
Andusomeran Primary Series Adults 18+ Years	Table 20-19
Andusomeran Primary Series 12 to < 18 Years of Age (Adolescents)	Table 20-20
Andusomeran Primary Series 5 to < 11 Years of Age (Adolescents)	Table 20-21
Andusomeran Primary Series 6 month to < 4-Year-Old (Pediatrics)	Table 20-22
Andusomeran Single dose in Adults 18+ Years	Table 20-23
Andusomeran Single dose in patients 12 to < 18 Years of Age (Adolescents)	Table 20-24
Andusomeran Single dose in patients 5 to < 11-Year-Old Indication (Pediatrics)	Table 20-25
Andusomeran Third dose in immunocompromised patients 5 to < 11-Year-Old Indication (Pediatrics)	Table 20-26
Andusomeran Third dose in immunocompromised patients 6 month to < 4-Year-Old (Pediatrics)	Table 20-27
Andusomeran Booster Adults 18+ Years	Table 20-28
Andusomeran Booster 12 to < 18 Years of Age (Adolescents)	Table 20-29
Andusomeran Booster 5 to < 11-Year-Old Indication (Pediatrics)	Table 20-30
Andusomeran Booster 6 month to < 4-Year-Old (Pediatrics)	Table 20-31

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting period, the following safety-related actions were taken:

- Since Oct 2023, reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age, were received from various sources, including spontaneous reports, quality complaints and HCP inquiries. This issue was

restricted to the US and is limited to the US EUA of Moderna COVID-19 vaccine (andusomeran) for individuals 6 months through 11 years of age. The pediatric SDV contains notably more than 0.25 mL of vaccine, which has led to provider confusion or administration errors, including overdose. Several risk minimization activities were conducted, including the creation and distribution of a Dear Healthcare Provider Letter (DHCP) for clarification on the dosage and administration instructions for the US pediatric presentation of the Moderna COVID-19 vaccine (2023-2024 Formula)/andusomeran. The US Fact Sheet for Providers and for Consumers were updated providing correct dosage administration of the vaccine for the pediatric age group, specifically within the context of the US presentation. The US FDA and CDC distributed a notification to health care providers advising them to ensure appropriate dosing was provided to pediatric patients. No patient safety or quality issue were found to be associated with this incident. This medication error issue does not impact andusomeran approved in other countries.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The Reference Safety Information (RSI) for marketed Moderna vaccines targeting SARS-CoV-2 in effect at the end of the reporting period (DLP 17 Dec 2023) and used for this report is the CCDS v18.0 (dated 12 Oct 2023). 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.

During this reporting period, the RSI (CCDS) was updated from v16.0 (dated 03 Jan 2023) to v17.0 (dated 11 Sep 2023) and further from v17.0 (dated 11 Sep 2023) to v18.0 (dated 12 Oct 2023). 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
17.0	11 Sep 2023	**Section 4.1,** Updates to most recent age expansions for imelasomeran and davesomeran plus new andusomeran variant. **Section 4.2**: Updates to Posology per most recent approvals plus andusomeran variant, including simplified schedule and immunocompromised table. **Section 4.4**, Updated myocarditis, and immunocompromised text per Pharmacovigilance recommendations. **Section 4.8**, Updates to anaphylaxis and urticaria frequencies per latest data, Addition of andusomeran safety data per P205, Part J Addition of P203 Part 3 single dose data (12 to 17 years), Addition of solid organ transplant safety data per P304. **Section 5.1,** Updates to Mechanism of action for andusomeran, Addition of P901 RWE data, Addition of P203 Part 3 single dose data (12 to 17 years), Addition of andusomeran data per P205, Part J, Addition of GRADE Meta-analysis data.
18.0	12 Oct 2023	**Section 4.4**, Warnings and precautions, to update information related to myocarditis and pericarditis, as well as to update information related to immunocompromised. Addition of co-administration data for flu and herpes zoster (shingles) (**Sections 4.5, 4.8 and 5.1**). Clarification of text in **Section 6** per Tech Dev.

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative Subject Exposure in Clinical Trials

Cumulatively, 59,907 subjects have been exposed in CTs 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, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 (including its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administered with mRNA-1010 or co-administered with mRNA-1345, or co-administered active licensed sFLU vaccines (Fluzone HD or Fluarix) in the mRNA-1083 clinical development program sponsored by ModernaTx, Inc. The total count of 59,907 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 clinical trials (CTs) and the enrolment/randomization schemes for ongoing and blinded trials is provided in Table 5-1. Further details on cumulative subject exposure categorized by age, gender,

racial group and ethnicity are 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[a]
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	20[a]
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	mRNA-1273.222 50 ug	388[a]
mRNA-1273-P203	mRNA-1273 Booster	155[a]
mRNA-1273-P203	Primary series+mRNA-1273 Booster	1,427
mRNA-1273-P204	Placebo	883[a]
mRNA-1273-P204	mRNA-1273	11,032[a]
mRNA-1273-P204	mRNA-1273 10 ug Booster	212
mRNA-1273-P204	mRNA-1273 25 ug Booster	2,925
mRNA-1273-P204	mRNA-1273.214 10 ug Booster	2,768
mRNA-1273-P204	mRNA-1273.214 25 ug Booster	209
mRNA-1273-P204	mRNA-1273.214 5 ug Booster	6
mRNA-1273-P205	mRNA-1273 Booster	681[a]
mRNA-1273-P205	mRNA-1273.211 Booster	758[a]
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	135[a]
mRNA-1273-P205	mRNA-1273.213 Booster	951[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	424[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.231 Booster	45[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.815 Booster	42[a]
mRNA-1273-P205	mRNA-1273.529 Booster	508[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	1,167[a]
mRNA-1273-P205	mRNA-1273.815 Booster	8[a]
mRNA-1273-P205	mRNA-1273.231 Booster	6[a]
mRNA-1273-P206	mRNA-1273.214	68[a]
mRNA-1273-P301	Placebo	2,503[a]
mRNA-1273-P301	mRNA-1273	27,833[a]
mRNA-1273-P301	Primary series+mRNA-1273 Booster	19,609
mRNA-1273-P301	Placebo+mRNA-1273 Booster	10[a]
mRNA-1273-P304	mRNA-1273	81[a]
mRNA-1273-P304	mRNA-1273	71[a]
mRNA-1273-P304	mRNA-1273 Booster	82[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	87
mRNA-1273-P305	mRNA-1273 Booster	1,759[a]
mRNA-1273-P305	mRNA-1273.214 Booster	1,422[a]
mRNA-1273-P305	mRNA-1273.529 Booster	367[a]
mRNA-1273-P306	mRNA-1273.214	391[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	5[a]
mRNA-1283-P101	mRNA-1273	22[a]
mRNA-1283-P201	mRNA-1273 Booster	57[a]
mRNA-1283-P301	mRNA-1273.222	5,716[ab]
mRNA-CRID-001	mRNA-1273	60[a]
mRNA-1073-P101	mRNA-1010+mRNA-1273 co-administration	101[a]
mRNA-1073-P101	mRNA-1273+Placebo	49[a]
mRNA-1083-P101	mRNA-1273.222	102[ab]
mRNA-1083-P301	mRNA-1273.815	4,013[ab]
mRNA-1230-P101	mRNA-1273.214	44[ab]
mRNA-1345-P302	Overall (mRNA-1273.214, or mRNA-1345 + mRNA-1273.214 co-administration)	1,690[ab]

[a]=These numbers were counted to get the total for each study.
[b]=Estimated numbers per randomization scheme as the study is currently blinded.

Table 5-2 Cumulative Subject Exposure to Investigational Drug from Completed and Ongoing Unblinded/Open-label Clinical Trials by Age[a]

Age Range	mRNA-1273									mRNA-1283		mRNA-CRID	mRNA-1073	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	P101	
<2 years	0	0	2,601	0	68	0	0	0	244	0	0	0	0	**2,799**
2 to <6 years	0	0	3,882	0	0	0	0	0	686	0	0	0	0	**4,142**
6 to <12 years	0	0	4,549	0	0	0	0	0	0	0	0	0	0	**4,549**
12 to <16 years	0	2,397	0	0	0	0	0	0	0	0	0	0	0	**2,397**
16 to <18 years	0	780	0	0	0	0	0	1	0	0	0	0	0	**781**
18 to <65 years	475	0	0	3,869	0	20,679	184	2,349	0	27	51	56	127	**24,819**
65 to <75 years	120	0	0	1,035	0	5,825	43	1,118	0	0	5	4	22	**7,342**
75 to <85 years	20	0	0	236	0	1,256	7	75	0	0	1	0	1	**1,415**
>=85 years	3	0	0	22	0	83	0	5	0	0	0	0	0	**98**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Total	**618**	**3,177**	**11,032**	**5,162**	**68**	**27,843**	**234**	**3,548**	**930**	**27**	**57**	**60**	**150**	**48,342[b]**

[a]=Data from completed and ongoing unblinded/open-label till 17 Dec 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 of mRNA-1273 studies is only counted once in total number.

Table 5-3 Cumulative Subject Exposure to Investigational Drug from Completed and Ongoing Unblinded/Open-label Clinical Trials by Sex[a]

Sex	mRNA-1273									mRNA-1283		mRNA-CRID	mRNA-1073	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	P101	
Male	222	1,638	5,616	2,407	38	14,588	124	1,757	478	18	25	22	56	**24,708**
Female	369	1,539	5,416	2,755	30	13,255	110	1,791	452	9	32	38	94	**23,634**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Total	**618**	**3,177**	**11,032**	**5,162**	**68**	**27,843**	**234**	**3,548**	**930**	**27**	**57**	**60**	**150**	**48,342[b]**

[a]= Data from completed and ongoing unblinded/open-label till 17 Dec 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 of mRNA-1273 studies is only counted once in total number.

Table 5-4 Cumulative Subject Exposure to Investigational Drug from Completed and Ongoing Unblinded/Open-label Clinical Trials by Racial Group[a]

Race	mRNA-1273									mRNA-1283		mRNA-CRID	mRNA-1073	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	P101	
White	586	2,353	8,071	4,368	44	22,131	160	3,348	661	19	47	51	122	**38,146**
Black or African American	15	253	721	391	18	2,848	39	12	150	1	6	7	19	**4,157**
Asian	8	151	764	208	1	1,182	13	92	32	1	3	2	5	**2,264**
American Indian or Alaska Native	4	15	41	22	0	213	2	0	5	0	0	0	1	**283**

Race	mRNA-1273									mRNA-1283		mRNA-CRID	mRNA-1073	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	P101	
Native Hawaiian or Other Pacific Islander	1	3	11	9	0	58	0	0	2	0	0	0	0	**75**
Multiple	2	134	1,152	75	5	597	3	56	73	1	1	0	2	**1,986**
Other	2	250	182	59	0	544	9	17	2	0	0	0	0	**1,011**
Not Reported	0	11	68	21	0	160	6	20	4	5	0	0	0	**275**
Unknown	0	7	22	9	0	110	2	3	1	0	0	0	1	**145**
Missing	0	0	0	0	0	0	0	1	0	0	0	0	0	**1**
Total	**618**	**3,177**	**11,032**	**5,162**	**68**	**27,843**	**234**	**3,548**	**930**	**27**	**57**	**60**	**150**	**48,342[b]**

[a]= Data from completed and ongoing unblinded/open-label till 17 Dec 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 of mRNA-1273 studies is only counted once in total number.

Table 5-5 Cumulative Subject Exposure to Investigational Drug from Completed and Ongoing Unblinded/Open-label Clinical Trials by Ethnicity[a]

Ethnicity	mRNA-1273									mRNA-1283		mRNA-CRID	mRNA-1073	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	P101	
Hispanic or Latino	44	722	1,740	668	18	5,624	22	0	120	9	11	15	17	**8,363**
Not Hispanic or Latino	573	2,431	9,195	4,458	50	21,966	210	0	806	17	45	45	127	**36,034**

Ethnicity	mRNA-1273									mRNA-1283		mRNA-CRID	mRNA-1073	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	001	P101	
Not Reported	1	22	71	31	0	173	2	0	2	1	1	0	4	285
Unknown	0	2	26	5	0	80	0	0	2	0	0	0	2	112
Missing	0	0	0	0	0	0	0	3,548	0	0	0	0	0	3,548
Total	**618**	**3,177**	**11,032**	**5,162**	**68**	**27,843**	**234**	**3,548**	**930**	**27**	**57**	**60**	**150**	**48,342[b]**

[a]= Data from completed and ongoing unblinded/open-label till 17 Dec 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 of mRNA-1273 studies is only counted once in total number.

5.2 Cumulative and Interval Exposure from Marketing Experience

Cumulatively, a total of 1,776,284,733 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered to 92 countries. North America, Europe, and Asia accounted for approximately 91% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed (Table 5-6). Cumulatively, 130,546,560 (7.3%) doses had been distributed in lower- and middle-income countries.

In this PBRER reporting period (18 Jun 2023 to 17 Dec 2023), a total of 111,594,410 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered and an estimated total of 65,561,716 doses had been administered. North America, Europe, and Asia accounted for approximately 91% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed (Table 5-6).

Given that elasomeran distribution was discontinued worldwide after Jun 2023, no new doses were distributed during this PBRER reporting period.

A total of 129,007,543 booster doses of elasomeran/imelasomeran had been delivered to 42 countries and an estimated total of 70,954,149 doses had been administered. North America, Europe, and Asia accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 245,792,144 booster doses of elasomeran/davesomeran had been delivered to 43 countries and an estimated total of 135,185,679 doses had been administered. North America, Europe, and Asia accounted for approximately 93% of all doses delivered and administered (Table 5-7 and Table 5-8).

Andusomeran was introduced as a new marketed Moderna vaccine targeting SARS-CoV-2 in Sep 2023. As of 17 Dec 2023, 83,301,090 doses of andusomeran had been delivered to 19 countries and an estimated total of 45,815,600 doses were administered. North America, Europe, and Asia accounted for approximately >95% of all doses delivered and administered (Table 5-9).

Table 5-6 Total Doses Distributed and Administered for All Marketed Moderna Vaccines Targeting SARS-CoV-2

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	1,776,284,733	100.0	1,043,567,281	100.0	111,594,410	100.0	65,561,716	100.0

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
North America	673,022,534	37.9	370,162,394	35.5	39,298,840	35.2	21,614,362	33.0
US	604,271,844	34.0	332,349,514	31.8	31,050,290	27.8	17,077,660	26.0
All Europe	508,715,193	28.6	279,793,356	26.8	18,621,070	16.7	10,241,589	15.6
European Economic Area	421,024,343	23.7	231,563,389	22.2	1,573,750	1.4	865,563	1.3
Asia	427,640,616	24.1	235,202,339	22.5	43,822,380	39.3	24,102,309	36.8
Latin America	77,124,950	4.3	42,418,723	4.1	6,654,950	6.0	3,660,223	5.6
Africa	32,474,530	1.8	17,860,992	1.7	5,250	0.0	2,888	0.0
Oceania	29,068,080	1.6	15,987,444	1.5	1,336,880	1.2	735,284	1.1
Middle East	28,238,830	1.6	15,531,357	1.5	1,855,040	1.7	1,020,272	1.6
International donations	-	-	66,610,677	6.4	-	-	4,184,790	6.4

Table 5-7 Doses Distributed and Administered for Elasomeran/Imelasomeran

Region	Elasomeran/Imelasomeran							
	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	129,007,543	100.0	70,954,149	100.0	10,250	100.0	5,638	100.0
North America	10,521,450	8.2	5,786,798	8.2	0	0.0	0	0.0
US	21,600	0.0	11,880	0.0	0	0.0	0	0.0
All Europe	83,496,993	64.7	45,923,346	64.7	0	0.0	0	0.0
European Economic Area	58,739,963	45.5	32,306,980	45.5	0	0.0	0	0.0
Asia	29,554,550	22.9	16,255,003	22.9	0	0.0	0	0.0
Latin America	1,100,150	0.9	605,083	0.9	0	0.0	0	0.0
Africa	104,850	0.1	57,668	0.1	5,250	51.2	2,888	51.2
Oceania	2,891,400	2.2	1,590,270	2.2	0	0.0	0	0.0
Middle East	1,338,150	1.0	735,983	1.0	5,000	48.8	0	0.0

Table 5-8 Doses Distributed and Administered for Elasomeran/Davesomeran

Elasomeran/Davesomeran								
	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	245,792,144	100.0	135,185,679	100.0	28,283,070	100.0	15,555,689	100.0
North America	69,347,234	28.2	38,140,979	28.2	0	0.0	0	0.0
US	67,846,884	27.6	37,315,786	27.6	0	0.0	0	0.0
All Europe	65,556,530	26.7	36,056,092	26.7	0	0.0	0	0.0
European Economic Area	59,256,930	24.1	32,591,312	24.1	0	0.0	0	0.0
Asia	93,671,610	38.1	51,519,386	38.1	21,801,750	77.1	11,990,963	77.1
Latin America	12,826,800	5.2	7,054,740	5.2	5,644,550	20.0	3,104,503	20.0
Africa	0	0	0	0	0	0.0	0	0.0
Oceania	1,999,970	0.8	1,099,984	0.8	836,770	3.0	460,224	3.0
Middle East	2,390,000	1.0	1,314,500	1.0	0	0.0	0	0.0

Table 5-9 Doses Distributed and Administered for Andusomeran

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	83,301,090	100.0	45,815,600	100.0	83,301,090	100.0	45,815,600	100.0
North America	39,298,840	47.2	21,614,362	47.2	39,298,840	47.2	21,614,362	47.2
US	31,050,290	37.3	17,077,660	37.3	31,050,290	37.3	17,077,660	37.3
All Europe	18,621,070	22.4	10,241,589	22.4	18,621,070	22.4	10,241,589	22.4
European Economic Area	1,573,750	1.9	865,563	1.9	1,573,750	1.9	865,563	1.9
Asia	22,020,630	26.4	12,111,347	26.4	22,020,630	26.4	12,111,347	26.4
Latin America	1,010,400	1.2	555,720	1.2	1,010,400	1.2	555,720	1.2
Africa	0	.	0	.	0	0.0	0	0.0
Oceania	500,110	0.6	275,061	0.6	500,110	0.6	275,061	0.6

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Middle East	1,850,040	2.2	1,017,522	2.2	1,850,040	2.2	1,017,522	2.2

Countries in the regions
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, United Kingdom
Asia: Bangladesh, Bhutan, Cambodia, Hong Kong, 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.

Summaries of ModernaTx, Inc. distribution administered by country and distribution by lots/batches are included in Appendix 12.1.

5.2.1 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.

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.

5.2.2 Post authorization use in Special Populations

5.2.2.1 Use in Elderly

Evaluation of information received during the PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in the elderly population has not identified any additional clinically relevant new safety information for this subpopulation. Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category

SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

The number of cases received during this reporting period and the associated MAH comment are presented by product in Table 5-10. Most of the cases with fatal outcome (48, 80.0%), irrespective of product type, were assessed as unlikely related to the products due to concurrent comorbidities that provided alternate etiologies. Review of the data did not reveal any differences from the general population. Refer to Appendix 12.3 for more information.

Table 5-10 Case Reports and MAH Comment by Product

Source of New Information	• ModernaTx, Inc. Global Safety Database (GSDB) • Literature Sources: o Search Criteria Applied: See Appendix 13.4 o New and Significant Safety Information: None (0)

Product	Exposed Population by Age groups	Number of Case Reports Received	Comment on Benefit and/or Risk (any observed differences from overall population)
Elasomeran	>65 years of age	1,648	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/imelasomeran	>65 years of age	177	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/davesomeran	>65 years of age	491	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Andusomeran	>65 years of age	1,051	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
SPIKEVAX (NOS)	>65 years of age	64	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.

Andusomeran

During this reporting period, the MAH received 1,051 cases (210 serious, 717 medically confirmed, 11 fatal) with 3,182 events (511 serious) in the elderly population (>65+ years of age)

who received andusomeran. When gender was known, most cases were reported in females (604, 57.5%) compared to males (336, 32.0%), with small proportion of cases (111, 10.6%) having no gender reported. The mean patient age was 75.6 years (SD: 7.8) and median age of 74.0 years (range: 65.0 to 106.0 years). Almost half of the cases were reported in United States (487, 46.3%) followed by UK (313, 29.8%) and Canada (176, 16.7%).

During the reporting period, when dose number and time to onset (TTO) could be determined, events were most often reported after Dose 5 (238, 7.5%) followed by Dose 6 (232, 7.3%) and Dose 4 (221, 6.9%), typically within 14-30 days of vaccination. When outcome was recorded, 17.6% of events had resolved (561 events), 11.0% were resolving (350 events) and 26.0% of events had not resolved (828 events), at the time of report. Most of the cases with fatal outcome (7, 63.6%) were evaluated as unlikely related to the use of the product. Concurrent polymorbid conditions provided alternate etiologies for the occurrence of the event.

SPIKEVAX (NOS)

During this reporting period, the MAH received 64 cases (17 serious, 45 medically confirmed, 3 fatal) with 141 events (21 serious) in the elderly population (>65+ years of age) who received a marketed Moderna vaccine targeting SARS-CoV-2 but for which there was insufficient information to attribute the relationship of the case and events to a specific vaccine (SPIKEVAX [NOS]). When gender was known, there were more cases reported in females (38, 59.4%) compared to males (23, 35.9%), with 3 cases (3, 4.7%) having no gender reported. The mean patient age was 74.0 years (SD: 6.7) and median age was 73.5 years (range: 65.0 to 94.0 years). The majority of the cases were reported in United States (51, 77.3%) followed by the EEA (5, 7.6%) and Asia/ UK (3, 4.5%).

Overall, the events reflected reactogenicity or those known to occur following vaccination with Moderna vaccine targeting SARS-CoV-2. Other reported events did not reveal any new or unusual patterns.

No new safety concerns were identified in these reports.

5.2.2.2 Use in Children

Evaluation of information received during the PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in children has not identified any additional clinically relevant new safety information for this subpopulation. The number of cases received during this reporting period and associated MAH comment are presented by age group in Table 5-11. Refer to Appendix 12.4 for additional information.

During the reporting period, the MAH received 1,315 cases (26 serious, 1,263 medically confirmed, 1 fatal) with 2,575 events (40 serious) reported for children <18 years of age who received any marketed Moderna vaccine targeting SARS-CoV-2. When gender was known, no significant difference was noted in cases involving males (655; 49.8%) and females (596; 45.3%), with small proportion of cases (64; 4.9%) having no gender reported. The mean patient age was 4.0 years (standard deviation: 4.2) and median age of 3.0 (range: 0.0 to 17.0 years). Most of these reports were from regulatory authorities (873; 66.4%), of which 783 (59.5%) reports were received in batch from Peru health authority following a new paediatric vaccination campaign initiated in Peru in Jun 2023. The highest number of cases were reported in Latin America (801; 60.9%), followed by The United States (419; 31.9%) and European Economic Area (51; 3.9%).

During the reporting period, the majority of events (1,678; 65.2%) did not provide information on dose number and TTO (1,266, 49.2%). When dose number and TTO could be determined, events were most often reported after Dose 1 (484, 18.8%) followed by Dose 2 (298, 11.6%) and Dose 3 (79, 3.1%), typically within 7 days of vaccination.

The most frequently reported events in children were "Vaccination site pain" (466; 18.1%), "Pyrexia" (447; 17.4%) and "No adverse event (395; 15.3%)".

Table 5-11 Case Reports and MAH comment by Age group

Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources: o Search Criteria Applied: Refer to Appendix 13.4 o New and Significant Safety Information: None (0)	
Exposed Population by Age groups	**Number of Case Reports Received**	**MAH Comment on Benefit and/or Risk (any observed differences from overall population)**
<6 months of age	Total cases • Andusomeran: 2 non-serious cases • Elasomeran: 9 cases (3 serious, 0 fatal) • Elasomeran/imelasomeran: 1 serious case • Elasomeran/davesomeran: 4 non-serious cases • SPIKEVAX NOS: No cases were reported during this reporting period.	[redacted] describes occurrence of neonatal brady arrhythmia in a 1-month-old male. Please refer to Section 16.3.5.1 for further details. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children (6 months to 5 years)	• Andusomeran: 88 cases (1 serious, 0 fatal) • Elasomeran: 775 cases (6 serious, 0 fatal) • Elasomeran/imelasomeran: No cases were reporting during this reporting period. • Elasomeran/davesomeran: 179 non-serious cases • SPIKEVAX NOS: 4 non-serious cases	One case ([redacted] described occurrence of foetal growth restriction in 1-year-old female. Please refer to Section 16.3.5.1 for further details. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children 6-11 years	• Andusomeran: 84 non-serious cases • Elasomeran: 30 non-serious cases • Elasomeran/imelasomeran: No cases reported during this reporting period. • Elasomeran/davesomeran: 19 cases (1 serious, 0 fatal) • SPIKEVAX NOS: No cases reported during this reporting period.	The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

Adolescents (12 to 17 years)	• Andusomeran: 55 cases (2 serious, 0 fatal) • Elasomeran: 52 cases (10 serious, 1 fatal) • Elasomeran/imelasomeran: No cases were reported during this reporting period. • Elasomeran/davesomeran: 12 cases (1 serious, 0 fatal). • SPIKEVAX NOS: 1 serious case (0 fatal).	There were 6 cases reported concerning myocarditis /pericarditis. Please refer to Section 16.3.1.2 for further details. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

5.2.3 Other clinical topics

5.2.3.1 Overdose

Table 5-12 Overdose

Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources: o Search Criteria Applied: See Appendix 13.4 o New and Significant Safety Information: None (0)
Background	Assessing harm due to administration of an extra dose of a vaccine is not well understood. Among reports where an AE could be included, most of the common events refers to expected conditions such as pyrexia, injection site erythema, pain, and headache. Since Oct 2023, reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age were received by the MAH. This issue was restricted to the United States and was limited to US EUA of ModernaTx, Inc COVID-19 Vaccine (andusomeran). The paediatric SDV contains notably more than 0.25 mL of vaccine, which had led to provider confusion or administration errors, including overdose.
Methods	The MAH queried the GSDB for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for Marketed Moderna vaccines targeting SARS-CoV-2. The search criteria applied for identification of Overdose cases included the following terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.
Results	***Overdose Cases Involving use of elasomeran*** During the review period, the MAH received 3 cases (3 events) of overdose with 2 serious cases (1 serious event), and no cases with a fatal outcome. Two cases (66.7%) were medically confirmed, and the reported events were "Overdose" (3; 100.0%). Of the three events reported, two events occurred prior to the

	discontinuation of elasomeran in Jun 2023. However, these events were not reported till after the discontinuation of elasomeran. ***Overdose Cases Involving use of elasomeran/imelasomeran*** During this review period, there were no cases of overdose reported involving elasomeran/imelasomeran. ***Overdose Cases Involving use of elasomeran/davesomeran*** During the review period, the MAH received 4 medically confirmed cases (4 events) of overdose with no serious cases and no cases with a fatal outcome. The reported events were "Overdose" and "Accidental Overdose" (2 events; 50% each). ***Overdose Cases Involving use of andusomeran*** It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new Omicron variant XXB 1.5. Since its approval, the MAH has received 204 cases (204 events) of and no cases with a fatal outcome. A total of 202 cases (99.0%) were medically confirmed. The reported events were "Accidental overdose" (128; 62.7%) and "Overdose" (76; 37.3%). Most of these reports of overdose in the context of overfill of the single-dose vial (SDV) indicated for individuals 6 months to 11 years of age have been received. This issue was mostly restricted to the United States and was limited to US EUA of ModernaTx, Inc COVID-19 Vaccine (andusomeran). The paediatric SDV contains notably more than 0.25 mL of vaccine, which had led to provider confusion or administration errors, including overdose. The MAH considered Overdose in children aged 6 months to 11 years in the context of overfill of SDV in the US as an important potential risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified is it considered a potential risk. Additional risk minimization measure in place. Refer Section 16.2.5. ***Overdose Cases Involving use of Unspecified SPIKEVAX COVID-19 Vaccine-SPIKEVAX (NOS)*** During the review period, the MAH received 2 medically confirmed cases (2 events) no cases with a fatal outcome. The reported events were "Accidental overdose" and "Overdose" (1 event; 50.0% each).
Discussion	A review of the data received during the reporting period of this PBRER, showed that among reports of overdose where an AE was reported, no harm was caused to any vaccinee, with most of the events reported included reactogenicity events. The reports of accidental overdose in the paediatric population were not associated with adverse events. These reports concerned medication use error where the entire volume of the SDV (0.5 mL) of andusomeran was administered to children 6 months through 11 years of age rather than the indicated 0.25 mL dose for this age group as described in the EUA Fact Sheet. The MAH decided on the following risk minimization actions:

	• Update of the current Fact Sheet, to clarify the dosage and administration instructions to providers. • Update of corresponding websites to clarify dosage and administration information. • Communication of the findings to the appropriate health authorities, including CDC. • Distribution of a DHCP letter in the US only and in addition, the MAH is closely monitoring overdose in children in the context of overfill of SDV and associated harms as a part of routine pharmacovigilance activities. Overall, the events reflected reactogenicity or those known to occur following vaccination with marketed Moderna vaccines targeting SARS-CoV-2. Other reported events did not show any new or unusual patterns. The Benefit-risk evaluation remains positive. No new safety concerns were identified in these reports.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Overdose reported in temporal association with the administration of marketed Moderna vaccines Targeting SARS-CoV-2 did not raise any safety issue of concern. The MAH will continue to monitor events of overdose using routine surveillance. The benefit-risk evaluation remains positive.

Refer to Appendix 12.5 for more detailed information.

5.2.3.2 Off-Label use

Table 5-13 Off-Label use

Source of New Information	• ModernaTx, Inc, GSDB • Literature Sources: o Search Criteria Applied: See Appendix 13.4 o New and Significant Safety Information: None (0)
Background	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 Good Pharmacovigilance Practices Annex 1 – Definitions [Rev 4]) [6].
Methods	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, and Intentional product use issue. If warranted, the Company causality assessment is provided utilizing the World Health Organization-Uppsala Monitoring Center (WHO-UMC) standardized case causality assessment for serious cases classified as meeting the definition of Off-label use.
Results	***Off-label Use Cases involving use of elasomeran*** During the review period, the MAH received 20 cases (21 events) of Off-label use with 16 serious cases (15 serious events), and no cases with a fatal outcome. In one case the event off label use was reported non serious but based on other reported events the case was serious (at case level). There were 12 medically confirmed cases involving elasomeran. These cases were reported mostly in females (13 cases, 65.0%) and in males (7 cases, 35.0%). The mean age was 54.1 years (Standard deviation: 12.2) and median age was 55 years (range: 32.0 to 73.0 years). The country with the most frequent cases of Off-label use was Canada (12; 60.0%) followed by Germany (6; 30.0%). The events reported were "Off-label use" (20; 95.2%) and "Intentional product misuse" (1; 4.8%). ***Off-label Cases involving use of elasomeran/imelasomeran*** During this review period, there were no cases of Off-label use reported involving elasomeran/imelasomeran. ***Off-label Cases Involving use of elasomeran/davesomeran*** During the review period, the MAH received 45 cases (45 events) of Off-label use with 2 serious cases (2 serious event) and no case with a fatal outcome. There were 44 medically confirmed cases involving elasomeran/davesomeran. There were 2 cases reported in females (4.4%), and 1 case reported in males (2.2%), Gender information was missing in 42 cases (93.3%) The mean age was 77.7 years (SD: 10.7) and median age was 72.0 years (range: 71.0 to 90.0 years). The country with the most cases of Off-label use reported was the United States (42; 93.3%). The events reported were "Off-label use" (45; 100%). ***Off-label Cases involving use of andusomeran*** It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new Omicron variant XXB 1.5. Since its approval, the MAH has received 1 non serious, medically confirmed case (1 event) of Off-label use and no cases with a fatal outcome. The case involved a 77-year-old female from the United States. ***Off-label Cases involving Use of Unspecified SPIKEVAX COVID-19 Vaccine-SPIKEVAX (NOS)*** During this review period, there were no cases of Off-label use reported involving SPIKEVAX (NOS).
Discussion	The total number of cases of off-label use was lower during the current reporting period compared to the prior reporting period (47 vs 67 cases) as were the number of medically

	confirmed cases (25 vs 56 cases). During this reporting period, majority of the off-label use cases had limited information, missing ages and no associated AEs reported. Consistent with the prior reporting period, "off-label use" was the most frequently reported Preferred Term (PT) during the current reporting period. Off-label use observed during the review period did not change the safety profile of Moderna vaccines Targeting SARS-CoV-2.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases of off-label use reported in temporal association with the administration of Moderna vaccines Targeting SARS-CoV-2 did not raise any safety issue of concern. The information provided does not support evidence of causality between Moderna vaccines Targeting SARS-CoV-2 exposure. The MAH will continue to monitor events for off-label use using routine surveillance. The benefit-risk evaluation remains positive.

Refer to Appendix 12.6 for more detailed information.

6. DATA IN SUMMARY TABULATIONS

6.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 was used for the coding of 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 PT.

6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative (18 Dec 2020 to 17 Dec 2023) summary tabulation of Serious Adverse Events (SAEs) from Company-sponsored CTs is provided in Appendix 3. 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, mRNA-1273.214, mRNA-1273.222, mRNA-1273.815 and mRNA-1273.231, 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 2023) and interval (18 Jun 2023 to 17 Dec 2023) summary tabulation of ADRs (serious and non-serious) is provided in Appendix 4. 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

During the reporting period, ModernaTx, Inc sponsored clinical trial of mRNA-1273-P301 was completed.

mRNA-1273-P301: A 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.

Country: USA

Final Summary: This study aimed at long-term immunogenicity, safety follow-up and effectiveness (COVID-19 incidence rates) data following the 2-dose primary series (Part A and Part B) and booster dose, with a median follow-up of 415 days following Dose 1 and a median of 385 days following Dose 2. As of the end of study, the overall median duration of follow-up after the booster dose was 330 days (range: 1 to 478 days).

Efficacy

Long-term COVID-19 incidence rates for the mRNA-1273 and placebo-mRNA-1273 groups in Part A and Part B showed the rates during both the Delta and the Omicron variant waves were similar between the mRNA-1273 (earlier vaccinated) and the placebo-mRNA-1273 (later vaccinated) groups, suggesting durability of protection after the primary series in the mRNA-1273 group despite the longer interval. However, the higher incidence in both groups during the Omicron wave demonstrates the need to boost immune responses to enhance protection.

Analysis of incidence rates in Part C booster participants showed the majority of COVID-19 cases were detected during the Omicron variant waves. Incidence rates coinciding with Omicron BA.1 predominance (01 Dec 2021 to 31 Mar 2022), Omicron BA.2 predominance (01 Apr 2022 to 30 Jun 2022), and Omicron BA.4/5 predominance (01 Jul 2022 to 30 Nov 2022) were 25.845 (95% CI: 24.542, 27.199), 33.151 (95% CI: 31.252, 35.136), and 36.469 (95% CI 34.148, 38.906) cases per 1,000 person-months, respectively.

Safety

Long-term follow-up data for participants who received the mRNA-1273 primary series vaccination in Part A do not suggest any safety concerns based on events occurring beyond 6 months after vaccination. Safety findings for participants who received the primary series during the Open-Label Observational Phase (Part B) of the study were consistent with those for the double-blind period in Part A. Based on post-authorization data (subsequent to reporting of the double-blind period), myocarditis and pericarditis are included in the CCDS and labels as an important identified risk. No new safety concerns were identified based upon review of the data for this final study report, including long-term safety follow-up.

The mRNA-1273 50 µg booster dose was well-tolerated and no new safety concerns were identified. The incidence of all TEAEs, including those considered by the investigator to be related to study vaccine, as well as the types and frequencies of events by SOC and PT, were similar among participants with positive SARS-CoV-2 status at pre-booster baseline compared with participants with negative status at pre-booster baseline. In the overall population of participants who received a booster dose, the types and incidence of reported events were generally consistent with observations for the primary series and with known risks, including very rare events of myocarditis and pericarditis.

Immunogenicity

Overall, following Dose 2 of the primary series, nAb levels were increased by 119-fold (Geometric Mean Fold Rise [GMFR {95% CI} = 119.058 [110.663, 128.089]) at Day 57 (28 days after Dose 2). A reduction in nAbs was apparent at Day 209 (GMFR [95% CI] = 25.744 [23.754, 27.900]) and at pre-booster BD-Day 1 (GMFR [95% CI] = 17.965 [16.146, 19.988]).

The VAC62 neutralizing antibody in PPIS was significantly higher post-booster (BD-Day 29) nAb GMCs (GMC [95% CI] = 8122.189 [7603.021, 8676.808]) compared to pre-booster BD-Day 1 participants (GMC [95% CI] = 163.848 [147.977, 181.421]). The booster dose induced a significant rise in nAb GMC (GMFR [95% CI] = 50.157 [45.642, 55.120]) by BD-Day 29, with SRR = 94.5 % [92.5, 96.1]. Levels decreased at BD-Day 181 but were still markedly elevated (GMC [95% CI] = 2951.123 [2701.648, 3223.636]).

Superiority of the booster as compared with the 100 µg mRNA-1273 primary series (Part C BD-Day 29 / Part A Day 57) was demonstrated based on nAb (6.996 [95% CI: 6.509, 7.520]) and SRR difference (0.9% [95% CI: 0.1, 1.8]) in the PPIS-Neg. Results of bAb S-protein were consistent with nAb.

7.2 Ongoing Clinical Trials

There was a total of 16 ModernaTx, Inc. sponsored CTs with mRNA-1273 ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P206, mRNA-1273-P304, mRNA-1273-P305, mRNA-1273-P306, mRNA-1283-P101, mRNA-1283-P201, mRNA-1283-P301, mRNA-CRID-001, mRNA-1083-P101, mRNA-1083-P301, mRNA-1273-1073-P101, mRNA-1230-P101, and mRNA-1345-P302), during the current reporting period. Of these 16 ongoing CTs, nine trials (mRNA-1283-P101, mRNA-1283-P201, mRNA-1283-P301, mRNA-1083-P101, mRNA-CRID-001, mRNA-1083-P301, mRNA-1273-1073-P101, mRNA-1230-P101, and mRNA-1345-P302) included mRNA-1273 treatment arms as active controls. Cumulative exposure by study has been presented in Table 7-1.

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

Table 7-1 Summary of Estimated Cumulative Subject Exposure to mRNA-1273 and its variants by Study[a]

Study ID	Total subjects exposed
mRNA-1273-P203	3,177
mRNA-1273-P204	11,032
mRNA-1273-P205	5,162
mRNA-1273-P206	68
mRNA-1273-P304	234
mRNA-1273-P305	3,548
mRNA-1273-P306	930
mRNA-1283-P101	27
mRNA-1283-P201	57
mRNA-1283-P301	5,716
mRNA-CRID-001	60
mRNA-1083-P101	102
mRNA-1083-P301[b]	4,013
mRNA-1073-P101[b]	150
mRNA-1230-P101[b]	44
mRNA-1345-P302[b]	1,690

[a]=Data from ongoing trials till 17 Dec 2023.
[b]=Estimated numbers per randomization scheme as the study is currently blinded.

Refer to Appendix 6 for further details of all the ongoing and completed studies during the reporting period.

7.3 Long-term Follow-up

The Phase 3 study mRNA-1273-P301 includes a total of 24 months follow-up; no long-term safety concerns have been identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days).

In the adolescent Phase 3 Study mRNA-1273-P203, participants from the age of 12 through 17 years had a median follow-up of 342 days after Dose 1, 312 days after Dose 2 and 204 days after a booster dose. In the paediatric Phase 3 Study mRNA-1273-P204, participants 6 months through 11 years had a median follow-up ranging between 183 and 363 days across age groups from Dose 1 and 183 to 266 days from Dose 2. In the paediatric Phase 3 Study mRNA-1273-P306, participants 6 months through 5 years had a median follow-up of 187 (1,386) days from Dose 1 and 168.5 (9,355) days from Dose 2. These studies are ongoing, and no findings related to long-term safety have yet been identified.

Post-authorization safety studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911 are ongoing, and no findings related to long-term safety have yet been identified.

As of the DLP of this PBRER, no clinically important safety concerns have been identified upon review of long-term follow-up data in CTs.

7.4 Other Therapeutic Use of Medicinal Product

Marketed Moderna vaccines targeting SARS-CoV-2 have not been investigated for any other therapeutic use during the reporting period.

7.5 New Safety Data Related to Fixed Combination Therapies

For Moderna vaccines Targeting SARS-CoV-2 there were two combination therapies in which marketed Moderna vaccines Targeting SARS-CoV-2 are part of the fixed combinations: mRNA-1073, and mRNA-1230. There are separate Development Safety Update Reports (DSURs) for each of these fixed combination therapies. No new safety information has been identified from the fixed combination therapies that are in development.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

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

Study ID	Country	Study Title	Study results
mRNA-1273-P903	United States	Post-marketing safety of SARS-CoV-2 SPIKEVAX vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity.	The final report for this study was submitted 30 Jun 2023, however final analyses were reported in PBRER 5.
mRNA-1273-P915	Japan	Survey on Shock and Anaphylaxis for Persons with Underlying Diseases with High Risk of Severe COVID-19 Using Vaccination Information.	The overarching goal of this post-marketing surveillance (PMS) activity was 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 provisional report for this database survey was submitted to Pharmaceuticals and Medical Devices Agency (PMDA) on 17 May 2023. Based on the analysis of 13,309 individuals, the occurrence of hypersensitivity in individuals at high risk for COVID-19 infection was consistent with the known safety profile of elasomeran.
mRNA-1273-P916	Japan	Survey on acute phase safety for persons with underlying diseases with high risk of worsening of COVID-19 using vaccination information.	The overarching goal of this PMS activity was 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 provisional report for this database survey was submitted to PMDA on 17 May 2023. Based on the analysis of 8,844 individuals, the occurrence of solicited AEs, particularly, reactogenicity had an occurrence of > 1% within 8-days of vaccination in individuals at high risk for COVID-19 infection.
mRNA-1273-P928	United States	Relative effectiveness of the BNT162b2 (Pfizer–BioNTech), mRNA-1273 (ModernaTx, Inc), and Ad26.COV2.S (Johnson &	This observational cohort study consistent of two pats. Part I: To determine the rVE of 2 doses of the mRNA-1273 vaccine vs. 2 doses of the BNT162b2 vaccine and 2 doses of the Mrna-1273 vaccine vs. 1 dose

Study ID	Country	Study Title	Study results
		Johnson–Janssen) COVID-19 Vaccine in adults with COVID-19 related at-risk conditions.	of the Ad26.COV2.S vaccine in individuals aged 18 years and older who have at least one underlying medical condition (endpoints: medically-attended COVID-19 illness/COVID-19 illness in outpatients/ COVID-19 illness requiring hospitalization). Part II: To determine the Rve of a single homologous booster dose of the Mrna-1273 vaccine vs. a single homologous booster dose of the BNT162b2 vaccine in adults aged 18 years and older who have at least one underlying medical condition associated with higher risk for severe COVID-19 (endpoints: medically-attended COVID-19 illness/ COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization). Protocol was approved on 02 Mar 2023 and interim updates were done on 12 May 2023. At this time, no safety findings have been identified. Results were presented at ID Week 2023. No safety outcomes were assessed.
Mrna-1273-P930	United States	Relative effectiveness of BNT162b2, Mrna-1273, and Ad26.COV2.S vaccines and homologous boosting in preventing COVID-19 in adults in the US.	This study evaluated the relative effectiveness (Rve) of a primary series of Mrna-1273 vs BNT162b2 and Ad26.COV2.S and a homologous Mrna booster against any medically attended, outpatient, and hospitalized COVID-19. Following adjustment, Part 1 Rve for Mrna-1273 vs BNT162b2 was 23% (95% Confidence Interval [CI], 22%–25%), 23% (95% CI, 22%–25%), and 19% (95% CI, 14%–24%), while the rVE for mRNA-1273 vs Ad26.COV2.S was 50% (95% CI, 48%–51%), 50% (95% CI, 48%–52%), and 57% (95% CI, 53%–61%) against any medically attended, outpatient, and hospitalized COVID-19, respectively. The adjusted rVE in Part 2 for mRNA-1273 vs BNT162b2 was 14% (95% CI, 10%-18%), 13% (95% CI, 8%–17%), and 19% (95% CI, 1%–34%) against any medically attended, outpatient, and hospitalized COVID-19, respectively. rVE against medically attended COVID-19 was higher in adults age ≥65 years (35%; 95% CI, 24%–47%) than in those age

Study ID	Country	Study Title	Study results
			18-64 years (13%; 95% CI, 9%–17%) after the booster. No safety outcomes were assessed.
mRNA-1273-P931	United States	Relative effectiveness of the Bivalent COVID-19 mRNA Vaccines (ORIGINAL AND OMICRON BA.4/BA.5) in adults in the US.	This study estimated the rVE against COVID-19-related hospitalizations (primary outcome) and outpatient visits (secondary) for 1,034,538 mRNA-1273.222 and 1,670,666 BNT162b2 Bivalent vaccine recipients, with an adjusted rVE of 9.8% (95% CI: 2.6-16.4%) and 5.1% (95% CI: 3.2-6.9%), respectively, for mRNA-1273.222 versus BNT162b2 Bivalent. The incremental relative effectiveness was greater among adults ≥ 65; the rVE against COVID-19-related hospitalizations and outpatient visits in these patients was 13.5% (95% CI: 5.5-20.8%) and 10.7% (8.2-13.1%), respectively. Overall, we found greater effectiveness of mRNA-1273.222 compared with the BNT162b2 Bivalent vaccine in preventing COVID-19-related hospitalizations and outpatient visits, with increased benefits in older adults. No safety outcomes were assessed.
mRNA-1273-P932	United States	Real-world comparative effectiveness of a third dose of mRNA-1273 versus BNT162b2 among immunocompromised adults in the US.	The main objective of this retrospective cohort study was to compare real-world effectiveness of third doses of mRNA-1273 versus BNT162b2 at multiple time points on occurrence of COVID-19 hospitalization and medically-attended COVID-19 among IC adults in the US. In propensity score-adjusted analyses, receiving mRNA-1273 vs BNT162b2 as third dose was associated with 32% (relative risk [RR] 0.68; 95% CI 0.51-0.89), 29% (0.71; 0.57-0.86), and 23% (0.77; 0.62-0.93) lower risk of COVID-19 hospitalization after 90, 180, and 270 days, respectively. Corresponding reductions in medically-attended COVID-19 were 8% (0.92; 0.86-0.98), 6% (0.94; 0.90-0.98), and 2% (0.98; 0.94-1.02), respectively. No safety outcomes were assessed.
mRNA-1273-P933	United States	Real world comparative effectiveness of a booster dose of SPIKEVAX versus Comirnaty among adults age 65+ in the US.	In this study, 94,587 and 92,377 individuals received a third dose of mRNA-1273 and BNT162b2, respectively. Among the weighted population, the median age was 69 years (interquartile range, 66-74), 53%

Study ID	Country	Study Title	Study results
			were female, and 46% were commercially insured. COVID-19 hospitalization rates per 1000 person-years (PYs) were 5.61 (95% CI, 5.13-6.09) for mRNA-1273 and 7.06 (95% CI, 6.54-7.57) for BNT162b2 (Hazard ratio [HR], 0.82; 0.69-0.98). Medically attended COVID-19 rates per 1000 PYs (95% CI) were 95.05 (95% CI, 93.03-97.06) for mRNA-1273 and 106.55 (95% CI, 104.53-108.57) for BNT162b2 (HR, 0.93; 0.89-0.98). No safety outcomes were assessed.
mRNA-1273-P936	United States	Comparative Effectiveness of the Bivalent (Original / Omicron BA.4/BA.5) COVID-19 mRNA Vaccines, mRNA1273-222 and BNT162b2 Bivalent in Adults at Higher Risk for Severe COVID-19 Outcomes in the US.	In this study, mRNA-1273 prevented more medically-attended COVID-19 cases than BNT162b2 and Ad26.COV2.S, with rVEs of 24% (95% CI: 22-25%) and 51% (49–52%), respectively. Similarly, mRNA-1273 also prevented more outpatient and hospitalized COVID-19 cases than the two comparator vaccines. Findings were consistent across age groups. In Part 2, rVE of mRNA-1273 vs. BNT162b2 against medically attended COVID-19 cases was 14% (95% CI: 9 19%). Following a booster dose, mRNA-1273 prevented more hospitalizations than BNT162b2 with an rVE of 22% (95% CI: 3–37%) in the overall study population and increased with age, with estimates of 32% (13–47%) and 46% (19–65%) in adults ≥ 50 years and ≥ 65 years, respectively. No safety outcomes were assessed.

Ongoing studies

A summary of safety findings from non-interventional studies that were ongoing during the report follows. Additional details for ongoing studies with the Primary Aim of Identifying, Characterizing, or Quantifying a Safety Hazard; Confirming the Safety Profile of the Medicinal Product; or Measuring the Effectiveness of Risk Management Measures, including those with no safety findings due to study stage, is shown in Appendix 7.

mRNA-1273-P901

Title: Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the US.

Summary: Secondary database study using electronic healthcare data from an integrated healthcare system in the US (Kaiser Permanente Southern California). Vaccination information and SARS-CoV-2 related outcomes (symptomatic illness, hospitalization, and death) will be identified using electronic healthcare data. Both matched cohort and test-negative study designs will be used to estimate relative and absolute vaccine effectiveness of mRNA-1273. The study population includes individuals ≥ six months of age. Start date for this study was 18 Dec 2020 and anticipated study completion date is 30 Apr 2024. The final clinical study report (CSR) date for this study is currently anticipated to be submitted by 14 Apr 2025.

Real-world effectiveness data of authorized COVID-19 mRNA vaccines have become available from study P901, a cohort study utilizing electronic healthcare data collected in the Kaiser Permanente Southern California integrated healthcare system. As of the latest interim report dated Jun 2023, Study P901 estimated the relative vaccine effectiveness and absolute vaccine effectiveness among individuals who received mRNA-1273.222 (following receipt of 2 or more doses of monovalent mRNA COVID vaccine) against COVID-19 hospitalization, SARS-CoV-2 infection requiring emergency department/urgent care, and in-hospital death between 31 Aug 2022 and 31 Jan 2023, a time when the omicron variants (e.g., BA.5) were circulating. The analysis population was composed of 290,292 individuals who received mRNA-1273.222 and 580,584 comparators who received 2 or more doses of monovalent mRNA COVID vaccine only (for relative vaccine effectiveness analyses), and 204, 655 who were unvaccinated for any COVID-19 vaccines (for absolutely vaccine effectiveness analyses). Comparators were matched to bivalent vaccinees on age, sex, race/ethnicity, and date receipt of bivalent vaccination. Compared to individuals who did not receive any bivalent mRNA vaccine but received ≥2 doses of any monovalent mRNA vaccine, the relative vaccine effectiveness (rVE) against hospitalization for COVID-19 disease was 70.3% (95% CI). Relative vaccine effectiveness against SARS-CoV-2 infection requiring emergency department/urgent care and against COVID-19 hospital death was 55.0% (50.8%-58.8%) and 82.7% (63.7%-91.7%), respectively. Compared to individuals who were unvaccinated for any COVID-19 vaccine, the absolute Vaccine effectiveness against hospitalization for COVID-19 disease was 82.8% (78.8%-86.0%). Absolute vaccine effectiveness against SARS-CoV-2 infection requiring emergency department/urgent care and against COVID-19 in-hospital death was 55.4% (50.3%-60.1%) and 89.7% (77.7%-95.2%), respectively.

Since the last interim report dated Jun 2023, Study P901 also estimated the relative and absolute vaccine effectiveness among individuals who received mRNA-1273.222 (following receipt of 2 or more doses of monovalent mRNA COVID vaccine) against SARS-CoV-2 infection overall,

SARS-CoV-2 infection requiring emergency department/urgent care, COVID-19 hospitalization, and COVID-19 in-hospital death by Omicron sub-variant BA.4/BA.5 and XBB-sub-lineages between 01 Sep 2022 and 30 Jun 2023. Utilizing a test-negative case control design, the relative vaccine effectiveness analysis included 20, 966 cases and 62, 898 controls. Relative vaccine effectiveness against BA.4/BA.5 was 46.8% (41.5%-51.6%) for infection, 58.3% (50.0%-65.1%) for ED/UC encounters, 67.2% (43.9%-80.8%) for hospitalization, and 53.1% (-84.2%-96.5%) for death. Relative vaccine effectiveness against XBB was 9.3% (-0.6%-18.2%) for infection, 25.9% (13.2%-36.7%) for ED/UC encounters, 59.9% (37.0%-74.5%) for hospitalization, and 31.8% (-83.7%-92.4%) for death. The absolute vaccine effectiveness analysis included 10, 366 cases and 31, 008 controls. Absolute vaccine effectiveness against BA.4/BA.5 was 18.6% (8.1%-27.9%) for infection, 51.9% (40.3%-61.3%) for ED/UC encounters, 78.4% (58.3%-88.8%) for hospitalization, and 45.9% (-66.1%-90.1%) for death. Absolute vaccine effectiveness against XBB was -25.0% (-35.0-[-]13.5%) for infection, 8.2% (-12.2%-26.1%) for ED/UC encounters, 73.3% (51.2%-85.4%) for hospitalization, and 31.0% (-92.6%-96.5%) for death.

Prior analyses conducted from the P901 study assessing relative vaccine effectiveness of receipt of a single booster dose of the monovalent mRNA-1273 (following receipt of 2 doses of monovalent mRNA COVID vaccine) between 20 Oct 2021 and 31 Dec 2021 demonstrated rVE against hospitalization, SARS-CoV-2 infection and death to be 89.0% (95% CI: 86.2%-91.2%), 61.3% (95% CI: 60.5% – 62.2%), and 96% (95% CI: 68.0%-99.5%), respectively among 431,328 immunocompetent adults receiving a single booster dose of mRNA-1273 (and a similar number of matched comparators who received a 2 dose mRNA monovalent COVID vaccine only) [7]. In addition, an analysis conducted between 01 Jan 2022 and 30 Jun 2022 among 30,809 SARS-CoV-2 cases and 92,427 matched controls looking at Omicron variant specific relative vaccine effectiveness of a booster dose of mRNA-1273 against hospitalization for COVID-19 demonstrated the rVE against BA.1, BA.2, and BA.4/5 Omicron sub-variants to be 88.8% (95% CI: 83.3-92.5); 75.0% (95% CI: 47.6-88.1); and 87.5% (95% CI: 51.8%-96.8%) [8].

mRNA-1273-P904

Title: Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of SPIKEVAX in the EU.

Summary: A preliminary screening stage analyzes for selected databases in this observational study using large administrative databases in Denmark, Norway, Spain, and the UK was presented in Interim Report 4 on 31 Mar 2023.

During the study period covered by Interim Report 4, the number of eligible elasomeran recipients with at least one dose of elasomeran and no previous record of a COVID-19 vaccine was 564,137 in Denmark, 543,429 in Norway, 621,240 in Spain, and 228,889 in the UK. Rates of the AESI varied widely across the databases. The variation is attributable both to the database characteristics, to algorithm refinement activities that are in progress within the VAC4EU network, and to data limitations (specifically, in Norway, inflation of some rates was due to lack of specific diagnosis subcodes in the current data extraction, which will be corrected for the final report).

The MAH identified more than 50 strata with standardized mortality ratio ≥2.0 based on ≥5 elasomeran exposed cases in at least one country for the AESIs diabetes type 1, idiopathic thrombocytopenia, heart failure, myocarditis, pericarditis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalized convulsions, acute respiratory distress syndrome, anosmia/ageusia, multisystem inflammatory syndrome, and death of any cause. There was a maximum of 11 to 50 signals in at least one country for the AESIs microangiopathy, coronary artery disease, arrhythmia, cerebrovascular disease, SOCV, encephalitis/meningoencephalitis, Bell's palsy, erythema multiforme, and anaphylaxis. The MAH did not identify any signals for narcolepsy, cerebral venous sinus thrombosis, Kawasaki disease, transverse myelitis, and sudden death. For the remaining AESIs, there was a maximum of 10 signals for each country. Most signals were detected in Spain (Information System for Research in Primary Care).

In the squamous cell carcinoma of the skin signal evaluation analyses, IRR with point estimates exceeding 1.5 were observed in at least one of the three countries for the AESIs (idiopathic) thrombocytopenia, stress-induced cardiomyopathy, myocarditis, pericarditis, splanchnic vein thrombosis, Acute liver injury, generalized convulsions, anaphylaxis, and Vaccine-induced immune thrombotic thrombocytopenia. The largest effect sizes were observed for myocarditis and pericarditis.

No indication of VAED was identified in Norway, the only country for which these analyses were performed in the Interim Report. Concerning cohort analyses of myocarditis and pericarditis, the majority of myocarditis and pericarditis cases was male; among those exposed to elasomeran, exposed the majority had received the second dose of elasomeran before diagnosis of myocarditis in Norway and Denmark or before the diagnosis of pericarditis in Denmark.

Discussion

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-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. This retrospective observational cohort study used secondary, de-identified individual level medical and pharmacy claims data provided by HealthVerity. The interim report was submitted 15 Sep 2023. The incidence of AESI among patients who receive at least one dose of elasomeran bivalent to two concurrent comparator groups (influenza vaccine and medically-attended COVID-19, analyzed separately). Where a potential increase in the rate of an AESI following elasomeran vaccination was identified, SCRI analyses for signal refinement is planned.

Statistical analysis:

For the primary analyses, propensity scores (PS) were calculated to estimate the probability of receiving a dose of elasomeran bivalent conditional on measured covariates. The PS was calculated via multivariable logistic regression model using inverse probability treatment weights (IPTW) method. Cox proportional hazards regression was used to evaluate the relationship between vaccine group and AESI. The Cox proportional hazard regression models estimated HR with 95% CI and cumulative incidence curves for the time-to-AESI stratified by exposure status, plotted for the PS-weighted populations. If the proportional hazard assumptions were not met an alternative outcome model for restricted mean survival time (RMST) was used. Weighted rates of endpoints were reported as the number of patients with the event of interest per 100,000 person-years. Analyses of the medically-attended COVID-19 concurrent comparator was limited to weighted estimates of the incidence rates; HRs were not estimated.

As a secondary analysis for influenza vaccine cohort, eligible vaccine episodes with elasomeran bivalent and influenza vaccine administration on the same day or within 14 days of each other were included as eligible elasomeran bivalent vaccine episodes into the exposed group. As a

subgroup analysis, a separate exposure cohort consisting of only eligible, concurrent elasomeran bivalent and influenza vaccine episodes occurring on the same day or within 14 days was identified; the date of the elasomeran bivalent administration was considered the index date for this subgroup. These concurrent vaccine episodes were compared to eligible influenza vaccine episodes that do not overlap with an elasomeran bivalent vaccine episode. PS-weighted incidence rates and weighted HRs were estimated with 95% CIs within this secondary analysis.

In the final report, self-controlled risk interval analysis will be conducted for myocarditis, pericarditis, and AESI with increased lower bound of HR >1.

Results:

There were 519,838 and 5,332,765 episodes of elasomeran bivalent and influenza vaccinations among adults at least 18 years of age, respectively, that met inclusion criteria in comparator 1 analyses. In contrast, there were 1,061,073 and 1,051,868 episodes of elasomeran bivalent and medically-attended COVID-19 episodes among adults, respectively, that met inclusion criteria in comparator 2 analyses. Among children less than 18 years of age, 10,500 and 2,646,986 episodes of elasomeran bivalent and influenza vaccinations were included in comparator 1 analyses, while 26,489 and 247,538 episodes of elasomeran bivalent and medically-attended COVID-19 episodes met inclusion criteria for the comparator cohort 2 without excluding any prevalent AESI.

Myocarditis:

Among the 519,390 and 5,327,428 elasomeran bivalent and influenza vaccine administrations included in the comparator 1 analyses, there were only 2 and 17 myocarditis cases observed in the 1-7 days following each type of vaccination episodes, respectively. The weighted incidence rate (IR) among the elasomeran bivalent episodes was 27.10 (95% CI: 16.55 - 41.85) per 100,000 person-years (PY) compared to a weighted IR of 19.81 (95% CI: 12.03 - 29.91) per 100,000 PY following influenza vaccination. The estimated HR from the weighted Cox model indicated no increased risk of myocarditis in the 1-7 days following elasomeran bivalent compared to influenza vaccination (weighted HR= 1.54, 95% CI: 0.32 - 7.34). However, the proportional hazards assumption was not met in this model, though estimation of the RMST was consistent with the observed weighted HR indicating no increased risk of myocarditis following elasomeran bivalent (RMST = 1.000001, 95% CI 0.999999 - 1.000002).

There were 1,060,257 and 1,050,345 elasomeran bivalent and medically-attended COVID-19 episodes included in the comparator 2 analyses, for which 8 and 51 myocarditis cases were observed, respectively. The weighted IR in the 1-7 days following elasomeran bivalent

administration was 57.30 (95% CI 36.56 - 88.80) per 100,000 PYs compared to a weighted IR of 281.70 (95% CI 229.89 - 341.92) per 100,000 PYs following medically-attended COVID-19.

Among children less than 18 years of age, there were no cases of myocarditis observed in the 1-7 days following elasomeran bivalent administration.

Pericarditis:

Among the 518,842 and 5,320,809 elasomeran bivalent and influenza vaccine administrations included in the comparator 1 analyses, there were only 1 and 29 pericarditis cases observed in the 1-7 days following vaccination, respectively. The weighted IR among the elasomeran bivalent episodes was 13.57 (95% CI: 6.50 - 24.95) per 100,000 PYs compared to a weighted IR of 32.97 (95% CI: 23.04 - 46.32) per 100,000 PYs following influenza vaccination. The estimated HR from the weighted Cox model indicated no increased risk of pericarditis in the 1-7 days following elasomeran bivalent compared to influenza vaccination (weighted HR= 0.44, 95% CI: 0.06 - 3.33).

There were 1,059,209 and 1,048,589 elasomeran bivalent and medically-attended COVID-19 episodes included in the comparator 2 analyses, for which 7 and 38 pericarditis cases were observed, respectively. The weighted IR in the 1-7 days following elasomeran bivalent administration was 47.30 (95% CI 27.40 - 74.13) per 100,000 PYs compared to a weighted IR of 159.03 (95% CI: 119.88 - 203.86) per 100,000 PYs following medically-attended COVID-19.

Among children less than 18 years of age, there were no cases of pericarditis observed in the 1-7 days following elasomeran bivalent administration for comparator 1 analyses and 1 case for comparator 2 analyses.

Other AESIs:

There were no observed increased risks or elevated incidence rates of any AESI following SPIKEVAX bivalent compared to either comparator 1 or 2 in pre-weighted and propensity score weighted estimates of incidence rates or HR among elasomeran bivalent episodes unique to adults or children.

Discussion:

This interim analysis supports the known safety profile of elasomeran bivalent, and new associations with AESI have not been observed. The final report will also include additional sensitivity and exploratory analyses, as well as signal evaluation for myocarditis and pericarditis through self-controlled risk interval analyzes, and any other AESI that meets the specified

threshold.

Other studies describing risks or benefits of Moderna vaccines targeting SARS-CoV-2 are described here:

Study ID	Country	Study Title	Status
mRNA-1273-P905	Denmark, Norway, Italy, Spain, United Kingdom	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries.	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 Mar 2023 interim study update
mRNA-1273-P910	Denmark, Norway, Italy, Spain, United Kingdom	Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARSCoV-2.	The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and elasomeran bivalent vaccination. Startup activities including creation of the case adjudication system and preliminary analyses of structured data are currently in progress
mRNA-1273-P911	United States	Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA).	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. An interim feasibility report was completed 31 Oct 2023. Cases of myocarditis identified in routine clinical practice meeting the CDC case definition, including those occurring following administration of elasomeran as well as cases not secondary to vaccines targeting SARS-CoV-2 were described.
mRNA-1273-P917	Japan	Survey on non-acute phase safety for persons with underlying diseases who are considered to be at high risk of aggravation of COVID-19 using vaccination information.	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 provisional report for this database

Study ID	Country	Study Title	Status
			survey was submitted to PMDA on 20 Dec 2023. The final report will be submitted on 17 Mar 2024.
mRNA-1273-P918	Japan	General use-results survey (follow-up of participants in the priority survey at the early stage of inoculation with COVID-19 vaccine [SPIKEVAX {monovalent: original strain}]).	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. Enrolment for this survey ended in Dec 2022. There were 8,637 individuals in the safety and efficacy analysis set. At this time, no safety findings have yet been identified. The observation of the final subject was completed in Apr 2023, and final analyses are ongoing. A provisional report for this database survey was submitted to PMDA on 20 Dec 2023. The final report will be submitted on 17 Mar 2024.
mRNA-1273-P919	United States	An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to SPIKEVAX During Pregnancy.	This observational study will evaluate the risk of adverse pregnancy and infant outcomes following maternal exposure to elasomeran during pregnancy. Analyses are currently in progress. At this time, no safety findings have yet been identified given the early stage of the study.
mRNA-1273-P922	United States	DisCOVEries 2 - An Observational Study to Evaluate the Immunogenicity of mRNA COVID-19 Bivalent Vaccines (Original and Omicron BA.4/BA.5) and 2023 Updated mRNA COVID-19 Vaccines	The study was amended and includes two parts: Part A: 2022-2023 mRNA COVID-19 Bivalent Vaccine (Original and Omicron BA.4/BA.5) A six-month observational prospective study (with an optional long-term follow-up of up to 12 months), to investigate antibody levels with respect to time since receiving a bivalent

Study ID	Country	Study Title	Status
		(XBB.1.5).	COVID-19 booster dose. The protocol was approved on 06 Dec 2022. At this time, no safety findings have been identified. Part B: 2023 mRNA COVID-19 Updated Vaccine (XBB.1.5) A six-month observational prospective study (with an optional long-term follow-up of up to 12 months), to investigate antibody levels with respect to time since receiving an updated monovalent COVID-19 vaccine (XBB.1.5). The protocol was amended and approved on 25 Jul 2023.
mRNA-1273-P924	South Korea	A Multi-Centre, Prospective, Observational Post-marketing Surveillance to Investigate the Long-term Safety of SPIKEVAX BIVALENT Under Routine Clinical Care in Korea.	This PMS activity aims to evaluate safety of elasomeran elasomeran/imelasomeran (SARS-CoV-2 mRNA vaccine)] and elasomeran/davesomeran in Korea. Enrollment for this study is ongoing. No safety findings have been identified given the early stage of the study.
mRNA-1273-P934	United States	Effectiveness Comparison Between the Two mRNA Monovalent COVID-19 Vaccine Boosters in Medicare Fee-For-Service.	The objective of this study was to compare the real-world effectiveness of a first original booster dose (1.BD) of mRNA-1273 versus BNT162b2. Analyses are ongoing.
mRNA-1273-P935	Australia	Vaccine effectiveness against COVID-19 variants in Victoria, Australia.	The objectives of this study are to assess (i) the VE of several COVID-19 vaccinations (Vaxzevria, elasomeran, Comirnaty and Nuvaxovid, including various combinations of primary course and booster vaccines) in Victorian adults and children using two alternative study designs (a cohort study and a test-negative case-control study) and (ii) how this VE wanes over time in adults and children. Analyses are ongoing.
mRNA-1273-P937	Denmark	Real-world comparative effectiveness of 3rd dose of mRNA-1273 and BNT162b2 vaccines in Denmark	The primary aim of this study is to compare the real-world effectiveness of the third monovalent dose of mRNA-1273 versus the third monovalent dose of BNT162b2 on medically attended COVID-19 infection among populations who have

Study ID	Country	Study Title	Status
			completed the primary series of mRNA-based COVID-19 vaccines. Analyses are ongoing.
mRNA-1273-P940	United States	Effectiveness of mRNA-1273 original booster vaccination against medically attended post-acute sequelae of SARS-CoV-2 infection (PASC) in a cohort of primary series recipients of mRNA vaccines in the United States.	The aim of this study is to assess effectiveness of mRNA-1273 booster vaccination against PASC. Analyses are ongoing with study results anticipated in 2024 Q2.

In addition, the following studies are planned as of the DLP of this PBRER:

Study ID	Country	Study Title	Status
mRNA-1273-P921	Saudi Arabia	Evaluation of Post-marketing safety of elasomeran in the Kingdom of Saudi Arabia (KSA).	The overarching aim of this study is to characterize the safety of Moderna vaccines targeting SARS-CoV-2 in Saudi Arabia. A feasibility assessment in development.
mRNA-1273-P923	South Korea	Post-marketing safety of SPIKEVAX vaccine in South Korea.	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 in development for a retrospective database study supporting this aim.
mRNA-1273-P929	Japan	Special Use-Results Survey: Assess the safety of marketed Moderna vaccines targeting SARS-CoV-2 in the Japanese pediatric population.	The overarching aim of the study is to characterize the safety of Moderna vaccines targeting SARS-CoV-2 in the pediatric population in Japan. A protocol is under review.

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other Clinical Trials

9.1.1 Investigator-sponsored Studies

The following Investigator-sponsored Studies were completed during the reporting period:

Short Title: SCQM

Title: Real-world dynamics of anti-S1-binding antibodies after COVID-19 vaccination in patients with inflammatory rheumatic diseases

Summary: For this study enrolment is complete, first patient first visit was 03 Apr 2021 and final report date was 28 Feb 2023. The total number of subjects enrolled was 912. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

The following Investigator-sponsored Studies were ongoing during the reporting period:

Short Title: T-Cell immunity

Title: T-Cell immunity

Description for T-Cell immunity: Recently, two mRNA vaccines for 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. The MAH found that vaccinated individuals had robust T-cell responses to the wild type of spike and nucleocapsid proteins, even more so than convalescent patients. The MAH 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: Enrolment is complete, first patient first visit dated in 2022 and projected end date is 31 Mar 2024. The total number of subjects enrolled was 62. No AEs have been reported and no significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: COVERALL Extension

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 is complete, first patient first visit was 26 Oct 2022 and planned final report date is 31 Mar 2024. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: CoviBoost 2

Title: AP-HA (ARNCOMBI). Multicenter, Randomized, Open-label Trial Comparing the Immunological Efficacy of a Vaccine Regimen Combining Two COVID-19 mRNA Vaccines (Pfizer-BioNTech and ModernaTx, Inc) With That of a Homologous Vaccination of Each COVID-19 mRNA Vaccine: Non-inferiority Trial.

Summary: For this study enrolment was complete, first patient first visit was 22 Aug 2022 and planned final report date is 01 Jun 2024. The total number of subjects enrolled was 414. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: SCQM Extension

Title: Real-world dynamics of anti-S1-binding antibodies after COVID-19 vaccination in patients with inflammatory rheumatic diseases.

Summary: For this study enrolment was complete, first patient first visit was 03 Apr 2021 and planned final report date is 01 Jun 2024. The total number of subjects enrolled was 917. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: MIViral

Title: Mucosal Immunity Influence on Infectious Viral Load prospective observational study.

Summary: For this study enrolment was complete, first patient first visit was in Oct 2022 and planned final report date is 01 May 2024. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: Fukushima Community Vaccine Study.

Title: A cohort study of antibody titer and cellular immunity assessment after bivalent vaccination among medical personnel and elderly people in the affected area of Fukushima Prefecture, Japan.

Summary: Planned enrolment for this study is about 1,500-2,000. No subjects have been enrolled till DLP. This study started on 31 Aug 2023 and the projected end date for this study is 31 Mar 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: PARACOV Study in Japan.

Title: Prophylactic Antipyretics to Reduce Adverse Reactions after COVID-19 Vaccination in Japan.

Summary: Planned enrolment for this study is about 80. No subjects have been enrolled till DLP. This study started on 01 Nov 2023 and the projected end date for this study is 01 Dec 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

9.1.2 License partner studies

9.1.2.1 Completed trials

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 140 subjects and actual subjects exposed to mRNA-1273 was 120. Start date for this study was 16 Mar 2020 and end date was 26 Apr 2023. The estimated completion date for the CSR is Oct 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. 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. Clinical Safety report preparation been completed.

9.1.2.2 Ongoing trials

Sponsored by DMID of National Institute of Allergy and Infectious Diseases (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 two different arms and further 2nd arm was divided into eight 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 210 subjects and actual subjects exposed to mRNA-1273 was 135. Start date for this study was 29 Mar 2020 and end date was in Apr 2023. The estimated completion date for the CSR is Jan 2024. 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. CSR review and finalization for Cohorts 1/2 is underway.

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 433 subjects and actual subjects exposed to mRNA-1273 were 423. Start date for this study was 28 May 2021 and final database lock was 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. Final CSR is estimated Apr 2024.

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 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.

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 is administered in 2 doses, 28 days apart. Participants 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 tumour 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 leukaemia, lymphoma, multiple myeloma and participants post-allogeneic stem cell transplant will be enrolled based on their perceived risk of immunosuppression. As of 17 Dec 2023, 19 subjects were exposed to mRNA-1273. Start date for this study was 30 Apr 2021 and estimated study completion date is 01 Jun 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 Adult Lung Transplant Recipients.

Country: US

Dosing details: 50 ug (n=20), 100 ug (n=20), and 200 ug (n=20).

Summary: Planned enrolment was 60 subjects and number of subjects enrolled and exposed to mRNA-1273 were 19. Enrolment was terminated due to the availability of the bivalent mRNA-1273.222 vaccine. Start date for this study was on 10 Mar 2022, enrolment stopped by 27 Feb 2023. Data analysis is completed, and final study report was submitted after the DLP of this PBRER, in Feb 2024. 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.

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 15,000 subjects and number of subjects enrolled and exposed to mRNA-1273 was 12,340 subjects. Actual recruitment end date was 12 Nov 2022 and last subject visit was on 09 May 2023. One hundred and fifteen adverse events have been reported. Seventeen SAEs were reported, all of which were assessed as not related to the study product. Eight adverse Events of Special Interest have been reported, 4 of which were related to study product. Five hundred and seventy-five cases of Reactogenicity have been reported, none of which were Grade 3 or higher. Three hundred and ninety-eight Breakthrough infections have been reported, 1 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 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 23-Valent Pneumococcal Polysaccharide Vaccine (Vl10) or 15-Valent Pneumococcal Conjugate Vaccine (Vl14) (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive placebo (blinded) in the left arm 30 days later at Visit 3 (Day 30). Participants enrolled in the non-concomitant groups will receive placebo (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive V110 or V114 (blinded) in the left arm 30 days later at Visit 3 (Day 30).

Summary: Planned enrolment was 1,300 subjects and total subjects enrolled were 850 subjects and 843 subjects enrolled were exposed to mRNA-1273. The early closure of enrolment was due to the rescinding of the monovalent mRNA-1273 booster EUA. Start date for this study was 12 Jan 2022 and last participant last visit was on 21 Feb 2023. Database lock was Oct 2023. The CSR is targeted for finalization in Feb 2024. 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 was 400 subjects and total number of subjects enrolled were

165 and out of which 162 subjects were exposed to mRNA-1273. Start date for this study was 28 Mar 2022 and projected end date is 14 Jun 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 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 and mRNA-1273.214 50 µg

Summary: For mRNA-1273.529 50 µg, planned enrolment is 205 subjects and the number of subjects enrolled and exposed to mRNA-1273 were 209. Start date for this study was 18 Feb 2022 and projected end date is 31 Mar 2024. Last patient last visit was conducted on 05 Dec 2022. Study analysis was ongoing with joint paper on mRNA-1273.529 and mRNA-1273.214 planned. No SAEs have been 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 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 Mar 2024. Last patient last visit was conducted on 02 May 2023. Study analysis was ongoing with joint paper on mRNA-1273.529 and mRNA-1273.214 planned. 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

Table 9-1 Medication errors

Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o New and Significant Safety Information: None (0)
Background	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. EU

	legislation requires information on medication errors to be collected and reported through national pharmacovigilance systems.
Methods	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.
Results	Refer to Appendix 9.g for additional information. **Medication Errors Involving Use of elasomeran** During this review period, the MAH received 447 cases (1,831 events) of Medication errors with 192 serious cases (558 serious events), and 3 cases with a fatal outcome. There were 317 medically confirmed cases involving elasomeran. The most frequently reported PTs were "Interchange of vaccine product" (149; 8.1%), followed by "No adverse event" (148; 8.1%) and "Expired product administered" (95; 5.2%). During the review period, there were 261 cases (1,088 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (81; 7.4%), followed by "Fatigue" (29; 2.7%) and "Pyrexia" (20; 1.8%). **Medication Errors Involving Use of elasomeran/imelasomeran** During the review period, the MAH received 162 cases (471 events) of Medication errors with 5 serious cases (12 serious events), and no cases with a fatal outcome. There were 145 medically confirmed cases involving elasomeran/imelasomeran. The most frequently reported PTs were Expired product administered" and "No adverse event'' (152 events; 32.2% each), followed by "Product storage error" (72; 15.3%), and "Product temperature excursion issue" (54; 11.5%). During the review period, there were 7 cases (12 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" and "Drug ineffective" (2 events; 16.7% each). **Medication Errors Involving Use of elasomeran/davesomeran** During the review period, the MAH received 1,366 cases (3,390 events) of Medication errors with 13 serious cases (36 serious events), and 1 case with a fatal outcome. There were 1,309 medically confirmed cases involving elasomeran/davesomeran. The most frequently reported PTs were "No adverse event" (1,234; 36.4%) followed by "Expired product administered" (889; 26.2%) and "Product storage error" (404, 11.9%). During the review period, there were 34 cases (98 events) of medication error reported with an associated AE. The most frequent AE reported were "Pyrexia" (14; 14.3%), followed by "Chills" and "COVID-19" (7 events; 7.1% each). **Medication Errors involving use of andusomeran** It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new Omicron variant XXB 1.5. Since its approval, the MAH received 2,038 cases (4,765 events) of Medication errors with 4 serious cases (13 serious events), and no cases with a fatal outcome. There were 1,947 medically confirmed cases involving andusomeran. The most frequently reported

	PTs were "No adverse event" (1,988; 41.7%) followed by "Expired product administered" (1,100; 23.1%) and "Poor quality product administered" (181; 3.8%). During the review period, there were 99 cases (228 events) of medication error reported with an associated AE. The most frequent AE reported were "Product packaging quantity issue" (37; 16.2%) followed by "Pyrexia" (12; 5.3%), and "fatigue" (10; 4.4%). The reports coded as "Product packaging quantity issue" concerned medication use error where the entire volume of the SDV (0.5 mL) of andusomeran was administered to children 6 months through 11 years of age rather than the indicated 0.25 mL dose for this age group as described in the EUA Fact Sheet. Please refer to Section 5.2.2.2 (Use in children) for further details. **Medication Errors involving use of unspecified SPIKEVAX COVID-19 Vaccine-SPIKEVAX (NOS)** During the review period, the MAH received 24 cases (75 events) of Medication errors with 4 serious cases (8 serious events), and no cases with a fatal outcome. There were 22 medically confirmed cases involving SPIKEVAX (NOS). The most frequently reported PTs were "COVID-19 Immunisation" and "Interchange of vaccine products" (11 events; 14.7% each). During the review period, there were 17 cases (31 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (7; 22.6%) and "Illness" (3; 9.7%).
Discussion	A review of the data received during the reporting period of this PBRER, showed that events of medication errors do 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 Marketed Moderna vaccines targeting SARS-CoV-2 vaccine beyond the primary series or any interchange of other COVID-19 vaccine products. There seemed no difference for the nature of reported medication errors and importantly associated AEs among the Marketed Moderna vaccines targeting SARS-CoV-2 in general. AEs associated with reported medication errors were usually known to the elasomeran, Marketed Moderna vaccines targeting SARS-CoV-2 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	Evaluation of the data during this reporting period did not provide any new safety information that would suggest medication errors associated with administrations of Marketed Moderna vaccines targeting SARS-CoV-2 impact the benefit-risk profile for Marketed Moderna vaccines targeting SARS-CoV-2. The benefit-risk evaluation remains positive. Medication errors reported to ModernaTx, Inc. will continue to be monitored using the routine pharmacovigilance measures implemented for Marketed Moderna vaccines targeting SARS-CoV-2.

9.3 Medical device incidents

A review of reports of device related issues from elasomeran or andusomeran containing vaccines did not reveal any patterns or other safety information relevant to the benefit-risk assessment for marketed Moderna vaccines targeting SARS-CoV-2.

10. NON-CLINICAL DATA

No relevant new safety finding was identified in non-clinical *in vivo* and *in vitro* studies during the period of this PBRER.

11. LITERATURE

A global literature search and analysis were performed utilizing Embase, Medline and PubMed databases for the reporting period 18 Jun 2023 to 17 Dec 2023. 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, Modernatx 1273, elasomeran/davesomeran, mRNA-1273.214 (BA.1), mRNA-1273.222 (BA.4/BA.5), SPIKEVAX XBB1.5, andusomeran, elasomeran/imelasomeran, SPIKEVAX X injection, SPIKEVAX XBB1.5 PFS, SPIKEVAX XBB.1.5, SPIKEVAX intramuscular injection (Monovalent: Omicron XBB.1.5), SPIKEVAX XBB.1.5 Prefilled Syringe, SPIKEVAX (COVID-19 Vaccine, mRNA) 2023-2024 Formula (Pre-filled Syringe). Find the complete global literature search strategy used for Medline and Embase search under Appendix 13.1 and search strategy used for PubMed under Appendix 13.2.

A local literature search was performed for the journals which were not indexed in Medline or Embase using product names as key search terms for the review period 18 Jun 2023 to 17 Dec 2023. Please find the journal list under Appendix 13.3.

During the reporting period, there were a total of 30,182 abstracts retrieved and upon removal of duplicates, 11,532 abstracts reviewed from the global searches. There were 9,793 local journal searches performed and 321 abstracts were reviewed. From all the searches performed, there were no articles identified with any new relevant safety information.

12. OTHER PERIODIC REPORTS

No other PBRERs have been written for Marketed Moderna vaccines targeting SARS-CoV-2.

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 Marketed Moderna vaccines targeting SARS-CoV-2. Following initial review of available data, a determination is made based on 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 [EVDAS], Vaccine AEs 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 analysis), signals of disproportionate reporting from regulatory databases (e.g., EVDAS, VAERs), published literature that involves targeted keyword searches in widely recognized databases (i.e., Medline, Embase and PubMed), 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 12.2.

During the reporting period of this PBRER, 5 signals were closed as refuted by the MAH, and 1 signal was closed as important potential risk. The list of closed signals as of DLP of this report is presented in Table 15-1 below and detailed summary tabulation of all signals is included in Appendix 5.1.

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 flare-up	EMEA/H/C/PSUSA/00010897/202112 Swissmedic request	Closed	Refuted	PBRER#5 PBRER#6 MSSR#22
Sensorineural hearing loss	TGA request	Closed	Refuted	PBRER#5 PBRER#6 MSSR#24
Breast swelling*	TGA request	Closed	Refuted	PBRER#6 MSSR#27
Mastitis*	TGA request	Closed	Refuted	PBRER#6 MSSR#24
Overdose in children in the context of overfill of the SDV indicated for individuals 6 months through 11 years of age in the US	ModernaTx, Inc internal signal detection activities	Closed	Substantiated	PBRER#6 MSSR#29
Postmenopausal haemorrhage	PRAC (EPITT No. 20015)	Closed	Refuted	PBRER#6 MSSR#30

*For Breast swelling and Mastitis, a single SER has been appended and evaluated together in Section 16.2, however while counting signals and the data to be considered in Appendix 5, individual signals are counted.

15.2 Requests from Health Authorities or regulatory bodies

15.2.1 Autoimmune hepatitis

Following the review of PBRER#5, a request from a health authority was received to provide a cumulative review of autoimmune hepatitis (AIH) with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran exposure in the next PSUR.

Source of the AIH Review:

A Health Authority requested the following information on AIH as part of the final assessment report of PBRER #5:

- The MAH is requested to provide a cumulative review of AIH with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran exposure in the next PSUR.
- Information from all relevant data sources including the literature, spontaneous case reports, randomised clinical trials (RCTs) and non-interventional studies should be considered.
- The MAH should also present and evaluate the literature case reports and observational studies related to elasomeran mentioned in the article by Uzun (PSUR page 7,558) [9].
- The MAH should ensure that all cases of autoimmune hepatitis are included and therefore any MedDRA PT which could possibly overlap with AIH (i.e., acute hepatic failure, drug-induced liver injury, hepatitis acute, hepatitis fulminant, immune-mediated hepatic disorder and immune-mediated hepatitis) should be checked.
- The MAH should perform a causality assessment of all retrieved cases preferably using the WHO-UMC causality assessment criteria and provide a justification for the chosen causality category.
- Cases assessed by the MAH as "possible", "probable" or "certain" and all cases with positive re-challenge should be presented and discussed. Case narratives should be provided in an appendix. Eudravigilance case numbers should be provided when available.
- The MAH should also evaluate retrieved cases using the simplified diagnostic criteria of the International AIH Group and present the cases according to the score they achieve by this set of criteria. However, otherwise well-documented cases that are not evaluated as

"definite" or "probable" cases of AIH according to these criteria should also be presented and discussed.

- Furthermore, the cumulative review should include a discussion of the potential mechanism of action.
- If the MAH considers an update of the product information warranted, a wording and frequency for inclusion in the SmPC and package leaflet should be proposed with presentation of the used method for calculation of frequency.

Background of Information:

Autoimmune Hepatitis is a non-resolving chronic liver disease that affects mainly women and is characterized by hypergammaglobulinaemia even in the absence of cirrhosis, circulating autoantibodies, association with human leukocyte antigens (HLA) DR3 or DR4, interface hepatitis on liver histology, and a favourable response to immunosuppression (e.g., with corticosteroids). The disease, if untreated, often leads to cirrhosis, liver failure and death. It is well established that AIH is a clinically distinct syndrome characterized by a large heterogeneity of clinical, laboratory and histological manifestations. Therefore, AIH should be considered in any patient with acute or chronic liver disease, particularly if hypergammaglobulinemia is present, and if the patient has features of other autoimmune diseases. The disease also affects males (25–30% of all AIH patients) and may present at any age and in all ethnic groups. In most studies, a bimodal age pattern at presentation has been reported with one peak during childhood/teenage years and another in middle age between the 4th and 6th decade of life. Recent studies have shown that an increasing number of patients are diagnosed also at older ages (above 65 years). Recently it has been shown that appropriate attention should also be paid to the health-related quality of life (HRQoL) parameters, since a high rate of previously unrecognised mental impairment with depression and anxiety symptoms are present in patients with AIH. Manifestations were reported in 31% cases at diagnosis.

The diagnosis of AIH is usually based on the presence of the typical phenotype of the disease along with the exclusion of other causes of chronic liver diseases. The diagnostic criteria for AIH and a diagnostic scoring system have been codified by a group of experts in the IAIHG in 1993, revised in 1999 and more recently proposed in a simplified manner for routine clinical use.

According to the PRAC final assessment report (**Procedure no.: EMEA/H/C/PSUSA/00010897/202206**) (Reporting Period 01 Jan 2022 to 18 Jun 2022) the following conclusions were discussed:

"*As of 18 Jun 2022, there has cumulatively been 10 reported cases classified as "definitive" or "probable" cases of AIH according to the European Association for the Study of the Liver (EASL) guidelines, while 201 cases were categorized as not cases of AIH according to the Simplified Classification Guidelines or that were unassessable based on missing information.*

The reporting rate of AIH is low being 0.01 per million doses administered, and there is not sufficient data to indicate a causal association between AIH and Elasomeran despite any temporal association. No new safety issue of concern was identified. AIH-related events are not presently a safety issue of concern, and the MAH will continue to evaluate events of "AIH-related events" using routine surveillance, which is supported."

Methods:

The Company clinical database and the GSDB were queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 Dec 2020 to 17 Dec 2023, worldwide, reported for the mRNA-1273 vaccine (ModernaTx, Inc COVID-19 vaccine) using the following PTs: "*Autoimmune Hepatitis, Alloimmune hepatitis, Immune-mediated hepatitis, Immune-mediated hepatic disorder, Liver injury, Drug-induced liver injury, Hepatitis acute, Hepatitis toxic, Hepatocellular injury, Hepatitis fulminant, Hepatotoxicity, Acute hepatic failure, and Hepatic failure*". The CT data is from the 3 adult CTs (mRNA-1273-P301, mRNA-1273-P205 and mRNA-1273-P205).

All retrieved cases were classified into two categories, following the Simplified diagnostic criteria of the International AIH Group: Definite AIH and not an AIH case (Table 15-2).

Case of AIH:

- Definite autoimmune hepatitis: 7 Points or more
- Probable autoimmune hepatitis: 6 Points

Not a Case of AIH: Those cases for which there were insufficient information to provide a diagnostic classification were classified as "Unassessable".

Table 15-2 Simplified diagnostic criteria of the International Autoimmune Hepatitis Group

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1*
ANA or SMA+	≥1:80	+2*
or LKM+	≥1:40	+2*
or SLA/LP+	Any titer	+2*
IgG or γ-globulins level	>upper limit of normal >1.1x upper limit	+1 +2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical of AIH Atypical	+1 +2 0
Absence of viral hepatitis	No Yes	0 +2

ANA= antinuclear antibodies SMA= smooth muscle antibodies LKM= liver kidney microsomal antibodies
SLA= soluble liver antigens LP= liver pancreas
Addition of points achieved for all autoantibodies (maximum, two points).
Typical liver histology for AIH = each of the following features had to be present namely, interface hepatitis, lymphocytic/lymphoplasmacytic infiltrates in portal tracts and extending into the lobule, emperipolesis (active penetration by one cell into and through a larger cell), and hepatic rosette formation.
Compatible liver histology for AIH = chronic hepatitis with lymphocytic infiltration without all the features considered typical.
Atypical = showing signs of another diagnosis, like steatohepatitis.

For those cases classified as definite and probable AIH, the Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

It is important to note that the MAH has conducted previous cumulative reviews of AIH as per request from a health authority from 18 Dec 2020 to 02 Feb 2022 (SPIKEVAX EPITT ref. No. 19,750), as well as in PBRER # 3 (Reporting Period 01 Jan 2022 to 18 Jun 2022).

The signal of AIH was triggered from PRAC signal assessment report (EPITT 19750) (dated 02 Dec 2021), based on the available evidence from case reports published in the literature and submitted to Eudravigilance (EV). Following assessment based on the review of all available sources, no cases of AIH were reported in the CT setting. Analysis from the Company global safety database retrieved 165 cases, 11 cases (7%) were suggestive of AIH, and of these, 8 cases were considered as related (including cases where only temporal association with elasomeran was reported). No disproportionate reporting of AIH was found in EVDAS or VAERS. The O/E analysis for PT AID did not provide observed counts higher-than-expected. In age-stratified O/E analysis interpretability of data was limited due to small numbers. Several articles described AIH and mRNA vaccine, but none showed a direct temporal association with mRNA vaccines against COVID-19 disease. No plausible pathognomonic findings were found to support a possible causal

association between the administration of elasomeran and the occurrence of AIH. In conclusion MAH considered AIH in association with elasomeran as refuted.

Review of Data from All Sources:

Clinical Trial Data:

The topic of AIH was cumulatively reviewed in the Company clinical database from 3 adult CTs to identify unsolicited events (serious and non-serious), reported using the following MedDRA PT "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury".

The review performed in mRNA-1273-P301 (as of 04 May 2021); for mRNA-1273.222-P205-Part H (as of 23 Sep 2023), and mRNA-1273.815-P205- Part J (as of 25 May 2023), did not retrieve any cases for AIH related terms.

Review of the Global Safety Database

The MAH queried the GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature as of 17 Dec 2023, for Marketed Moderna vaccines targeting SARS-CoV-2 and SPIKEVAX (NOS) for cases of AIH including the MedDRA PTs: "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury" (see Appendix 12.8).

Of note, throughout the document for simplicity reasons AIH is used in text or tables to describe the entire topic; it is inclusive of all the PTs from the search strategy i.e., "Acute hepatic failure, Autoimmune hepatitis, Drug-induced liver injury, Hepatic failure, Hepatitis acute, Hepatitis fulminant, Hepatitis toxic, Hepatocellular injury, Hepatotoxicity, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Liver injury".

Results

Cumulatively, through 17 Dec 2023, the MAH received 315 cases (327 events) of AIH related PTs involving Moderna vaccines targeting SARS-CoV-2, of which 306 cases (317 events) involved elasomeran, six (6) cases involved elasomeran/imelasomeran, one (1) case involved elasomeran/davesomeran, and two (2) cases involved andusomeran. There were no cases of AIH reported for SPIKEVAX (NOS). There were 310 serious cases, and 232 cases were medically confirmed. There were 30 cases with a fatal outcome. A total of 133 cases (42.2%) involved males

and 177 cases (56.2%) involved females and 5 (1.6%) cases missing gender. The mean age was 54.7 (SD: 17.9), with a median 56.0 years (range 0.0 to 96.0 years). Most of the events reported had an outcome of recovered/ recovering (121; 37.0%).

During the initial cumulative review of AIH as of 31 Dec 2021, a total of 165 cases (171 events) of AIH-related terms were retrieved, with 138 (74.3%) cases medically confirmed. Out of those, 163 were serious cases with 22 cases with a fatal outcome. The majority of the reports were in females 96 (58.2%) and in patients >50 years of age. Same demographic information as during this second updated cumulative review. Information on these cases and its initial evaluation is included in Appendix 12.8.

During this updated review of AIH (01 Jan 2022 to 17 Dec 2023), there were 152 cases (156 events) of AIH-related terms retrieved, with 94 (61.8%) cases medically confirmed. Out of those, 147 were serious cases with 8 cases with a fatal outcome. During this updated review there were no important differences between males (77; 50.56%) and females (81; 53.3%). Mean reporting age was 54.7 years. Information on these cases and its evaluation is included in Appendix 12.8.

Cases Classification by the Simplified diagnostic criteria of the International AIH Group

1. Cumulative review as of 31 Dec 2021

Out of the 165 case reports identified in the first cumulative evaluation, there were two cases that were considered duplicate and one case report that was miscoded ([redacted] was a cases of myocarditis injury that was mistakenly coded to liver injury).

After evaluation of the 165 cases, there were 155 cases that were classified as not cases of AIH or that were unassessable, based on missing information including clinical course, laboratory data, dose and/or TTO. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history not reported, as well as concomitant medications. Of the 165 cases there was a follow-up information reported on two cases [redacted] and [redacted] rest of the cases, there is no change or updated information as of 17 Dec 2023.

There were 7 case reports that were considered confirmed AIH according to the EASL Simplified diagnostic criteria. All those reports were considered possible according to the WHO causality assessment by the MAH. Two reports were considered probable by the PRAC assessor. As mentioned above, the following case [redacted] had follow-up information and upon

internal review, it was identified that the case [redacted] is duplicate of original case [redacted]. All the information from case [redacted] has been incorporated into case [redacted] Another case [redacted] which was assessed as not an AIH case in the initial review was assessed as AIH case due to follow-up information. both these cases are reviewed and commented in the updated review. Information on all these 163 cases is included in Appendix 12.8.

2. Updated review as of 17 Dec 2023

Out of the 152 new reports of AIH-related events identified during this updated review, there were 141 cases that were classified as not cases of AIH or that were unassessable, based on missing information including clinical course, laboratory data, dose and/or TTO. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history not reported, as well as concomitant medications.

Review of AIH Exacerbations

During the updated cumulative review, there were 5 cases [redacted] and [redacted] in which it was reported as having previous history of AIH or related- liver conditions (including HBV) that may have been considered as indicators of a possible pre-existing asymptomatic AIH. It has been reported that classical AIH takes an asymptomatic subclinical course in about half of cases [10].

Review of WHO Probable and Possible Cases:

During this updated review of cases with AIH-related events, there were 11 cases that were considered confirmed AIH according to the EASL Simplified diagnostic criteria. According to the WHO causality assessment, there were seven cases considered "Possible", and 4 cases considered "Unlikely" related to vaccination (Note: one case [redacted] was re-assessed as AIH case from previous assessment due to the follow-up case details and another case [redacted] had merged data from case [redacted]. Information on all these 163 cases is included in Appendix 12.8.

Review of the 11 cases demonstrates that most are heavily confounded by the presence of multiple confounding factors such as, medical history, concurrent medications, drug hypersensitivity and underlying diseases, and pre-existing conditions making it difficult to establish a causal association. Additionally, several cases involved patients taking medications such as statins,

hormonal therapies, and pain relievers like ibuprofen and paracetamol. These medications have known hepatotoxic potential and are important confounders for an appropriate causality assessment. Details of these cases are presented in Appendix 12.8.

Literature Review

Literature search review:

A focused cumulative search of published literature was conducted in PubMed, from 18 Dec 2020 through 17 Dec 2023. A total of 278 articles (See Appendix 13.4 for search criteria) were retrieved.

Review of the 278 articles did not show any causal association between elasomeran vaccination and AIH. These articles encompassed different types of studies, including case reports (31), observational studies (7), and others were general literature reviews on importance of vaccination or other general AIH topic. There are not pathognomonic findings to link vaccine to these AIH adverse events.

Among these articles, the following article Uzun et al [9], was summarized in detailed as requested by health agency. There were six individual cases created based on this article [redacted]; and [redacted] of these 6 cases 4 were considered as a true case of AIH and two case was categorized as not a case of AIH. All these cases were described in PBRER#5 and there are no changes from earlier assessment of this article.

Probable Mechanism(s) for Vaccine-associated AIH

During this updated cumulative review of AIH, no new information was identified related to probable mechanism associated with the reported cases of AIH after COVID-19 vaccination. Several hypotheses have been presented in several articles reporting cases of patients with AIH following COVID-19 mRNA vaccination. Among these it is postulated that COVID-19 mRNA vaccination, through activation of the innate immune system and subsequent non-specific activation of autoreactive lymphocytes, may lead to the development of autoimmune diseases including AIH or trigger a drug-induced liver injury with features of AIH [11]. The trigger, if any, may become more apparent over time, especially following withdrawal of immunosuppression.

Other authors have suggested that given that the COVID-19 mRNA vaccines lacks immune adjuvants, genetic susceptibility, exposure to foreign peptides homologous to human peptides (molecular mimicry), and immune system stimulation by vaccine adjuvant may not be part of the problem, but the homology between the SARS-CoV-2 spike protein and soluble liver antigen may

be a clue: i) similar native or glycosylated amino acid epitopes shared between the protein expressed in the host after vaccination and soluble liver antigen, and ii) structural similarities between the proteins. It is also possible that other liver autoantigens (different from SLA) share sequence homology with the protein expressed by the host after SARS-CoV-2 vaccination with mRNA vaccines. In other words, the mechanism for the development of AIH is still not well understood. AIH has also been reported following immunization with other vaccines (not directed against SARS-CoV2, e.g., seasonal influenza, HPV). Causative mechanisms are similarly unclear for these cases. None of the hypotheses presented in the literature provide a clear mechanism for Vaccine-associated AIH.

Discussion

An updated cumulative search of GSDB as of 01 Jan 2022 to 17 Dec 2023, was performed. The search retrieved additional 152 cases (156 events) for a cumulative total of reported cases from 18 Dec 2020 to 17 Dec 2023 of 315 cases (327 events). After evaluation of all these cases, there were 297 cases that were classified as not cases of AIH based on missing information including clinical course, laboratory data, dose and/or TTO. Most of these cases report transaminases elevation, not always with values, and no clinical description explaining the reported PTs (hepatitis, hepatic failure), medical history is not reported, as well as concomitant medications. There were 18 cases confirmed as AIH according to the EASL Simplified diagnostic criteria.

For all reports identified cumulative, there were more women (177; 56.2%) than men (133; 42.2%) which is what have been described in the general population where AIH preferentially affects women more than men by a ratio of 3.6/1.05 [12]. As of 17 Dec2023, there have been 1,776,284,733 doses of elasomeran distributed worldwide, with 1,043,567,281 doses that are estimated to have been administered.

Based on the cumulative identification of 18 reported cases classified as confirmed cases of AIH, the reporting rate of AIH after administration of elasomeran is 0.02 per million doses administered.

No unique or novel risk factors were identified from this aggregate sample. Insufficient information was present in the literature to suggest a relationship between elasomeran administration and the event of AIH. Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of AIH to be consistent with the known safety profile of Moderna vaccines targeting SARS-CoV-2 and the benefits of vaccination far outweigh any possible vaccine-associated risks, including the risks of AIH. Based on this information the MAH does not consider necessary at this time that an update of the product information is warranted.

Conclusion

Overall, based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers that cases included under AIH, are heavily confounded, have alternative reasons for the reported events, and do not provide sufficient information to establish a causal relationship to the administration of any marketed Moderna vaccines targeting SARS-CoV-2. No new safety issue of concern was identified that would differ from the known safety profile of Moderna vaccines targeting SARS-CoV-2. The available data does not warrant an update to the product information. The benefit-risk evaluation remains positive.

15.3 Other Safety Topics

15.3.1 Postural orthostatic tachycardia syndrome (POTS)

Table 15-3 Postural orthostatic tachycardia syndrome

Source of New Information	• Moderna GSDB • Evaluation of cases of POTS is presented in this PBRER, cumulative as of 17 Dec 2023, given that the observed number of cases was higher than the expected number of cases. In the observed to expected analyses, the lower bound of 95% CI of rate ratio was > 1 for the 50-64 years subgroup. These were based on 2 case reports observed in this subgroup for the interval period. • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 25 articles o New and Significant Safety Information: None (0)
Background	Postural orthostatic tachycardia syndrome is a chronic and often disabling disorder characterized by orthostatic intolerance with excessive heart rate increase without hypotension during upright posture. Patients often experience a constellation of other typical symptoms including fatigue, exercise intolerance and gastrointestinal distress. A typical patient with POTS is a female of child-bearing age, who often first displays symptoms in adolescence. The onset of POTS may be precipitated by immunological stressors such as a viral infection. A variety of pathophysiologies are involved in the abnormal postural tachycardia response; however, the pathophysiology of the syndrome is incompletely understood and undoubtedly multifaceted [13]. The prevalence of POTS is based largely on clinical experience, ranging from 0.2% and 1% of the US population, which would suggest approximately 1–3 million affected persons [14-16]. Most patients present with POTS between the ages of 12 to 50 years old and more than 75% are female (F:M ratio > 4:1). POTS is also common in patients with

	chronic fatigue syndrome [16]. The cause of this condition remains unclear. Although there is a consensus clinical definition for POTS, misdiagnosis is common. The syndrome is heterogeneous in the sense that the spectrum of clinical features varies among patients, multiple etiologies may produce similar clinical phenotype and there is overlap with other clinically defined syndromes. The clinical evaluation of patients with suspected POTS is not standardized, nor are treatment approaches. There is a lack of familiarity with POTS in the medical community, and the epidemiology of the disorder and natural history are not known [17]. According to Sheldon et al., POTS is a clinical syndrome usually characterized by (1) frequent symptoms that occur with standing, such as light-headedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue; (2) an increase in heart rate of ≥30 beats per minute (bpm) when moving from a recumbent to a standing position (or ≥40 bpm in individuals 12 to 19 years of age); and (3) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure). The symptoms associated with POTS are those that occur with standing, such as light-headedness and palpitations; not associated with particular postures, such as bloating, nausea, diarrhoea, and abdominal pain; and systemic, such as fatigue, sleep disturbance, and migraine headaches. The standing (or orthostatic) heart rate of individuals with POTS is often ≥120 bpm and undergoes greater increases in the morning than in the evening. The increases in orthostatic heart rate gradually decrease with age and not abruptly at age 20. Many patients with POTS faint occasionally, although presyncope is much more common. It is important to note that the diagnoses of POTS and vasovagal syncope are not mutually exclusive. In addition, POTS has been found to overlap with or occur in certain conditions such as migraine, hypermobile Ehlers-Danlos syndrome (hEDS), mast cell activation syndrome (MCAS) or chronic fatigue syndrome (CFS), inappropriate tachycardia syndrome and some other forms of orthostatic intolerance such as neurocardiogenic syncope [18]. Amyloidosis, Sjogren's syndrome, multiple sclerosis, mast cell activation disorders and hypermobility syndrome (Ehlers-Danlos syndrome type III) are other diseases associated with or thought to cause POTS. This subset of POTS patients commonly reports episodes of flushing, urticaria, dyspnoea, headache, excessive diuresis, and gastrointestinal symptoms such as diarrhoea, nausea, and vomiting, which may be accompanied by elevated urine methylhistamine or 11-ß-Prostaglandin F2 excretion or elevation of other mast cell mediators [19]. Some researchers have suggested that there is a neuropathic basis underlying at least half of patients with POTS and found that about 1:7 of patients studied had ganglionic acetylcholine receptor antibodies suggesting an autoimmune etiology for this proportion of patients with POTS. Several mechanisms have been described in patients with POTS, including autonomic denervation, hypovolemia, hyperadrenergic stimulation, deconditioning, and hypervigilance, which is a careful and at times unusual focus on bodily sensations. These mechanisms often appear to co-exist in patients with POTS.

	The onset of POTS may be precipitated by a typical immunological stressor such as viral syndrome (often upper respiratory or gastrointestinal and for example, with Epstein–Barr virus (EBV)), physical trauma (such as concussion), menarche, pregnancy, or surgery and autoimmunity as with paraneoplastic conditions in small cell lung and pancreatic cancers as well as with autoimmune autonomic neuropathy. An antecedent history of suspected viral infection is reported in 20–50% of patients [20]. The presentation seems to have two patterns – acute onset after one of the above triggers or with slowly progressive symptoms over a longer period of time [21]. Significant symptomatic recovery has been reported by a subset of patients, but a majority report chronic symptoms with recurrent exacerbations. POTS is now known as one of many possible features of post-acute COVID-19 syndromes that can develop after SARS-CoV-2 infection. While the acute impacts of COVID-19 were the initial focus of concern, it is becoming clear that in the wake of COVID-19, many patients are developing chronic symptoms that have been called Long-COVID. Some of the symptoms and signs include those of POTS [22]. Commonly described symptoms of Long-COVID include some combination of breathlessness, palpitation, chest discomfort, fatigue, pain, cognitive impairment ("brain fog"), sleep disturbance, orthostatic intolerance, peripheral neuropathy symptoms (pins and needles, and numbness), abdominal discomfort, nausea, diarrhea, joint and muscle pains, symptoms of anxiety or depression, skin rashes, sore throat, headache, earache, and tinnitus. These symptoms, when combined with excessive orthostatic tachycardia, can lead to a diagnosis of POTS post-COVID-19 [22]. The UK National Institute for Health and Care Excellence (NICE) has defined various symptomatic phases of COVID-19 [23]. These include: • "Acute COVID-19" which includes signs and symptoms up to 4 weeks following onset of illness. • "Ongoing symptomatic COVID-19" for signs and symptoms of COVID-19 from 4 to 12 weeks after the onset of illness • "Post-COVID-19 syndrome" for signs and symptoms that develop during or after an infection consistent with COVID-19, continue for > 12 weeks and are not explained by an alternative diagnosis. • "Long-COVID" that includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Given that SARS-CoV-2 infection can trigger POTS and other cardiovascular dysautonomia's, it has been hypothesized that COVID-19 infection might be a potent immune trigger that evokes an autoimmune response in susceptible individuals [24]. The post-COVID-19 cardiovascular autonomic dysfunction can affect global circulatory control, producing not only a POTS-like pattern but also tachycardia at rest, blood pressure instability with both hypotension and hypertension, and local circulatory disorders such as migraine, coronary

	microvascular dysfunction, or Raynaud-like symptoms. Microvascular dysfunction with inadequate regional microvascular and macrovascular responses, such as vasospasm and circulatory mismatch between local oxygen demands and supply, and venous retention leading to pooling and reduced venous return after standing, might explain the plethora of symptoms that are frequently observed in POTS. There are sparse reports suggesting that microvascular dysfunction is an important mechanism of post-COVID-19 complications. All these dysautonomic phenotypes might coexist, and, more importantly, they preferentially affect young and middle-aged women, possibly suggesting a genetic predisposition and/or a mechanistic role for sex hormones. Of note, POTS is extremely rare among either prepubertal girls or postmenopausal women. There have been reports of POTS in the medical literature, from Japan, Korea, and the US, about new onset POTS in previously healthy people who had recently received a messenger RNA (mRNA) COVID-19 vaccine. A large cohort study [25] identified a possible association between COVID-19 vaccination and POTS as well as a much stronger link between SARS-CoV-2 infection and POTS. Kwan AC et al. used a retrospective cohort of patients 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 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 authors found the post-Dose 1 odds of new POTS -associated diagnoses (1.33, 95% CI=1.25–1.41) was slightly higher than for CPC diagnoses (OR=1.21, 95% CI=1.18–1.23) in the vaccinated cohort, and post-infection odds 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. Although this single medical center study identified a slightly elevated risk of receiving a POTS diagnosis after COVID-19 vaccination, the interpretation of the results requires caution given the following limitations, and additional studies are required to verify the association as the authors recommended. First, the primary analysis was restricted to vaccinated persons and consequently may have had bias away from the null because people who experienced POTS may have delayed or may not have received a COVID-19 vaccine, violating a key assumption of the SSA analytic methodology (i.e., the event of interest [POTS] does not alter the probability of subsequent exposure [vaccination]). No distribution of POTS diagnoses pre- and post-vaccination was 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, the authors acknowledged that "the lack of a standard single ICD code for capturing a formal diagnosis of POTS can lead to overlap with other medical conditions and variation in the application of available ICD codes". Moreover, 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 ICD codes". The degree of misclassification pre- and post-vaccination may not necessarily be non-differential because diagnostic vigilance of POTS may be intensified after vaccination, biasing the association away from the null; moreover, symptoms associated with common vaccine reactogenicity such as fever and fatigue might lead to patient complaints that overlap some POTS criteria. 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 that occurred pre and post vaccination. Fourth, diagnosis of POTS, as noted above, requires a three-month duration of symptoms; however, the authors did not confirm this important temporal aspect, relying instead on ICD codes that are not specific for POTS and may only represent acute diagnoses. In summary, POTS is a chronic multi-system disorder involving the autonomic nervous system that is characterized by an exaggerated sinus tachycardia, and symptoms upon standing. POTS primarily affects females starting around puberty and through their child-bearing age and is associated with significant functional disability, such as decreased ability to participate in education, limited ability to work and generate an income, and decreased quality of life. The pathophysiology is incompletely understood, which is likely responsible for limited data on effective treatments. Postural tachycardia syndrome cases associated with COVID-19 infection have been reported, as well as cases occurring after COVID-19 vaccination.
Methods of Evaluation	The ModernaTx, Inc. GSDB was queried cumulatively to 17 Dec 2023 for valid case reports received from HCPs, HAs, consumers, and literature worldwide, for marketed Moderna vaccines targeting SARS-CoV-2 using the MedDRA PT of "Postural orthostatic tachycardia syndrome". Identified cases were evaluated according to the latest case definition presented by Vernino et al [13] as part of the National Institute of Health Expert Consensus meeting of 2019, based on the different previous definitions by major international neurologic, autonomic, cardiac and pediatric societies [16,22,26] as requiring: • **Confirmed**:

	○ A sustained HR increment of not less than 30 beats/minute within 10 min of standing or head-up tilt. For individuals who are 12 to 19 years old, the required HR increment is at least 40 beats/minute; **and** ○ An absence of orthostatic hypotension (i.e., no sustained systolic blood pressure drop of 20 mm Hg or more); **and** ○ Frequent symptoms of orthostatic intolerance during standing, with rapid improvement upon return to a supine position. Symptoms may include light-headedness, palpitations, tremulousness, generalized weakness, blurred vision, and fatigue; and ○ Duration of symptoms for at least 3 months; **and** ○ Absence of other conditions explaining sinus tachycardia such as anorexia nervosa, primary anxiety disorders, hyperventilation, anaemia, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, use of cardioactive drugs (e.g., sympathomimetics, anticholinergics) or severe deconditioning caused by prolonged bed rest. • **Unassessable**: A reported event of POTS with insufficient evidence to meet the case definition. • **Not a Case**: Alternative diagnosis for the described events. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

Results:

Refer to Appendix 12.9 for additional information, on case evaluations, and assessments.

During the reporting period, a total of 22 cases (21 serious, 5 medically confirmed), with 22 events (17 serious) with the reported term of POTS have been received for marketed Moderna vaccines targeting SARS-CoV-2. No case report noted a fatal outcome. The majority of cases were reported in females (15 cases; 68.2%) compared to males (7 cases; 31.8 %). The mean patient age was 35.1 years of age (SD: 10.4) and median age of 35.0 years of age (range: 22.0 to 61.0 years). Of note, 4 cases (18.2%) did not provide information on age. The majority of the events (13; 59.1%) did not report sufficient information to determine dose number, and 9 events (40.9%) did not report TTO.

Case Evaluation was performed according to the case definition described above in the Methods of Evaluation section. Causality assessment was conducted based on the WHO-UMC causality assessment.

Out of the 22 cases reported:

- Elasomeran (20 cases):

- One case reported in literature described a non-serious event of POTS in a 32-year-old female patient in the post-acute/long COVID-19 setting. The initial symptoms of POTS reportedly appeared 3-months after she had received her 2nd dose of elasomeran, following a concurrent severe COVID-19 infection requiring hospitalisation. It was reported that the symptoms worsened three months later following a recurrence of another episode of severe COVID-19 infection requiring another hospitalisation. The patient was treated with propranolol, event outcome was unknown. Patient's medical history is unknown. The authors postulated "Long COVID" to be related to a virus- or immune-mediated disruption of the autonomic nervous system resulting in orthostatic intolerance syndromes. The causality was deemed as unlikely in this case as a long latency was noted and the concurrent severe COVID-19 infection provided a more likely explanation for the reported POTS event.
- There was one case involving a potential flare-up of pre-existing POTS which occurred >12 months after receiving elasomeran. The patient had a concurrent relevant medical condition of CFS and was noted to be on prolong bed rest (>15 months), which together provide a more plausible explanation of the reported event of POTS. Accordingly, the WHO-UMC causality was assessed as unlikely.
- The remaining 18 cases were deemed unassessable as these lacked vital information including: detailed clinical course of events including relevant signs/symptoms for the reported condition of POTS, any supportive testing (laboratory or diagnostic) conducted to establish the diagnosis of POTS, patients' medical history and in some instances the COVID-19 vaccine dose number and the TTO of the POTS event in relation to elasomeran administration (latency), important to establish causal association with the vaccine.

- Elasomeran/imelasomeran (2 cases)
  - There were 2 reports, one involving a potential flare-up of pre-existing POTS, for both cases the causality was unassessable, as these contained insufficient information for a complete assessment (lacking vital information on the clinical course of events, latency, dose numbers, details of any supportive diagnostic investigations and any treatment given for POTS including the event outcome).

No cases with the reported term of POTS were received for elasomeran/davesomeran and andusomeran during the interval period.

Discussion

Evaluation of cases of reported POTS is presented, given that the observed number of cases were higher than the expected number of cases. In the observed to expected analyzes, the lower bound of the 95% CI of the rate ratio was > 1 for the 50-64 years subgroup. These were based on 2 case reports observed in this subgroup for the interval period.

During the reporting period, there were a total of 22 cases reports with the reported term of POTS for individuals that had been vaccinated with one or more doses of elasomeran (20 cases; 90.9%) and elasomeran/imelasomeran (2 cases; 9.1%). No cases were reported for elasomeran/davesomeran and andusomeran for the interval period. Overall, no new significant safety information was identified following a review of these cases for marketed Moderna vaccines targeting SARS-CoV-2.

As evident from published literature, POTS has been found to overlap with or occur in certain conditions such as migraine, hypermobile Ehlers-Danlos syndrome, MCAS or CFS, inappropriate tachycardia syndrome and some other forms of orthostatic intolerance such as neurocardiogenic syncope. In addition, the onset of POTS may be precipitated by a typical immunological stressor such as viral syndrome (often upper respiratory or gastrointestinal and for example, with EBV), physical trauma (such as concussion), menarche, haemorrhage, pregnancy, or surgery, prolong bed rest and autoimmunity as with paraneoplastic conditions in small cell lung and pancreatic cancers as well as with autoimmune autonomic neuropathy. Commonly described symptoms of Long-COVID include some combination of breathlessness, palpitation, chest discomfort, fatigue, pain, cognitive impairment ("brain fog"), sleep disturbance, orthostatic intolerance, peripheral neuropathy symptoms (pins and needles, and numbness), abdominal discomfort, nausea, diarrhea, joint and muscle pains, symptoms of anxiety or depression, skin rashes, sore throat, headache, earache, and tinnitus. These symptoms, when combined with excessive orthostatic tachycardia, can lead to a diagnosis of POTS post-COVID-19.

Cumulatively, based on the total number of doses administered, estimated (as of 17 Dec 2023), the reporting rates for cases reported as POTS in the GSDB per million doses administered of elasomeran is 0.2 cases; for elasomeran/imelasomeran is 0.07 cases and elasomeran/davesomeran is 0.01 cases. There have been no cases reported for andusomeran. There have been no reports with a fatal outcome.

Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported POTS event, no consistent or independent risk factors

were identified in any of the cases that could support a causal association with administration of marketed Moderna vaccines targeting SARS-CoV-2.

The MAH reviewed two articles concerning POTS and COVID-19 vaccination as per request from a health authority [27,28]. Review of the Tv P. et al article showed that this meta-analysis does not provide robust data nor adequate information on the possible association of COVID-19 vaccines and POTS, including as an important limitation the lack of original research data, but rather a summary of existing (published) literature and therefore no new information is provided. Similarly, the article postulates to reports of POTS following the HPV and Influenza (H1N1) vaccinations, probably attributable to a similar pathogenetic mechanism, however, the currently approved EU- labels for these vaccines do not contain the ADR of POTS (SmPCs Section 4.8 for Gardasil 9 and the Quadrivalent Influenza Vaccine (split virion, inactivated)), consequently these do not constitute as substantive evidence.

The article by Gomez-Moyano et al [28], is a meta-analysis that provides a review of POTS and related dysautonomic disorders following SARS-Cov-2 infection and COVID-19 mRNA vaccination and covers the general overview regarding the etiopathogenic basis, epidemiology, clinical manifestations, diagnosis, treatment, prognosis, and socioeconomic impact of the SARS-CoV-2 disease. The authors concluded that the potential for POTS following vaccination appears to be weaker than with the COVID-19 infection itself and that further research is needed.

Overall, the MAH do not consider that the above literature article provides any new significant safety information for the topic of POTS with elasomeran use. The benefit-risk profile of elasomeran continues to remain unchanged.

Conclusion

Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2. Information presented in those reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important safety information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of POTS, reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any new safety issue of concern and the information provided does not support evidence of causality

between marketed Moderna vaccines targeting SARS-CoV-2 exposure. The MAH will continue to monitor events for POTS events using routine pharmacovigilance. The benefit-risk evaluation remains positive.

16. SIGNAL AND RISK EVALUATION

16.1 Summary of Safety Concerns

Table 16-1 provides the Summary of Safety Concerns as per RMP v6.5 approved on 26 May 2023 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 v6.5 approved on 26 May 2023)

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., COPD, diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders.

During the reporting period, the following changes were made to the RMP:

- SPIKEVAX RMP v6.5 was updated to v6.6 and v6.7 (endorsed on 20 Jul 2023) with no additional changes to the list of safety concerns.
- Additionally, v6.3 was updated to v7.0 (endorsed by PRAC on 06 Jul 2023 in procedure EMEA/H/C/PSUSA/00010897/202212) to update the list of safety concerns by removing "VAED including VAERD" as an important potential risk, and "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.

- Also, v7.0 was updated to include mRNA-1273-P910 for pericarditis and study details for mRNA-1273-P901, mRNA-1273-P910 and mRNA-1273-P919 in Part II.C.2 as per Part III update. Of note, a consolidated SPIKEVAX EU RMP v7.1 including all versions endorsed/approved by PRAC/CHMP (v6.5, 6.7 and 7.0) received positive opinion by CHMP on 21 Jul 2023 and the opinion was adopted within procedure EMEA/H/C/005791/II/0104/G by European Commission on 11 Aug 2023.
- Further, RMP v7.0 was updated to v8.0 (endorsed on 16 Aug 2023) to add the INN SPIKEVAX XBB.1.5 (andusomeran) and indication for andusomeran with no further updates on safety concerns.
- Lastly, RMP v8.0 was updated to RMP V8.1 (CHMP favourable opinion received on 23 Oct 2023) to remove the Summary Safety Reports (SSRs) as a requirement for COVID-19 vaccine, core RMP19 guidance EMA/PRAC/709308/2022 and no further changes to list of safety concerns were made in this version.

Table 16-2 provides the Summary of Safety Concerns as per RMP v8.1 approved on 25 Sep 2023 valid at the end of the reporting period.

Table 16-2 Summary of Safety Concerns valid at the end of the reporting period (as per RMP v8.1 CHMP favorable opinion received on 23 Oct 2023)

Important identified risks	• Myocarditis • Pericarditis
Important potential risks	• None
Missing information	• Use in pregnancy and while breastfeeding • Long-term safety

Table 16-3 provides the Summary of the PSUR/PBRER list of Safety Concerns valid at the end of the reporting period.

Table 16-3 Summary of Safety Concerns for the PSUR/PBRER valid at the end of the reporting period

Important identified risks	• Anaphylaxis • Myocarditis • Pericarditis
Important potential risks	• IgA Nephropathy
Missing information	• Use in pregnancy and while breastfeeding

	• Long-term safety • Use in immunocompromised subjects • Use in frail subjects with unstable health conditions and co-morbidities (e.g. 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.

Six signals were closed by the MAH during the reporting period. Based on scientific evaluation of the available information, five closed signals were refuted [IgA nephropathy flare-up, Sensorineural hearing loss, Breast swelling, Mastitis, and Postmenopausal haemorrhage] and one signal restricted to the US and limited to the US EUA of ModernaTx, Inc COVID-19 vaccine (2023-2024 formula) for individuals 6 months through 11 years of age, of Overdose in children in the context of overfill of the SDV indicated for individuals 6 months through 11 years of age in the United States was confirmed as important potential risk by ModernaTx, Inc.

16.2.1 IgA nephropathy flare-up

Table 16-4 IgA nephropathy flare-up

Signal evaluation criteria	Summary
Source	The Swissmedic requested a signal analysis of Immunoglobulin-A-Nephropathy (IgAN) – Flare-Up. The signal was based on the publication Canney et. al. The MAH was requested to comment on the present signal, considering the following aspects and questions: • Current figures on a flare-up of glomerular disease associated with mRNA vaccination, both nationally and internationally. • Presentation and discussion of relevant case reports of a flare-up of glomerular disease from home and abroad, e.g., from the WHO database. • Presentation of current and relevant technical literature • Submission of any evaluation reports already available (in-house, external) • Any current status of this signal abroad. • Can you confirm the signal? • If so, what risk-minimizing measures do you propose? *Swissmedic Assessment / Considerations* Several reports [29,30] have described glomerular disease after 2019 coronavirus disease vaccination (COVID-19). Without adequate controls in these reports, assessment of a causal relationship is limited. In the population-based cohort of 1,105 adult patients [31]

Signal evaluation criteria	Summary
	with stable glomerular disease, the first dose of COVID-19 vaccine was not associated with risk of relapse; however, a subsequent dose of vaccine was associated with a 2-fold increase in risk of relapse. The increase in absolute risk associated with vaccination was small (1%-5%). These results represent the first accurate assessment of the relative and absolute risk of glomerular disease relapse associated with COVID-19 vaccination. In summary, there was no robust evidence for a causal relationship between mRNA vaccination and IgAN. However, based on current data [31], an association between preexisting lgAN and relapse after mRNA vaccination was possible but very rare. Nevertheless, the favorable risk-benefit ratio of vaccination in patients with glomerular disease remains positive. Patients and professionals should be instructed, as the data strengthen, to closely monitor patients with pre-existing lgAN.
Background	Immunoglobulin-A-Nephropathy is the most common cause of primary glomerulonephritis. This is often a silent condition that may go undetected for many years. Most common symptom of IgA nephropathy is hematuria (blood in the urine.). IgA nephropathy is diagnosed by renal biopsy. There is no Brighton definition. Flares usually diagnosed by hematuria and/or proteinuria, without re-biopsy. PRAC has noted "IgA nephropathy can follow a benign course, however, slow progression to end stage disease occurs in 25 to 30 percent of patients within 20 to 25 years of presentation." More common in men than women, IgA nephropathy can occur at all ages but is most common in the second and third decades of life. 80% of patients are ages 16-35 years at time of diagnosis. Brief Regulatory History of IgA Nephropathy and elasomeran: PRAC Assessment Report of PBER #2: It was acknowledged that there were cases reported indicating a potential causal association between elasomeran and IgA nephropathy, in particular flare up of underlying IgA nephropathy. This includes several cases reported in the scientific literature. However, the case number is low, especially considering that, by the DLP, an estimated 466,804,529 doses of elasomeran had been administered. Cumulative evidence is not sufficient to warrant amendment of the product information regarding IgA nephropathy at present. Immunoglobulin-A-Nephropathy can follow a benign course, however, slow progression to end stage disease occurs in 25 to 30 percent of patients within 20 to 25 years of presentation. Also, IgA nephropathy can be associated with acute kidney injury as well as rapidly progressive glomerulonephritis. The fact that IgA nephropathy was delineated from other renal PTs, both in disproportionality analyses as well as in case reviews, calls for a continuous alertness regarding this condition. The MAH is requested to add IgA nephropathy to the list of safety concerns as an important potential risk in the PSUR. As a consequence, a risk characterization and an evaluation of new information for the risk is expected in the next PSUR. The MAH was also requested to discuss in the next PSUR whether IgA nephropathy needs to be added to the list of safety concerns in the RMP." Consequently, validated signal on IgA Nephropathy was assessed and then closed by the MAH as a refuted signal on 29 Jul 2022. PRAC Assessment Report of PBER #3: The rapporteur thus agreed that at present there was not enough evidence to establish (nor to reject) a causal relationship between the administration of SPIKEVAX/elasomeran and the development of IgA nephropathy and that no changes to the product information regarding this issue are currently warranted.

Signal evaluation criteria	Summary
	However, the PRAC rapporteur still finds it warranted to consider IgAN an important potential risk in the PSURs. Also, based on the limited number of cases and the lack of a clear association, no changes to the RMP, neither concerning de novo IgAN nor flare of known IgAN, are currently considered warranted. PRAC Preliminary Assessment Report PBRER #4: The rapporteur concluded that reporting of IgAN is rare and that the evidence was 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 was therefore expected that the MAH will present new information on IgA nephropathy and risk characterization in PSUR section 16.3 and 16.4, respectively.
Methodology	The assessment of IgAN – Flare-Up 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: Three ModernaTx, Inc sponsored clinical studies (mRNA-1273-P203, mRNA-1273-P204 and mRNA-1273-P301) were queried as part of the response to the agency's request for information. For study mRNA-1273-P203 the data cutoff was 27 Jan 2022; for mRNA-1273-P204 the data cutoff date was 21 Feb 2022, and for mRNA-1273-P301 the data cutoff date was 04 May 2021. The topic of Glomerulonephritis and nephrotic syndrome was cumulatively reviewed for any PTs including in the HLT Glomerulonephritis and Nephrotic Syndrome in above mentioned studies. 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. Epidemiological studies: NA. External Databases: There is not a MedDRA PT for IgAN Flare-Up. Therefore, disproportionality for this event cannot be assessed in VAERS or EVDAS. Review of the Pharmacovigilance Database: Post marketing data for Glomerulonephritis and nephrotic syndrome was cumulatively reviewed in the MAH GSDB with a DLP of 17 Dec 2022. The term IgAN – Flare-Up was analysed by using a HLT glomerulonephritis and nephrotic syndrome Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Cases from all sources and supplemented with relevant literature case reports not yet in Moderna GSDB were included. Information

Signal evaluation criteria	Summary
	presented in results section includes analyzes performed on cases received by ModernaTx, Inc., for the elasomeran and for the elasomeran/davesomeran and elasomeran/imelasomeran. Literature search review: The MAH performed a focused search of PubMed for elasomeran and IgA Nephropathy to retrieve relevant literature during this reporting period.
Results	Clinical Trial Data: Overall, there were zero cases listed for any of these PTs from HLT of Glomerulonephritis and Nephrotic Syndrome. External Databases: NA Review of the Pharmacovigilance Database: Cumulatively as of the DLP (17 Dec 2022), a total of 237 cases (272 events) were retrieved using the MedDRA HLT of "Glomerulonephritis and Nephrotic Syndrome". 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. 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%). 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 IgAN 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. 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 adverse events 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. Currently, with the limited number of reports, this finding is an observation, as there is no clear biological explanation. The MAH has evaluated cumulatively all cases with IgA nephropathy, De Novo and flare, temporally associated with elasomeran according to the WHO-UMC causality assessment. Most of the cases (37; 54.4%) were considered possible due to temporal association and lack of adequate information for complete clinical evaluation. Review of counts of IgA nephropathy cases by initial receipt date and PSUR reporting period shows that in the PSUR#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.

Signal evaluation criteria	Summary
	The cumulative reporting rate remains < 1 case per 10 million doses. **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 search review: 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 [32] **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 **Abstract**. Diebold et al 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 (IR 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 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% CI 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

Signal evaluation criteria	Summary
	(95% CI 0.67-1.97, p=0.73) [32]. **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. Following receipt of a signal letter from Swissmedic, triggered by the publication Canney et al: A Population-Based Analysis of the Risk of Glomerular Disease Relapse after COVID-19 Vaccination., the MAH has opened a signal of IgA nephropathy flare-up and evaluated the information presented in this article. Using a centralized clinical and pathology registry (2000-2020) in British Columbia, Canada, this study identified patients who had been previously diagnosed with biopsy-proven glomerular disease. The primary study outcome was disease relapse based on eGFR and proteinuria. The investigators identified, patients whom they determined had stable disease, without a relapse in the year prior to 14 Dec 2020, the first day that COVID-19 vaccines became available in British Columbia. Total study follow-up duration was 281 days, ending on 21 Sep 2021. Of the 1,105 patients, 1,016 (92%) received at least one dose, and 986 (89%) received two or three doses of COVID-19 vaccine. The most common vaccine types were BNTl 62b2 (Pfizer-BioNTech, 67%) and mRNA-1273 (ModernaTx, Inc, 30%). Vaccine type was not a study focus. Of the 1,105 patients, 134 (12.1%) experienced a relapse; the relapse of 24 of these patients occurred within the 30-day window following vaccination. These 24 patients were a key element to this study, however the amount of detail about them was relatively sparse. The type of glomerular disease was reported as: ANCA-related, 3 patients: lupus nephritis, 4 patients; minimal change disease, 2 patients; membranous nephropathy, 5 patients; FSGS, 3 patients; and IgA nephropathy, 7 patients. The investigators reported: "Although a first vaccine dose was not associated with relapse risk ([HR]=0.67; 95% CI, 0.33 to 1.36), exposure to a second or third dose was associated with a two-fold risk of relapse (HR=2.23; 95% CI, 1.06 to 4.71). The pattern of relative risk was similar across glomerular diseases." They concluded their abstract by noting the "low absolute increased risk of relapse". The authors also noted that, of the 24 patients with relapse post-vaccination, only four had a change in immunosuppression, and none underwent repeat biopsy. The study by Canney et al has some important limitations that are further described below: The lower bound of the 95% CI of the HR that combines dose 2 and dose 3 was 1.06, as noted above, barely exceeding unity to achieve conventional statistical significance. As the authors stated, "It should be acknowledged that the HR estimates had wide CIs and need to be validated in an independent cohort with larger sample size to generate more precise estimates." The MAH agrees that this study's findings require confirmation in rigorous studies; such rigorous studies should also include clinical details of important cases of interest. The investigators reported that their interaction analyzes, with P-values for interaction

Signal evaluation criteria	Summary
	of ~0.5, "suggested that the relative risk of disease flare associated with any vaccine exposure was not significantly different on the basis of the type of glomerular disease." Given that there were only 24 patients with relapse linked to vaccination in the prior 30 days and that the study included six different glomerular disease types, the MAH questions whether this analysis had sufficient statistical power to be reliable. Canney et al article noted that on the study index date there were 4,390 adults with biopsy-proven glomerulonephritis. The vast majority of these were excluded from the main study analyses; only 1,105 patients (25%) were included in the study cohort. Large numbers of patients were excluded from study based on end-stage kidney disease (957 patients), recent relapse (550 patients), and <2 proteinuria measurements in 12 months prior to index date (1,734 patients). The exclusion of 75% of glomerular disease patients is a basis for a major caveat that the authors did not communicate. The authors did not note that their study protocol was registered. In an attempt to address the possibility of ascertainment bias, the authors reported "similar proportion of patients had a laboratory test performed within 30 days before vaccination and within 30 days after vaccination (41.6% versus 43.5%; P=0.39), suggesting that testing frequency was not correlated with vaccination status." However, the unexposed time used for calculating HRs in the main study analyses included all other study time outside the 30-day exposure window after each vaccine dose, not only the 30 days prior to vaccination. Thus, this seemingly reassuring methodological analysis is incomplete. A potential need for increased monitoring was raised by the authors. In this regard, it is relevant to note that this study included 1,016 COVID-19-vaccinated glomerular disease patients and reported that among them only four (0.4%) needed a change in immunosuppression following vaccination at some time in the 30-day period prior to relapse; no patient had a repeat biopsy. The glomerular diseases of these four patients were not reported. Regardless of vaccination, standard practice is that all glomerular disease patients should self-monitor for signs and symptoms of relapse. The data reported by Canney do not provide a sufficient basis for new recommendations or product labelling changes about IgA nephropathy in association with COVID-19 vaccine administration [31].
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

Signal evaluation criteria	Summary
	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 through 17 Dec 2022 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 bivalents (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. Final assessment report of this signal evaluation was received from SwissMedic, on 12 Jun 2023 confirming that no additional activities were requested, as stated in their notification letter: "Swissmedic examined your documents and came to the following conclusion: According to available data (clinical data, literature, post-marketing data, including O/E analyses), there are e.g., Currently there is no reliable evidence of a causal connection between an mRNA vaccination and an IgAN - be it de novo or an exacerbation of one existing IgAN. 1. No action is currently required regarding this signal. 2. The signal is completed."
Conclusion	Overall, based on the analysis of all available safety data as of 17 Dec 2022 including the literature articles discussed above, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran, or the bivalent ModernaTx, Inc vaccines, and the development of IgA nephropathy. No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor IgA Nephropathy events using routine pharmacovigilance surveillance. The data reported by Canney et al, reviewed in detail above, do not provide a sufficient basis for new recommendations or product labelling changes with regard to IgA nephropathy flare-up in association with COVID-19 vaccine administration. The signal of IgA nephropathy flare-up is closed and refuted.

16.2.2 Sensorineural hearing loss

Table 16-5 Sensorineural hearing loss

Signal evaluation criteria	Summary
Source	There have been multiple evaluations conducted on the medical topic of sensorineural hearing loss (SNHL) due to requests from health authorities, as well as internal evaluation through the signal detection process for hearing loss since Jun 2021. **01 Jun 2021:** The signal "Deafness" was evaluated and subsequently refuted. **06 Jul 2021:** PRAC agreed with this decision in the Assessment Report of MSSR5 mentioning the following: *"Overall, PRAC Rapporteur agrees on the MAH's conclusion that available evidence is currently insufficient to establish a causal association between the risk of hearing loss and COVID-19 vaccine ModernaTx, Inc,. The closure of the signal is accepted, and the MAH should continue to monitor cases reporting hearing loss as part of their routine pharmacovigilance practices."* **28 Mar 2022:** Sudden hearing loss was reviewed internally as a safety topic triggered by EVDAS results of DLP 28 Feb 2022. **27 Apr 2022:** Closed with the following conclusion: *"Based on review of available data, there is insufficient evidence to consider Hearing Loss as a potential signal. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities".* **31 May 2022:** Triggered by a RTQ from Health Canada, the topics "Tinnitus, vertigo, and hearing losses" were addressed in the RTQ response to the agency. **14 Sep 2022:** Hearing loss and Tinnitus were internally re-assessed as a safety topic review triggered by publication of the French Healthcare Authority (ANSM) on its website. **19 Sep 2022:** Closed with following conclusion: "*Based on the analysis of the cumulative data, the MAH considers that there remains insufficient evidence for an increased risk for tinnitus, vertigo, and hearing loss after vaccination with SPIKEVAX. The MAH will continue to evaluate these events using routine surveillance."* **On 22 Dec 2022:** PRAC requested the MAH to address the topic "Hearing loss" in the next PBRER4. This topic was addressed with following conclusions: *"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."* **11 May 2023:** PRAC confirmed that there is not sufficient evidence to establish a causal association between elasomeran and sudden hearing loss mentioning the following: *"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*

Signal evaluation criteria	Summary
	requested to present in detail (including case narratives and MAH's causality assessment) all reports that fulfil level 1-3 Brighton Collaboration (BC) case definition of sudden hearing loss AND that can be considered as 'index cases'."* **22 Jun 2023:** PRAC mentioned the following: *"Following review of additional data submitted by the MAH in response to RSI, the PRAC Rapporteur considers that a causal association between hearing loss and SPIKEVAX cannot currently be established. No further actions beyond routine PV pharmacovigilance are required. "* **TGA RTQ Request for Review of Signal SNHL:** TGA's Medicines and Vaccines Investigation and Surveillance Section reviewed signal of SNHL with elasomeran. Signal detected in Nov-Dec 2022 Disproportionality Analysis Report. Thirty-four reports of hearing loss associated with elasomeran (including one report associated with SPIKEVAX Bivalent Original/Omicron) in the TGA's Adverse Event Management System). Requests sponsor to provide *"updated signal analysis on hearing loss cases including age stratified and age specific observed versus expected analyzes in the next PSUR to enable further evaluation of this signal. Please confirm your agreement with this request by 23 Jun 2023.* On 09 Aug 2023, the validated signal of SNHL was evaluated at the SRMT Meeting. Results from this meeting and SER will be submitted with PBRER #5 (PSUR). The SRMT decision was to refute the signal of SNHL. There were no changes to the product information or RMP. Additionally, the following actions were recommended: **Routine PV monitoring** Sensorineural hearing loss will be included as an ad hoc adverse event to study mRNA-1273-P920 (Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States).
Background	Hearing loss is defined as a person who is not able to hear as well as someone with normal hearing–hearing thresholds of 20 dB or better in both ears–is said to have hearing loss. Sensorineural hearing loss is estimated to be the most common type of hearing loss and affects between 5-27 per 100,000 people each year, with approximately 66,000 new annual cases in the US. Incidence estimates of sudden sensorineural hearing loss after COVID-19 vaccination ranged from 0.3 to 4.1 per 100 000 per year. New onset is investigated by a full audiometric evaluation by a multidisciplinary team (e.g., otolaryngologist, audiologist, radiologist, and speech/language therapist). There are two types of hearing loss: conductive and SNHL. Sensorineural hearing loss results from pathology of the cochlea, auditory nerve, cranial nerve VIII, or central nervous system. Conductive hearing loss is secondary to lesions affecting the external auditory canal or middle ear. **Two types of hearing loss: conductive and SNHL** SNHL: results from pathology of the cochlea, auditory nerve, cranial nerve VIII, or central nervous system. Conductive: secondary to lesions affecting the external auditory canal or middle ear. Sensorineural hearing loss is more common in women than men and can be diagnosed in all ages; however, diagnosis is most common in older adults aged 50-64 years old and

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	elderly with bilateral HL in patients aged >70+ years at time of diagnosis. In sudden onset SSNHL, the exact pathophysiology is still unknown; however, it is most likely caused by a viral infection. Confounders for SNHL include the following: Infections: Viral cochleitis associated with herpesviruses, parainfluenza virus, influenza, mumps, measles, rubella, or HIV; bacterial meningitis; Mycoplasma pneumoniae infection; Lyme Disease; tuberculosis, syphilis or fungal infection Ototoxic Drugs: Aminoglycosides, vancomycin, erythromycin, loop diuretics, antimalarials, cisplatin, sildenafil, cocaine Endocrine: Diabetic vasculopathy, hypothyroidism Neoplasms: Acoustic neurinoma meningeal carcinomatosis; lymphoma, leukemia, or plasma cell dyscrasia. Trauma: Head injury, barotraumas; exposure to loud noise or music Autoimmune Disease: Autoimmune inner ear disease, Cogan's syndrome, Susac syndrome, systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, Sjogren's syndrome, Kawasaki disease, Wegener's granulomatosis, temporal arteritis of primary central nervous system vasculitis. Vascular Disorders: Vertebrocerebellar cerebral vascular accident or transient ischemic accident, cerebellar infarction, inner ear hemorrhage. Other Causes: Meniere's disease, osteosclerosis, Paget's disease, multiple sclerosis, age, idiopathic. Treatment includes steroids to improve the prognosis. Also, decrease exposure to loud music or sounds in cases due to noise-induced hearing loss observed in young adults is recommended. Autoimmune related causes are rare clinical entity in which progressive fluctuating bilateral asymmetric SNHL that develop over several weeks to months. Vestibular symptoms, tinnitus and aural fullness are present in up to 50% of patients.
Methodology	The assessment of SNHL 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: The Company clinical database was queried cumulative from 18 Dec 2020 to 17 Jun 2023. Safety data from six CTs in different age groups (adults, adolescents, and children) and in one clinical trial in immunosuppressed adults was reviewed to identify unsolicited events (serious and non-serious) reported using the MedDRA (version 23.0) PTs 'Deafness neurosensory', 'Hypoacusis' and 'Tinnitus'. The topic of SNHL was cumulatively reviewed in the clinical trial datasets, within the following studies: • mRNA-1273-P301, data as of 04 May 2021 • mRNA-1273-P203 Part 1A and Part 1B, data as of 31 Jan 2022 • mRNA-1273-P204 Part 1 and Part 2, data as of 21 Feb 2022 • mRNA-1273-P306 Part 1 and Part 2, data as of 05 Dec 2022 • mRNA-1273-P205:

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	• Day 91 Interim CSR, Part G (mRNA-1273.214), data as of 08 Sep 2022 • Day 29 Interim CSR, Part H (mRNA-1273.222), data as of 31 Oct 2022 • Immunocompromised Adults: mRNA-1273-P304, data as of 01 Sep 2022 Epidemiological studies: A total of 1,664,690,323 doses of elasomeran have been distributed as of 17 Jun 2023. Elasomeran was distributed in 91 countries, elasomeran/imelasomeran in 42 countries, and elasomeran/davesomeran in 41 countries. The estimated administered doses were used to calculate the denominator for the observed to expected analyses. Person-years were estimated by assigning 21 days after each dose including all products elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). The assumed age and gender distribution was based on CDC data as of 11 May 2023. External Databases: Disproportionality was performed for external safety databases. Review of the Pharmacovigilance Database: A cumulative search in the GSDB, through 17 Jun 2023 for reports under the MedDRA HLT of "Hearing losses" was performed. An additional search string of the narrative and PTs using an algorithm was applied to avoid any missing cases. Cumulative analysis of HLT of hearing loss cases focused on PTs of hypoacusis, and any combination of sensorineural hearing loss/deafness including: MedDRA Version 26.0 PTs: 'Deafness neurosensory', Neurosensori hypoacusis', 'Hypoacusis', 'Neurosensory Deafness'. All case reports identified from the above search (whether or not the PT SNHL was coded) were medically reviewed for evidence of SNHL based on BC case definition which included evidence of physical examination (e.g., Ear Nose and Throat) to rule out conductive hearing loss, and for specific diagnostics to determine index cases of SNHL (e.g., audiometry, MRI, tuning fork exams), medical diagnosis of SNHL or reported diagnosis of hypoacusis. The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system was used for the company's causality assessment. Literature search review: A targeted literature search was performed from 18 Dec 2022 to 17 Jun 2023 using PubMed.
Results	**Clinical Trial Data:** No imbalance was observed between the placebo arm and mRNA-1273 vaccination arm for PTs "Deafness neurosensory", "Hypoacusis" or "Tinnitus" in any of the studies were reports for the evaluated PTs were reported (P301 and P204). No cases associated with the PTs "Deafness neurosensory", "Hypoacusis" or "Tinnitus" were reported in: • mRNA-1273-P205 • mRNA-1273-P304 • mRNA-1273-P203 • mRNA-1273-P306 There was no imbalance or change to the benefit-risk safety profile. **Epidemiological studies:** In data from a US, administrative claims-based study of sudden sensorineural hearing

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	loss identified an incidence of 27 cases per 100,000 person-years [33]. Increases by age were consistent for men and women. The literature-based estimates varied widely: • Taiwan: 10.2/100,000 person-years [34] • Japan: 27.5/100,000 person-years [35] • Germany: 160/100,000 person-years [36] **External Databases:** VAERS: No Disproportionate Reporting of Events using EB05 > 2 (mRNA-1273 versus All vaccines in adults) in VAERS as of 10 May 2023. EVDAS: Disproportionality was observed in EVDAS (27 May 2023, to 09 Jun 2023). PTs for HLT of hearing loss including SNHL, deafness neurosensory, and hypoacusis showed Disproportionality as the ROR was >1. There was higher disproportionality in North America compared to other regions. Deafness neurosensory (ROR=7.38) was disproportionate in general population and in geriatric population and increased overall (All ROR: 2.03; N=170, ROR>1). While disproportionality is not uncommon in EVDAS, results should be taken with caution given the limitations in EVDAS and based on low case counts. For bivalents, regional disproportionality was seen in elasomeran/imelasomeran (deafness in EU and hypoacusis in Asia). For elasomeran/davesomeran, disproportionality was reported in North America only; deafness neurosensory was reported in general population. Review of the GSDB: Two analyses were performed. A cumulative review was submitted as part of a health authority request (EMA/PRAC) for PBRER4 (cumulatively from 18 Dec 2020 through 17 Dec 2022) and an updated analysis of cases reported during the reporting period for PBRER#5 (17 Dec 2022 to17 Jun 2023) based on a request received from another health authority (TGA). **Summary of Cumulative HLT Hearing Loss Cases (18 Dec 2022 to 17 Dec 2022):** 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-old age group (28.5%) followed by the elderly 65 years and older (24.4%), and the 25-39-year-old 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 UK (5.8%). The highest events were for the PTs of hypoacusis (33.3%) followed by deafness (25.9%). When 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 TTO of all doses was on average 13.7 days (SD: 33.9) with a median of 3.0 days (range of -217 to 379 days). Almost 60% of the 2,589 events (59.6%; 1,544) were not resolved, 14.4% (372 events) resolved, and 8.6% (224 events) were either resolving or resolved with sequelae. Note: Not resolved outcomes must be interpreted with caution as most reports

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	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. The MAH conducted a detailed evaluation of the cases of SNHL by searching both the narratives and filtering for the MedDRA PTs which contained verbatim combinations of SNHL or hypoacusis. Using the results from the MAH SAS algorithm of the 2,327 cases, there were 994 cases of SNHL/hypoacusis and 1,333 cases of 'Other hearing loss (HL)' identified. Of the 994 cases, 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. Of the 994 cases, over 76% of the cases reported treatment with steroids, antibiotics, or other medications; the remaining cases (237) had 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. Overall, there were no index cases for SNHL identified; there were 6 cases classified as Level 2 and 129 cases as Level 3. Among the 6 Level 2 cases, all cases were in adult age range 38 to 67 years. No cases had 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 >30 db-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 probable, which did not resolve with treatment. All Level 3 cases (129) had diagnostics studies (e.g., audiogram, MRI, etc.). In the 129 cases, the ages ranged from 27 to 90 years in 39 females 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. **Summary of HLT Hearing Loss Cases during the PBRER 5 reporting period (18 Dec 2022 to 17 Jun 2023):** During the reporting period of PBRER #5 (18 Dec 2022 to17 Jun 2023), a total of 152 cases were identified using the same search strategy as before, with the HLT of "Hearing losses". After application of the same SAS algorithm, a total of 82 cases of SNHL were identified (70 for elasomeran; 8 for elasomeran/ imelasomeran, and 4 for elasomeran/ davesomeran), of which, 18 cases provided information in order to

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	evaluated cases for SNHL. Given that the number of reported cases during this RP was small, all cases in the RP were medically reviewed and evaluated using the BC and WHO causality assessment. Overview of Reporting Interval Hearing Loss Cases: As part of this analysis, a comparison of SNHL cases reported for PBRER 4 (2,327 cases) vs those reported for PBRER 5 (152 cases) was performed and is presented below. No differences were observed between the two reports regarding gender, age and TTO. There were 3 cases reporting a fatal outcome during the PBRER 4; no fatal outcomes were reported during this RP. The demographic presentation was similar across both PBRERs with more cases reported for females compared to men, and higher proportion of reports in the 50-60 years old age group with a mean age of 56.87 years; TTO was similar for both analysis (<3 days). Young adults (18-49 years old) had similar proportion of cases compared to elderly. There was significant number of missing data during the RP, which impacted the assessment. No cases were reported in children during this reporting period. When dose number was known, events occurred more often after dose 1 and dose 2, and TTO was similar for both analysis (<3 days), regardless of dose number. Among the 152 new cases (168 events) of the SHNL HLT, the most commonly reported PT was hypoacusis (48; 12.5%), followed by deafness neurosensory (35; 9.1%). Overall, most of the cases did not report relevant medical history or concomitant medications and for those that provided that information most cases were confounded including use of ototoxic medications (loop diuretics) or relevant medical history (other vaccines, cardiovascular history or viral infections). Out of the 152 cases included in PBRER#5 RP, 82 Cases (383 events) were identified as SNHL using the described algorithm, of which 18 cases met diagnostic criteria. There were 55 serious cases and none with fatal outcomes. Most cases were medically confirmed (50; 61.0%). Most of the cases were reported after vaccination with elasomeran (70 cases); there were 12 cases after vaccination with the bivalent vaccines (8 for elasomeran/imelasomeran and 4 for elasomeran/davesomeran). **Literature search review:** From the search result 104 unique articles captured, 5 articles were related to SNHL and mRNA vaccination. Of the 5 relevant articles, 2 discussed the Moderna vaccine and SNHL and 3 discussed the Pfizer vaccine and SNHL. Ninety-nine articles were not relevant and consisted of 2 articles discussing SNHL/HL in COVID-19 infection, 3 editorials on SNHL studies in COVID-19 vaccine, and 43 about the Moderna vaccine with no SNHL. One article discussed a hypothetical mechanism of action and etiology of SNHL and mRNA vaccines [37]. Of note, hearing loss is associated with other medications and vaccines in the literature (Rabies, tetanus-diphtheria and meningococcal, MMR, Influenza, HBV, and oral poliomyelitis). **Thai-Van H, Valnet-Rabier MB, Anciaux M, et al** [38]**:** This is a nationwide retrospective study aimed to assess the relationship between SSNHL and exposure to mRNA COVID-19 vaccines and to estimate the reporting rate of SSNHL after mRNA vaccination per 1 million doses (primary outcome) in France between Jan 2021 and Feb 2022. This is a review of all suspected cases of SSNHL after mRNA COVID-19 vaccination spontaneously reported based on a comprehensive

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	medical evaluation, including the evaluation of patient medical history, side and range of hearing loss, and hearing recovery outcomes after a minimum period of 3 months. Demographics included a median age of 51 years (range: 13-83 years old) and 59.2% female and 40.8% male. The two comparator groups were tozinameran and elasomeran. The median TTO for SNHL in <21 days in the tozinameran arm (n=108, 76.1%) was 4 (2-9) days, the TTO for SNHL in >21 days in the tozinameran arm (n=34, 23.9%) was 41 days (25-67). In the elasomeran arm, the median TTO for SNHL in <21 days (n=26, 86.7%) was 8 (1-21) days, and the median TTO for SNHL in >21 days (n=3, 10.3%) was 50 (26-144) days. Autoimmune, cardiovascular, or audio-vestibular risk factors were present in approximately 29.8% (51/171) of the cases. Eligible SSNHL cases were selected using the MedDRA hierarchy, with PT selected from the narrow Standardized Medical Queries "Hearing impairment." All data analyzed according to the American Academy of Otolaryngology-Head and Neck Surgery Foundation guidelines; patients were categorized according to a grading system modified from the Siegel criteria. No mechanism of action was listed in the article. Steroids were administered orally in 47.2% of cases. There were 8 positive rechallenges. Limitations include a large population-based pharmacovigilance studies or a case-control study appropriate for rare events is needed to further define the role of mRNA COVID-19 vaccination in the occurrence of SSNHL. Nationwide post-marketing surveillance did not include any control group, thus preventing the consideration of potentially important variables such as age or SSNHL TTO. In conclusion, SSNHL after COVID-19 mRNA vaccines are very rare adverse events that do not call into question the benefits of mRNA vaccines but deserves to be known given the potentially disabling impact of sudden deafness. Therefore, it is essential to properly characterize post injection SSNHL, especially in the case of a positive rechallenge, to provide appropriate individualized recommendations. The lack of available data for the general population precluded comparisons with historical incidence or incidence in the unvaccinated population. Further studies are needed to establish the correlation between SSNHL and mRNA vaccination. **Leong S, Teh BM, Kim AH** [39]: This was a cross-sectional study of patients seen in the otology clinic at an academic center. Patients completed a questionnaire on the development of new otologic symptoms within 4 weeks of COVID-19 vaccination. Demographics included a median age of 56.6 years (range: 16-101 years), and 59.4% female and 40.2% male. All mRNA vaccines were studied. No TTO or risk factors were provided. Diagnostic and audiometric data were obtained via retrospective chart review and may not have been reflective of the full workup that patients received. No mechanism of action provided. Cochlear implant and steroids (intratympanic dexamethasone or oral prednisone) were used as corrective treatment. No mention of rechallenge or dechallenge. Limitations included no specified diagnostic criteria were used for the collected data. Retrospective chart review maybe reflective of the full workup the patients received. Otologic symptoms following COVID-19 vaccine are likely over-represented and thus cannot be generalized. Patients self-reported otologic symptoms. Patients were screened from otologic clinics only. Small sample size of 500 otology patients. In conclusion, patients reporting otologic symptoms following COVID-19 vaccination received various diagnoses of uncertain etiology. The incidence of SSNHL in these patients is comparable to the general otology patient population. Additional studies are required to determine the incidence of specific diagnoses following vaccination. Otologic symptoms following COVID-19 vaccination do not appear to have mechanistic associations with these

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	specific vaccines. This study further affirmed that the benefits of COVID-19 vaccination significantly outweigh the risk. **Cohen Michael O, Tamir SO, O'Rourke N, Marom T** [40]**:** This was a retrospective study that compared SSNHL incidence rates over the COVID-19 outbreak and the COVID-19 vaccination campaign periods to pre-COVID-19 periods. Patients >12 years with auditory-confirmed SSNHL were enrolled. COVID-19 status and BNT162 inoculation records ≤28 days before SSNHL diagnosis were retrieved. Patients were categorized according to their date of presentation over four equal periods. Demographics included in the pre-pandemic Period 1 (07/2018–04/2019) (N = 22), the median age was 52 years (23–81), 6 (27.3%) females, and 16 (72.7%) males. In the pre-pandemic Period 2 (05/2019–02/2020) (N = 21), the median age was 47.5 years (20–75), 10 (47.6%) females, and 11 (52.4%) males. In the post-pandemic Period 3 (03/2020–12/2020) (N = 23), the median age was 51 years (20–82), 11 (47.8%) females, and 12 (52.2%) males. In the post-pandemic Period 4 (01/2021–10/2021) (N=34), the median age was 49.5 years (17–82), 15 (44.1%) females, and 19 (55.9%) males. The BNT162b2 vaccine was studied. Eight out of 127,543 patients presented with SNHL on the median 13th day after vaccination. No risk factors were included. Patients with clinical history and audiometry supported an SNHL with other ICD-9 codes were determined to have SNHL. No mechanism of action discussed. Oral steroids, intratympanic steroids, and hyperbaric oxygen treatment were used as corrective treatment. Limitations included due to the pandemic, hearing tests were not routinely conducted, and confirmed COVID-19 patients were even less likely to be sent to undergo audiometric studies. At-home and mobile SSNHL tests have been developed and seem to be reliable but could not eventually replace an objective audiometry. Small sample size, no comparator. No mention of Moderna vaccine. No specified diagnostic criteria were used for the collected data. Large-scale audiometrically confirmed research is required. In conclusion, despite the increase in SSNHL cases during the period when vaccination with BNT162b2 had taken place, there was no increase in audiometrically confirmed SSNHL cases among these vaccine recipients. The association between COVID-19 disease and its vaccination warrants further large-scale, audiometrically confirmed research conducted over many years post-pandemic. **Fisher R, Tarnovsky Y, Hirshoren N, Kaufman M, Stern Shavit S** [41]: This was a retrospective chart review of all patients diagnosed with idiopathic sudden sensorineural hearing loss (ISSNHL) during 2021 was conducted and compared to patients who presented in 2018-2020. Patients collected in 2018 (n = 41) had a mean age of 51 (± 17.5) years, and 15 (37%) females. In 2019 (n = 38), the mean age was 49 (± 17.07) years, and 17 (45%) females. In 2020 (n = 31), the mean age was 49 (± 20.3) years, and 19 (63%) females. In 2021 (n = 51), the mean age was 48 (± 18.4) years, and 25 (50%) females. In 2021 of the nonvaccinated population (n = 38), the mean age was 47 (± 20) years, and 16 (43%) females. In 2021 of the vaccinated population (n = 13), the mean age was 52 (± 18.55) years, and 9 (70%) females. The 2018–2019 group was used as a control group before the SARS-CoV-2 pandemic and vaccination era. The 2020 group was used for the period in the presence of the pandemic and before the vaccination era. Comparisons were made between patients diagnosed in 2021 with previous years and between the vaccinated and nonvaccinated. The TTO was 14.9 ± 9.87 days. No risk factors were included. All medical records of patients diagnosed and treated with ISSNHL at a tertiary medical center between Jan 2018 and Dec 2021.

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	Patients were excluded if (1) their diagnosis did not meet ISSNHL criteria, (2) they had Meniere's disease, (3) were later diagnosed with vestibular Schwannoma per MRI, (4) had a progressive or bilateral loss, or (5) lacked information regarding their diagnosis, treatment, or vaccination status. The vaccinated group consisted only of vaccinated patients who received a vaccine dose in the 30 days preceding the ISSNHL presentation. No mechanism of action was discussed. Systemic prednisone for 7 days and intratympanic dexamethasone injection were used for corrective treatment. No rechallenge or dechallenge discussed. Limitations included this was a retrospective, relatively small cohort from a single center. As such, it was exposed to selection bias and may not accurately represent other medical centers, even though we found a similar incline as the Israeli large-scale population-based study. No statistically significant difference was found between different years or between the vaccinated and nonvaccinated groups. This study evaluated a population vaccinated with the Pfizer COVID-19 vaccine almost exclusively. No risk factors documented. In conclusion, a marked incline in ISSNHL incidence was seen in 2021, of which 25% of patients reported experiencing symptoms within a month post-anti-COVID-19 vaccination. While other causative factors could be sought, an association with the vaccine cannot be ruled out, and further large-scale research is needed. Nevertheless, the benefits of the anti-COVID-19 vaccine immensely outweigh any potential otologic adverse effects. **Ekobena P, Rothuizen LE, Bedussi F, et al** [37]**:** This was four case studies with only 1 case of SNHL in a 61-year-old female vaccinated with Pfizer-BioNTech. Time to onset was 10 days. No risk factors were discussed. Patient received a pure tone audiogram, bilateral otoscopy, and video head impulse test as diagnostic tests. Prednisone 5 days after and vestibular physiotherapy was initiated as corrective treatment. The patient declined the second vaccine. Limitations included this was an isolated case report with Pfizer-BioNTech vaccine. In conclusion, the occurrence of audio-vestibular manifestations following mRNA-based vaccines needs ENT monitoring to support their causality in such rare vaccine-related adverse events. Audio-vestibular disorders appeared of transitory nature, including hearing loss, and should not deter further efforts in large-scale vaccination campaigns against SARS-CoV-2. The benefits of the COVID-19 vaccination appear to outweigh the risks of audio-vestibular disorders, since reported cases are mostly transient with favorable outcome. **Conclusion:** In conclusion, the literature is consistent with findings from the GSDB. Overall, the literature search results did not provide evidence of causal association between mRNA vaccines or elasomeran and SNHL.
Discussion	The MAH conducted an extensive evaluation of a validated signal of SNHL due to a request from a health authority (TGA) received on 22 Jun 2023. The signal evaluation included a cumulative review (18 Dec 2020 to 17 Jun 2023) of clinical trial data as well as post-marketing information from the GSDB and the literature for reports included in the HLT of "Hearing Losses". SNHL is the most common type of hearing loss estimated at 5-27/100,000 per year with higher reported rates in men and elderly populations. In sudden onset sensorineural hearing loss (SSNHL), the exact pathophysiology is still unknown; however, it is most likely caused by a viral infection. According to the National Institute on Deafness and other Communication Disorders, men are twice as likely to experience hearing loss, but are less likely than women to seek help. There is evidence in the literature that sex and

Signal evaluation criteria	Summary
	gender may influence the development of SNHL. The prevalence of hearing impairment is higher among older men than older women. However, the GSDB cases showed the highest cases were seen in the 50–64-year-old age group and higher proportion seen in women compared to men. Potential triggers include infections and ototoxic medications, as well as other immune activation events resulting in inflammation to the ear as postulated in the literature. The exact etiology and pathophysiology of SNHL remain unknown. New-onset hearing loss should be investigated and undergo full audiometric evaluation by a multidisciplinary team (e.g., otolaryngologist, audiologist, radiologist, and speech/language therapist). There was no imbalance reported from CTs for events within the terms included in the MedDRA HLT "Hearing Losses", as well as for the specific PT of Hypoacusis, Tinnitus, and information from the GSDB as well as the literature supports the recommendations received from the PRAC from the review of PBRER#4 (Procedure EMEA/H/C/PSUSA/00010897/202212), that stated: "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." A review of cases identified during the reporting period did not show any prominent clinical pattern of occurrence of SNHL outside of what would be expected in a large, vaccinated population. Many of the reports were heavily confounded by historical conditions, concurrent illnesses, and concomitant medications. The observed reporting rates of SNHL are well below background incidence rates. Overall, 18 SNHL reports in 978,005,565 doses administered, shows an approximate reporting rate of 0.02 per 1 million doses administered.
Conclusion	A cumulative review, including an updated review conducted during the reporting period of PBRER 5, 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. Cumulative, as of 17 Jun 2023, the MAH identified 2,479 cases (2,757 events), including reports from the PBRER#5 RP, for individuals between the ages of 5 to 101 years old. The review of cases identified 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/imelasomeran 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

Signal evaluation criteria	Summary
	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 Jun 2023, the MAH considers there is insufficient evidence to consider Hearing Loss as a safety concern as this signal is considered refuted. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities, and the topic of SNHL will be added as an ad hoc adverse event to study mRNA-1273-P920 (Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States). No changes to the product information or inclusion in to the RMP are required at this time.

16.2.3 Mastitis/Breast Swelling

Table 16-6 Mastitis/Breast Swelling

Signal evaluation criteria	Summary
Source	On 05 Jul 2023, ModernaTx, Inc received a request from the TGA (TRIM No. D23-2098241) to update the SPIKEVAX PI with mastitis and breast swelling (Moderna Australia Pty Ltd) including: Request to make safety-related changes to the Product Information (PI) and Consumer Medicine Information for: elasomeran [ARTG No: 370599, 388245, 406730, 399553, 389513, 388244, 399552, 396452]. The TGA's Pharmacovigilance Branch has recently assessed the risk of mastitis and breast swelling with elasomeran. Our assessment concluded that there are sufficient safety grounds to request an update to the SPIKEVAX PI with mastitis and breast swelling.
Background	**Mastitis** Mastitis is a relatively common breast condition [42]. It can affect patients at any time but predominates in women during breastfeeding. It is defined as an inflammatory condition that may be due to several different etiologies, infectious or not, but most breast inflammation is expressed as a hard, swollen, and red breast area, accompanied by a fever above 38.5°C, chills, and general flu-like symptoms [43]. Mastitis with infection may be lactational (puerperal) or non-lactational (e.g., duct ectasia) [42]. *Types of mastitis* *Lactational or Puerperal mastitis* In lactational mastitis, it is likely that bacteria (often originating from the mouth of the infant) gain entry via cracks or fissures in the nipple surface. Once the primary defenses are breached, organisms have an ideal culture environment in nutrient rich maternal milk leading to rapid replication. This process can be augmented by milk stasis and overproduction leading to mastitis. The pathological process is similar to any acute inflammatory event, although the nature of the lactating breast architecture with its loose parenchyma and stagnation of milk in an engorged segment may allow the infection to spread quickly both within the stroma and through the milk ducts. Risk factors include previous mastitis, sore/cracked nipples, wearing tightfitting bra, improper nursing

Signal evaluation criteria	Summary
	techniques, poor nutrition, and tobacco usage [42] and [44]. *Non-lactational or Non-puerperal Mastitis (periductal)* In non-lactational or non-puerperal infectious mastitis (NLIM), it can be caused by different infectious agents. Staphylococcus is the main genus of bacteria associated with non-lactational infectious mastitis and up to 30% may be polymicrobial (e.g., Enterobacteriaceae, Peptostreptococcus, Propionibacterium, Bacteroides) [45]. In duct ectasia, the mammary duct-associated inflammatory disease sequence involves squamous metaplasia of lactiferous ducts causing blockage (obstructive mastopathy) with peri-ductal inflammation and duct rupture. Inflamed ducts are prone to bacterial infection [42]. Risk factors include chronic use of oral contraceptives, tobacco usage, long-term steroids, thoracic surgery, cat scratches, breast implants, reduction mammoplasty, diabetes mellitus, obesity, and tuberculosis [43,44,46]. *Non-infectious mastitis* Non-infection mastitis may result from underlying duct ectasia (periductal mastitis or plasma cell mastitis) and infrequently from foreign material (e.g., nipple piercing, breast implant, or silicone). Causes of non-infectious mastitis include idiopathic granulomatous inflammation, autoimmune disorders (e.g., sarcoidosis, thyroiditis, systemic erythematosus lupus, Sjogren's syndrome, Crohn's disease), trauma, hyperprolactinemia, and other inflammatory conditions (e.g., foreign body reaction) [42,44,47]. *Epidemiology* Worldwide, lactational mastitis occurs in 2%-30% of breastfeeding women. In the United States, the reported incidence is between 7%-10%. The incidence is highest in the first three weeks postpartum [48]. The global prevalence of mastitis in lactating women ranges from 1-10%; however, a Cochrane review suggested that the incidence of mastitis could be as high as 33%. The incidence is highest in the first few weeks of postpartum and decreases gradually after that. Duct ectasia (peri-ductal mastitis or dilated ducts associated with inflammation) occurs in 5-9% of non-lactating women [42]. Breast inflammation during breastfeeding requires immediate and appropriate treatment [43]. *Clinical Features and Diagnosis* Common signs and symptoms are fever, breast signs/symptoms (pain, swelling, warmth, thickening of skin, lump, tenderness, firmness, erythema, abscess), decreased milk outflow, enlargement of axillary lymph nodes, chills, myalgias, and malaise [42,44], [48].The diagnosis is usually based on history and clinical findings. However, useful diagnostic tools include ultrasound, fine needle aspiration, biopsy, milk sample, cultures, mammography, laboratory studies, and tuberculin skin test [42]. *Clinical course* If mastitis is left untreated, it may cause tissue destruction resulting in an abscess associated with bacteremia and sepsis. Lactational abscesses tend to be in the peripheral breast and are often a progression of mastitis or lactational breast inflammation. Non-lactational breast abscesses are often sub-areolar and were first described as fistulas of lactiferous ducts; this is proceeded by inflammation of the surrounding duct, infection of these terminal lactiferous ducts, duct rupture and subsequent peri-areolar fistula and sub-areolar breast abscess formation. These abscesses have a chronic course, often with recurrent obstruction of the ducts with keratin plugs and tend to form extensive fistulas [42].

Signal evaluation criteria	Summary
	Treatment Supportive treatment included effective milk removal, lymphatic massage, hot compresses, rest, nutrients, and increased fluid intake. Also, the following pharmacological treatment have been used in conjunction with supportive treatment: analgesics, antibiotics, topical antifungal preparations, and steroid combination ointment [43]. Surgical intervention may be required for mature fluctuant abscess [42]. **Breast Swelling/Breast Oedema** Breast oedema is fluid accumulation within breast tissue that may lead to visible swelling, increased breast parenchymal density, inflammation, skin dimpling (peau d'orange) and thickening, breast pain, and sagging of the breast. This fluid buildup is largely a result of compromised outflow due to an obstruction or disruption of lymphatic vessels that drain the breast, which may occur from a diverse spectrum of etiologies. *Etiology* The predominant cause is breast cancer treatment referred to as breast-conserving therapy (BCT) whereby breast-conserving surgery (also called lumpectomy or segmental mastectomy) is performed, followed by radiotherapy. Often coexistent with breast oedema attributable to BCT is lymphoedema of the arms, an entity that has been far more recognized and treated clinically as well as extensively explored and discussed in the literature. Less common causes of breast oedema include inflammatory breast carcinoma, congestive heart failure, mastitis, lymphatic obstruction (by axillary, chest wall, or intrathoracic lesions), metastasis, breast lymphoma, and trauma [49] .In addition, breast enlargement has been associated with medications (e.g., antiandrogen/inhibitors of androgen synthesis, chemotherapeutic agents, cardiac medications, hormones, psychoactive drugs, antiretrovirals) [48]. *Diagnosis* Current methods to detect breast oedema incidence tend to be suboptimal, often limited to subjective assessments (such as surveys, questionnaires, and self-reports) and clinical assessments based on cursory physical examinations. Diagnostic studies are plain radiology, mammograms, MRI, ultrasound imaging, and contrast-enhanced digital mammography (CEDM) [48]. *Treatment* Management of breast oedema can be facilitated if both the patient and clinician are aware of its presentation, its course, and [49] methods used for its detection and monitoring. If left untreated, breast oedema can have psychological effects leading to decreased quality of life, body image issues, and fear of cancer reoccurrence, as well as continued breast discomfort and pain. Treatment options include manual lymphatic drainage, compression banding, lymph-reducing exercises, and skin care [48].
Methodology	The assessment of Mastitis and Breast swelling in association with the use of elasomeran-containing vaccines in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources are described below. **Methodology for Mastitis and Breast Swelling:** The MAH's clinical database and the global safety database were queried for valid case reports of Mastitis and Breast Swelling received from HCP, HA, consumers, and literature, worldwide, for elasomeran, and for both bivalent vaccines

Signal evaluation criteria	Summary
	(elasomeran/imelasomeran and elasomeran/davesomeran) using the following PTs: "Mastitis, Breast swelling, Breast oedema, and Breast enlargement." Two different Medical Dictionary of Regulatory Activities (MedDRA) version were used. For the CTs MedDRA version 23.0 and 24.0 were used and for querying the global safety database, cumulative as of 17 Jun 2023, the MedDRA version 26.0 was used. Clinical Trial Data: The Company clinical database was queried cumulative from 18 Dec 2020 to 17 Jun 2023. Safety data from four CTs in different age groups (adults, adolescents, and children) was reviewed to identify unsolicited events (serious and non-serious) reported using the MedDRA (version 26.0) PTs "Mastitis," "Breast swelling," "Breast Oedema," and "Breast enlargement." The topics of Mastitis and Breast Swelling were cumulatively reviewed in the clinical trial datasets, within the following studies: • mRNA-1273-P301, data as of 04 May 2021 • mRNA-1273-P203 Part 1A and Part 1B, data as of 31 Jan 2022 Part 1C, data as of 15 Aug 2022 Part 3 Day 29 interim analysis (IA) (FDA Single Dose IR). Data as of 05 Jun 2023 • mRNA-1273-P204 Part 1 and Part 2, data as of 07 Sep 2022 • mRNA-1273-P306 Part 1 and Part 2, data as of 05 Dec 2022 • Booster sBLA (Part 2), data as of 21 Mar 2023 External Databases: Disproportionality was performed for the external safety databases VAERS and EVDAS. Review of the Pharmacovigilance Database: The MAH GSDB was queried cumulative as of 17 Jun 2023, for valid case reports of mastitis and breast swelling received from HCP, HA, consumers, and literature, worldwide for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, using the MedDRA dictionary, version 26.0 PT: "Mastitis, Breast swelling, Breast enlargement, and Breast oedema". Given that there is no established case definition for mastitis or breast swelling/breast oedema, the MAH created a case definition to establish a certainty level of whether a report could be classified as a case of mastitis or breast swelling. For mastitis, based on the case definition presented below, all identified cases meeting the case definition, were medically reviewed (regardless of seriousness or medically confirmed): Mastitis: This is an inflammatory condition that may be due to several different etiologies, infectious or not, but most breast inflammation is expressed as a hard, swollen, and red breast area, accompanied by a fever above 38.5°C, chills, and general flu-like symptoms. In addition, the mastitis cases were classified as lactational or non-lactational based on the information provided. Breast swelling: Breast swelling/edema is fluid accumulation within breast tissue that may lead to visible swelling, increased breast density, inflammation, skin dimpling and thickening, breast pain, and sagging of the breast.

Signal evaluation criteria	Summary
	In order to identify cases that met the case definition of breast swelling/breast enlargement/breast oedema, the medical review was focused on: • Serious cases (medically confirmed/not medically confirmed) • Non-serious medically confirmed cases • Non-serious not medically confirmed cases that contained diagnostic information (e.g., mammogram, breast ultrasound) • Male gender cases, and cases with ages < 18 years old. Breast swelling/breast edema/breast enlargement cases reported for males are often reported as events of gynecomastia. For thoroughness, the MAH global safety database was also queried cumulative as of 17 Jun 2023, for valid case reports of gynecomastia received from HCP, HA, consumers, and literature, worldwide, for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, using the MedDRA dictionary, version 26.0 PT: "Gynecomastia." There is no established case definition for gynecomastia. The MAH created a case definition to establish a certainty level of whether a report could be classified as a case of gynecomastia, and all identified cases meeting the case definition, were medically reviewed (regardless of seriousness or medically confirmed): Gynecomastia is an increase in the amount of breast gland tissue in boys or men, caused by an imbalance of the hormones estrogen and testosterone that may cause pain (particularly in adolescents), swollen breast tissue, breast tenderness, and nipple sensitivity. The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system was used for causality assessment for all cases of mastitis, breast swelling/breast oedema/breast enlargement, and gynecomastia. In the absence of an established risk window and established biological plausibility, MAH has chosen to use 42 days as the upper limit for TTO following vaccination consistent with risk window used for other AESIs for COVID-19 vaccines. Literature search review: A cumulative literature search was performed from 18 Dec 2020 to 17 Jun 2023 using PubMed for search strategies used to identify articles related to mastitis and breast swelling and COVID-19 mRNA vaccine, elasomeran.
Results	Clinical Trial Data: **mRNA-1273- P301 Study** Study mRNA-1273-P301 (randomized, stratified, observer-blind, placebo-controlled study) included healthy adults ≥ 18 years of age. 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. There were two participants in P301, reporting one event of "Breast swelling" and one event of "Breast enlargement". **mRNA-1273-P203 Study** Study mRNA-1273-P203 (Phase 2/3, randomized, observer-blind, and placebo controlled) included healthy adolescents in the age group 12 to < 18 years, there was one participant reporting an event of "Mastitis" was observed. **mRNA-1273-P204 Study**

Signal evaluation criteria	Summary
	Study mRNA-1273P204 (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. In mRNA-1273-P204, there was one participant reporting an event of "Mastitis". **mRNA-1273-P306 Study** Study mRNA-1273-P306 (An Open-Label, Phase 3 Study) included healthy pediatrics between 6 months to < 6 years. In study P306, there were no participants reporting any events of Mastitis and Breast swelling. Summary of clinical trial Data No imbalance was observed in any of the 4 studies for the PTs "Mastitis," "Breast swelling," "Breast oedema," or "Breast enlargement". Four participants identified with events of interest. All four cases were considered as "not related to product Investigational product" by the investigator. External Databases: VAERS: No disproportionate reporting of events was observed using EB05 > 2 (mRNA-1273 versus All vaccines in adults) in VAERS. EVDAS: The PTs for breast swelling, breast edema, and breast enlargement demonstrated disproportionality as the ROR was >1. Breast swelling (ROR= 2.17; n=260), Breast oedema (ROR=1.77; n=31) and Breast enlargement (ROR=1.31; n=135). While disproportionality is not uncommon in EVDAS, results should be taken with caution given the limitations in EVDAS and based on low case counts. Review of the Pharmacovigilance Database: Review of Mastitis Cases Cumulatively, as of 17 Jun 2023, the MAH received a total of 117 cases (120 events) with the PT of "mastitis". There were 66 serious cases (66 serious events). There were no fatal events, and 43 cases were medically confirmed. There were 113 cases (96.6%) reporting 116 events (65 serious) following vaccination with elasomeran; 4 cases (3.4%) reporting 4 events (1 serious) following vaccination with elasomeran/imelasomeran; no cases were reported following vaccination with elaosmeran/davesomeran. The majority of cases were reported in females (116 cases; 99.1%) especially among women of reproductive age (specifically 18-49 years of age), and no reports in the adolescent's group (12 to 17 years of age); there was 1 case (0.9%) reported in a male. In the 115 cases that provided age data, the mean patient age was 41.6 years (SD: 13.3) with a median age of 37.0 years (age range: 23.0 to 82.0 years). A considerable proportion of reports were received from regulatory authorities and in such cases, follow-up is not possible due to privacy restrictions. When TTO and dose number were known most events had a TTO within 7 days regardless of dose number. The median TTO was 2.5 days (range: 0 to 62 days) with an average TTO of 6.1 days (SD: 10.0) which reflects expected vaccine reactogenicity. Most of the events (71 events; 59.2%) reported an outcome of resolved/ resolving. According to the case classification of mastitis cases there were 31 lactational cases; and 32 non-lactational cases; 53 were classified as unknown; and 1 (male patient) was

Signal evaluation criteria	Summary
	considered not applicable. In most of the cases (108; 92.3%), mastitis was reported without breast swelling, breast oedema, or breast enlargement. In 5 cases, the diagnosis of mastitis was confirmed by breast ultrasound and/or mammogram. In three cases (WW Identifier: [redacted], the patients had a positive rechallenge with subsequent mRNA vaccines; however, all the patients had confounding factors such as concurrent breastfeeding and history of mastitis. In one case (WW Identifier: [redacted], the patient had a negative rechallenge with a subsequent mRNA vaccine. Overall, most cases, key missing information included medical history, concomitant medications, pregnancy status, onset of the event, clinical course, physical examination, treatment, dechallenge/rechallenge information, and diagnostic studies. There was one case (WW Identifier: [redacted] reporting events of mastitis in a male patient. The case involved a 34-year-old male with a history of hypogonadism who experienced mastitis in conjunction with pyrexia the same day he received his third dose of elasomeran vaccine. Concomitant medications included testosterone. Key information such as diagnostic studies, physical examination, and treatment were not provided. The reported outcome was "Not resolved" at the time of this report. **Risk Factors/ Confounders** Review of 117 cases, shows that for 74 cases (63.2%), the patients had risk factors and/or confounders for mastitis including: concurrent breastfeeding (29 cases), concurrent lymphadenopathy (18 cases), concomitant medications associated with gynecomastia/breast swelling (12 cases), thyroid disease (8 cases), COVID-19 infection (5 cases), previous mastitis (3 cases), menstrual disorder (3 cases), diabetes mellitus (2 cases), previous breast disorder (1 case), breast cancer (1 case), prolactin-producing pituitary tumor (1 case), obesity (1 case), endometriosis (1 case), breast prothesis user (1 case), galactostasis (1 case), unspecified autoimmune disorder (1 case), and herpes zoster (1 case). In 13 cases (11.1%), the patients had received prior COVID-19 vaccinations with Pfizer-BioNTech COVID-19 vaccine and/or AstraZeneca COVID-19 vaccine. **Serious Events of Mastitis** Out of the 65 serious events of mastitis, there were three cases (WW Identifier# [redacted]) concerning patients who were hospitalized for mastitis. One case (WW Identifier# [redacted]) concerned a 37-year-old female with a history of mitral valve prolapse who developed mastitis one day after receiving the third dose of elasomeran vaccine. It was unknown if the mastitis was associated with breastfeeding or a recent pregnancy. The patient was first treated with antibiotics; however, she was hospitalized 30 days later for a breast abscess due to mastitis. A breast biopsy revealed mixed acute suppurative inflammation, necrotizing granulomatous inflammation, micro abscess formation, focal granulation tissue formation, and no micro-organisms. Treatment included incision/drainage and debridement. The patient improved and was discharged. The remaining two cases (WW Identifier# [redacted] and [redacted] contained limited information regarding the hospitalization. According to the WHO-UMC causality assessment, the 65 serious events were assessed as follows: "Probable" (2 events), "Possible" (11 events), "Unlikely" (4 events), and

Signal evaluation criteria	Summary
	"Unassessable" (48 events). **WHO Causality Assessments** According to the WHO (World Health Organization)-UMC causality assessment, review of the 120 events were assessed as follows: "Probable" (4 events), "Possible" (17 events), "Unassessable" (94 events), and "Unlikely" (5 events). **Breast Swelling Cases (including Breast Oedema, and Breast Enlargement):** Cumulatively, as of 17 Jun 2023, the MAH received 616 cases (631 events) of breast swelling, breast oedema, and breast enlargement following vaccination with an elasomeran-containing vaccine. There were 90 serious cases (53 serious events), with no cases reporting a fatal outcome, and 188 cases were medically confirmed. There were 605 cases (98.2%), reporting 620 events (50 serious) following vaccination with elasomeran; 9 cases (1.5%) reporting 9 events (3 serious) following vaccination with, elasomeran/imelasomeran and 2 cases (0.3%) reporting 2 non-serious events following vaccination with and elasomeran/davesomeran. Most cases were reported in females (575 cases; 93.3%) when compared to males (33 cases; 5.4%); with 8 cases (1.3%) not reporting gender. Most cases (380; 66.2%) were among women of reproductive age (specifically 18-49 years of age). There were 2 reports received in the adolescent group of 12-17 years of age and one report in pediatric group of 0-5 months old. In the 574 cases that provided age data, the mean age was 44.5 years (SD: 14.3) with a median age of 43.0 years (age range: 9 days to 97 years). The most reported PTs were Breast swelling (440 events; 69.7%), Breast enlargement (152 events; 24.1%), and Breast oedema (39 events; 6.2%). A considerable proportion of reports were received from regulatory authorities. In such cases, follow-up is not possible due to privacy restrictions. Based on the case definition and on the evaluation, criteria presented above, for cases with reported PTs of breast swelling/breast oedema/breast enlargement, 320 cases involving 323 events were identified for focused medical review. Most of these 320 cases were reported in females (284 cases; 88.8%) with 33 cases (10.3%) reported in males and 3 cases (0.1%) that did not report gender. Most cases (158; 49.4%) were among women of reproductive age (specifically 18-49 years of age). In the 301 cases that provided age data, the mean age was 48.6 years with a median age of 48.0 years (age range: 9 days old to 97 years). When TTO and dose number were known (323 events), events most frequently occurred within 7 days of vaccination regardless of dose number. The median TTO was 2.0 days (range: 0 to 214 days) with an average TTO of 7.6 days (SD: 18.6) which reflects expected vaccine reactogenicity. There were 33 cases (7 serious) in which events of breast swelling, breast oedema, or breast enlargement were reported in a male patient. In the 30 cases that provided age data, the mean age was 57.5 years with a median age of 49.5 years (age range: 25 to 89 years). In 21 cases (63.6%), the patients had one or more risk factors and/or confounders for breast swelling, breast enlargement, or breast oedema as follows: concurrent lymphadenopathy/peripheral oedema (12 cases), concomitant medications associated with gynecomastia (9 cases), gynecomastia (2 cases), diabetes mellitus (2 cases), breast mass (2 cases), herpes zoster (1 case), weight increased (1 case), prostate cancer (1 case), and tobacco usage (1 case). In the remaining 12 cases, limited information was provided. The reported outcomes of the events were as follows:

Signal evaluation criteria	Summary
	"Resolved" (3 events), "Not resolved" (20 events), "Resolving" (2 events), and "Unknown" (8 events). There were 3 non-serious cases in which breast swelling or breast enlargement occurred in patients younger than 18 years of age. Case (WW Identifier: [redacted]) involved 9-day-old female, with an unknown medical history, who experienced bloody nipple exudate 24 days after the mother received the third dose of elasomeran vaccine; the event subsequently resolved after an unspecified period. Case (WW Identifier: [redacted]) involved a 12-year-old female with an unknown medical history who experienced breast swelling associated with pyrexia 1 day after receiving an unspecified dose of elasomeran; the event was reported as "Resolving". Case ([redacted]) involved 16-year-old female with an unknown medical history who experienced breast enlargement in conjunction with unspecified menstrual disorder an unknown time after receiving an unspecified dose of the elasomeran vaccine; the event was reported as "Not resolved". According to the WHO-UMC causality assessment, all events were assessed as "Unassessable". **Risk Factors/ Confounders from Breast Swelling Cases** Review of the 320 cases, showed that 241 (75.3%) cases were heavily confounded by the patient's risk factors and/or confounders for breast swelling, breast oedema, and breast enlargement including: concurrent lymphadenopathy/ lymphoedema/lymphadenitis (107 cases), concurrent medications associated with gynecomastia/breast swelling (65 cases), concurrent peripheral oedema/fluid retention (50 cases), menstrual disorder (41 cases), thyroid disease (19 cases), diabetes mellitus (13 cases), breast cancer (9 cases), breast mass (6 cases), herpes zoster (6 cases), obesity/overweight (6 cases), amenorrhea (5 cases), concurrent breastfeeding (4 cases), breast prothesis user (4 cases), endometriosis (4 cases), axillary mass (2 cases), tobacco user (3 case), concurrent COVID-19 infection (3 cases), previous breast disorder (2 cases), concurrent pregnancy (2 cases), polycystic ovarian syndrome (2 cases), gynecomastia (2 cases), weight increased (2 cases), fibrocystic disease (1 case), concurrent pulmonary embolism (1 case), concurrent deep vein thrombosis (1 case), unspecified autoimmune disorder (1 case), chronic kidney disease (1 case), benign pituitary tumor (1 case), and increased prolactin level (1 case). In 43 cases (13.4%), the patients had received prior COVID-19 vaccinations with Pfizer-BioNTech COVID-19 vaccine and/or AstraZeneca COVID-19 vaccine. In 9 cases (2.9%), breast swelling, or breast enlargement was reported in conjunction with mastitis. In 6 of those 9 cases, concurrent lymphadenopathy (5 cases) and/or concurrent breastfeeding (3 cases) were reported. In 283 cases (88.4%), breast swelling/breast enlargement/breast oedema were reported in conjunction with other PTs (e.g., pyrexia, chills, lymphadenopathy, axillary pain, lymph node pain, erythema, breast tenderness, breast mass, breast cyst, breast discharge, breast pain, breast implant infection, influenza like illness, lactation insufficiency, autoimmune thyroiditis, fluid retention, peripheral swelling, weight increased, COVID-19 infection, herpes zoster). In addition, 41 oedema cases (6.7%) were associated with menstrual disorders (e.g.,

Signal evaluation criteria	Summary
	unspecified menstrual disorder, polymenorrhea, menstruation delayed, intermenstrual bleeding, heavy menstrual bleeding, menometrorrhagia, menstruation irregular, vaginal hemorrhage) suggestive of physiological hormonal changes due to estrogen and progesterone. Additionally, for 9 cases, the patients had either pre-existing breast cancer (8 cases) or newly diagnosed breast cancer (1 case). The first case (WW Identifier#: [redacted]) involved a 57-year-old female with a history of breast cancer (status post mastectomy) who experienced breast swelling associated with lymphadenopathy and peripheral oedema; treatment and outcome were not provided. The second case (WW Identifier#: [redacted]) involved a 46-year-old female breast cancer (status post bilateral mastectomy) who experienced breast swelling associated with lymphadenopathy 2 days after receiving the first elasomeran vaccine; treatment and outcome were not provided. The third case (WW Identifier#: [redacted]) involved a 58-year-old female with a history of breast cancer who experienced breast swelling associated with axillary pain and peripheral oedema the same day she received an unknown dose of elasomeran vaccine; the reported outcome was "Not resolved" and treatment was not provided. The fourth case (WW Identifier#: [redacted]) involved a 75-year-old female with a history of breast cancer who experienced breast swelling associated with lymphadenopathy 3 days after receiving the first dose of elasomeran; the reported outcome was "Not resolved" and treatment was not provided. The fifth case (WW Identifier#: [redacted]) involved a 63-year-old female with a history of breast cancer who experienced breast swelling associated with lymphadenopathy and breast discoloration 9 days after receiving the second dose of elasomeran vaccine; the patient was treated with cephalexin and outcome was not provided. The sixth case (WW Identifier#: [redacted]) involved a 51-year-old female with a history of breast cancer who experienced breast swelling associated with lymphoedema and peripheral swelling; the reported outcome was "Not resolved" and treatment was not provided. The seventh case (WW Identifier#: [redacted]) involved a 57-year-old female with a history of breast cancer who experienced breast swelling associated with weight increased within 27 days of receiving the second dose of elasomeran vaccine; treatment and outcome were not provided. The eighth case (WW Identifier#: [redacted]) involved a 65-year-old female with a history of breast cancer who experienced breast swelling associated with pyrexia and erythema 1 day after receiving the second dose of COVID-19 vaccine; the reported outcome was "Resolved", and treatment was not provided. The ninth case (WW Identifier#: [redacted]) involved a 54-year-old female with an unknown medical history who was diagnosed with breast cancer 33 days after receiving the second dose of elasomeran vaccine; treatment and outcome were not provided. In the 95 events that reported location of breast swelling/breast enlargement/breast

Signal evaluation criteria	Summary
	oedema events, the locations were as follows: unilateral event with unknown vaccination site (46 events), unilateral event ipsilateral to the vaccination site (35 events), bilateral with unknown vaccination site (11 events), unilateral event contralateral to the vaccination site (2 events), and bilateral with vaccination site on left side (1 event). **WHO Causality assessment** According to the WHO- UMC causality assessment, 323 events were assessed as: "Probable" (8 events), "Possible" (65 events), "Unassessable" (238 events), "Unlikely" (11 events), and "Not applicable" (1 event occurred with another vaccine). In many cases, key missing information included medical history, concomitant medications, pregnancy status, onset of the event, clinical course, physical examination, treatment, dechallenge/rechallenge information, and diagnostic studies. **Literature review** The PubMed search retrieved 118 unique articles, including the six literature articles cited in the TGA request letter (4 case reports, 1 prospective cohort study, 1 literature review). But none of these articles were indicative or suggestive of a potential for a causal association or a potential MoA. Below is a summary of the six literature articles cited by the TGA. *Management Strategies for Patients Presenting with Symptomatic Lymphadenopathy and Breast Oedema After Recent COVID-19 Vaccination [50]* The authors reviewed the two recent publications on the combination of axillary lymphadenopathy and breast oedema after COVID-19 mRNA vaccination that subsequently resolved. Ipsilateral lymphadenopathy was often incidentally detected on multimodality imaging; sonographic findings included enlarged nodes with cortical thickening, loss of normal fatty hilum, and possible hypervascularity. They discussed a case of symptomatic lymphadenopathy confounded by profound unilateral breast swelling after recent vaccination with subsequent biopsy revealing invasive lobular carcinoma and nodal metastasis. They stated that although ipsilateral axillary and breast oedema associated with COVID-19 vaccination was uncommon, it was critical to consider differential diagnosis of unilateral breast oedema including both malignant (e.g., inflammatory breast cancer, primary or metastatic breast cancer, breast lymphoma) and benign (e.g., mastitis, congestive heart failure, venous occlusion, trauma, previous surgery, or radiation treatment) causes. Patients presenting with axillary lymphadenopathy and with other breast symptoms or additional abnormal imaging findings should be considered in a high-risk category and need prompt diagnostic evaluation and consideration of tissue sampling with punch biopsy. *Breast implant seroma: A SARS-CoV-2 mRNA vaccine side effect [51]* This was a case report of a 48-year-old female patient with a history of textured silicone gel breast implants for aesthetic reasons (5 years ago) who experienced bilateral breast swelling associated with breast pain and warmth 10 days after a second Pfizer-BioNTech SARS-CoV-2 mRNA vaccine dose. A clinical breast examination revealed enlarged, firm breasts without skin abnormalities. A breast ultrasound showed diffuse fluid collection surrounding the breast implants, no breast tissue abnormality, and no implant rupture. Laboratory tests revealed elevated C-reactive protein (6.3 mg/L) and positive rheumatoid antibodies (AntiENA, AntiSSA). The patient noticed symptom improvement 48 hours after nonsteroidal anti-inflammatory drug treatment and complete disappearance of symptoms after 10 days with seroma disappearance detected on

Signal evaluation criteria	Summary
	ultrasound. The authors hypothesized that a breast implant seroma as post-SARS-CoV-2 mRNA vaccine adverse event since other diagnoses had been excluded. *Mammographic and sonographic findings in the breast and axillary tail following a COVID-19 vaccine [52]* This was a case series of 3 female patients (ages 36, 60, 83 years old) who had abnormal findings on diagnostic mammography within 1-11 days after receiving an unspecified COVID-19 vaccination. In the literature, axillary lymphadenopathy on breast imaging after recent COVID-19 vaccination has been reported as immunization has become more widespread. While muscle oedema at the injection site has been observed on MRI secondary to an immune response, ipsilateral breast imaging observations of oedema have not been reported to be seen with the COVID-19 vaccinations. Mammographic findings such as trabecular and skin thickening, along with increased echogenicity on ultrasound, can be seen with oedema secondary to capillary leak or poor lymphatic drainage. The authors stated that these findings should be considered as a possible etiology for the observed breast oedema following a recent COVID-19 vaccine. Inflammatory changes observed in the breast and axillary tail post vaccination described in this case series were transient, but clinically relevant for patients who experience swelling following injection. Similar to evaluations for suspected mastitis, a short interval imaging follow-up to confirm resolution may be appropriate for patients with ipsilateral vaccination histories and could potentially reduce the number of false positive examinations in this clinical scenario. The authors concluded that inflammatory breast cancer can mimic inflammation and infection, therefore, close follow-up to resolution was critical as to not miss cancer. *Breastfeeding Mother and Child Clinical Outcomes After COVID-19 Vaccination [53]* This was a prospective cohort study of 88 lactating healthcare workers in Singapore who received two doses of BNT162b2 vaccination (Pfizer/BioNTech). The aims of the study were to determine solicited adverse effects (e.g., axillary lymphadenopathy, mastitis, and breast engorgement) as well as systemic and local adverse effects of BNT162b2 mRNA vaccine in mothers and potential effects on their breastfed infants. The outcomes of mother–child dyads within 28 days after the second vaccine dose were determined through a participant-completed questionnaire. The results revealed minimal effects related to breastfeeding were reported by the study cohort. Three of 88 (3.4%) participants had mastitis, one (1.1%) participant experienced breast engorgement, five of 88 (5.7%) participants reported cervical or axillary lymphadenopathy. There was no change in human milk supply after vaccination. The most common side effect was pain/ redness/swelling at the injection site, which was experienced by 57 (64.8%) participants. There were no SAEs of anaphylaxis or hospital admissions. There were no short-term adverse effects reported in the infants of 67 lactating participants who breastfed within 72 hours after BNT162b2 vaccination. The authors concluded that BNT162b2 vaccination was well tolerated in lactating participants and was not associated with short-term adverse effects in their breastfed infants. *Transient ipsilateral breast oedema following COVID-19 vaccination [54]* This was a case report of a 60-year-old female patient with an unknown medical history who experienced ipsilateral breast oedema 2 days after receiving her second booster dose of ModernaTx, Inc COVID-19 vaccination. The screening mammography revealed a new global asymmetry in the left axillary region comprised of trabecular thickening suggestive of oedema. Approximately 13 days later, the patient had repeat diagnostic

Signal evaluation criteria	Summary
	studies which revealed that the breast findings had resolved included the lymphadenopathy. While ipsilateral lymphadenopathy following COVID-19 vaccination is a relatively common finding on mammography, breast ultrasound transient ipsilateral breast oedema is rare with only a few published case reports. Radiologists should be aware of this potential imaging appearance of the breast and axilla following COVID-19 vaccination given the imaging features of oedema such as trabecular thickening, skin thickening, and increased echogenicity can overlap with benign and malignant breast conditions such as mastitis and inflammatory breast cancer. *Mammographic Findings of Diffuse Axillary Tail Trabecular Thickening After the Second Booster of COVID-19 Vaccination [55]* This was a case report of a female patient of unknown age with a history of hypertension, diabetes mellitus, hyperlipidemia, and morbid obesity who had a diffuse axillary tail trabecular thickening of the left breast on a screening mammogram 4 days after receiving her second Pfizer booster COVID-19 vaccination. Of note, the patient had completed the primary COVID-19 vaccination series and received a first booster (specific vaccines were not provided). Concomitant medications included nifedipine, furosemide, spironolactone, and unspecified diabetic medications. Four weeks, the patient had a diagnostic mammography which revealed that the breast findings had resolved including lymphadenopathy. The authors stated that both breast cancer and mastitis may present similar findings; however, ipsilateral injection of COVID-19 vaccine/booster and spontaneous resolution on follow-up provided clues to the etiology. It has been hypothesized that proinflammatory conditions (e.g., hypertension, obesity, and diabetes) may predispose to axillary tail trabecular thickening on mammography post-COVID-19 vaccination. The authors concluded that it was important to recognize these findings in the context of COVID-19 vaccinations and boosters to avoid unnecessary biopsies that would strain the healthcare system and to avoid needless patient anxiety. Overall conclusion, there were few articles describing mastitis and/or breast swelling as mostly transient events occurring within 14 days following administration of mRNA vaccine against COVID-19. Most articles described events of mastitis and breast swelling as a secondary manifestation stemming from the presence of axillary lymphadenopathy following vaccination. Overall, the literature review did not provide sufficient evidence of a direct causal association between mastitis and breast swelling and elasomeran vaccine administration. However, the articles suggest the presence of axillary lymphadenopathy following mRNA COVID-19 vaccine administration (which is a labeled adverse event for elasomeran) may be the precursor that contributes to events of mastitis and/or breast swelling.
Discussion	The MAH conducted an extensive evaluation of two validated signals of mastitis and breast swelling triggered by a request from a health agency received on 05 Jul 2023, requesting to update the SPIKEVAX PI to include these two medical topics in the warning and precautions section. The signal evaluation included a cumulative review of all safety data available to the MAH, including non-clinical data, clinical trial information, post-marketing reports as well as cumulative review of the literature. The review was conducted using four MedDRA PTs (Mastitis, Breast swelling, Breast oedema, and Breast enlargement) with a DLP of 17 Jun 2023. Mastitis is a relatively common breast condition that can affect patients at any time but occurs mainly in women who are breastfeeding; it is defined as inflammation of the

Signal evaluation criteria	Summary
	breast with or without infection. The most common signs and symptoms of mastitis are fever, chills, breast pain, breast swelling, and enlargement of axillary lymph nodes. There are three types of mastitis (e.g., lactational, non-lactational, non-infectious). Common causes of mastitis include bacterial infection, oral contraceptives, long-term steroids, and breast implants. Mastitis is usually diagnosed based on history and clinical findings; however, useful diagnostic tools include breast ultrasound and mammograms. If mastitis is left untreated, it may cause tissue destruction resulting in an abscess associated with bacteremia and sepsis. Breast oedema is fluid accumulation within breast tissue that may lead to visible swelling, increased breast parenchymal density, inflammation, breast pain, and sagging of the breast. This fluid buildup is largely a result of compromised outflow due to an obstruction or disruption of lymphatic vessels that drain the breast. Common causes of breast oedema include lymphatic obstruction, breast cancer, breast cancer treatment, congestive heart failure, mastitis, trauma, and concomitant medications. Breast oedema is usually diagnosed based on physical examination, mammograms, MRI, and plain radiology. The lymphatic system is a critical part of the immune system and consists of lymph fluid, vessels, and lymphoid tissues (e.g., lymph nodes, tonsils, spleen). In addition, lymph nodes play a key role in triggering the body's immune response to vaccines via development of lymphocytes (e.g., B cells and T cells). Figure-4 contains images of the lymphatic system in men and women as well as an image of the axillary nodes in a woman. At the injection site, there are several interactions between cells and the vaccine components that leads to the production of antibodies, effector cells, and memory cells. In the "draining lymph node" (lymph node downstream from the vaccination site), sites of B-cell development form in the B-cell zones of the lymph nodes. Immediately following vaccination, local innate cells release cytokines into the circulation to enable a coordinated response [56]. Information from the ModernaTx, Inc combined developmental and perinatal/postnatal reproductive toxicity study, there were no vaccine-related adverse effects on females, fetal development, or postnatal development. In non-clinical studies in rats, the highest mRNA concentrations were observed at the injection site followed by the popliteal and axillary lymph nodes, consistent with distribution via the lymphatic system. Also, repeat-dose toxicity studies in rats revealed macroscopic findings of enlarged lymph nodes and skin thickening at the injection site. Across ModernaTx, Inc sponsored clinical trials, there were 4 non-serious cases of mastitis. In one case, the TTO was 2 days after the second mRNA-1273 which resolved after 4 days without treatment. In the remaining 3 cases, the TTO was > 42 days which is suggestive of an alternative etiology. However, there was an imbalance between mRNA and placebo with regards to lymphadenopathy in both males and females as well as across all age groups. In the GSDB, the search criteria for mastitis yielded 117 cases (120 events) reported primarily with elasomeran (113 cases). Of the 120 events, 65 events were serious, and none had a fatal outcome. Most events involved females between the ages of 23-82 years old with most cases involving women of reproductive age. There was one case in a male patient; however, there were no reports of mastitis in the adolescent or pediatric groups. In 63.2% of the cases, the patients had risk factors and/or confounders for mastitis. In the cases that reported pregnancy status, there were an equal number of lactational and non-

Signal evaluation criteria	Summary
	lactational mastitis events. In 27 cases, unilateral breast swelling was reported with 11 events occurring ipsilateral to the vaccination site. Most mastitis events (54.7%) occurred in conjunction with other reactogenicity events (i.e., lymphadenopathy, pyrexia, chills, influenza like illness). In addition, 7 mastitis cases were associated with menstrual disorders suggestive of physiological hormonal changes due to estrogen and progesterone. Most of events occurred after Doses 1 and 2 with a TTO that ranged from same day to 60 days (median of 2.5 days; mean of 6.1 days). Seventy-one (71) events reported an outcome of either "resolved", "resolving", or "resolved with sequelae". Three patients were hospitalized for mastitis; one patient was hospitalized for a breast abscess due to mastitis 30 days after receiving third dose of elasomeran; the remaining two cases contained limited information regarding the hospitalization. Three patients had a positive rechallenge (all 3 patients had confounding factors) and one patient had a negative rechallenge with a subsequent mRNA vaccine. The WHO causality assessments were "probable" (4), "possible" (16), "unassessable" (95), and "unlikely" (5). The search criteria and case definition for breast swelling, breast enlargement, and breast oedema, yielded 320 cases (90 serious, 230 non-serious) involving 323 events reported predominantly with elasomeran (315 cases). Most of the events involved females between the ages of 9 days old and 97 years old with most cases involving women of reproductive ages. There were 33 male patients and 3 patients < 18 years of age. In the 70.6% cases, the patients had risk factors and/or confounders for breast swelling events. Most of the events (88.1%) of breast swelling events occurred in conjunction with other reactogenicity events (i.e., lymphadenopathy, pyrexia, chills, influenza like illness). Most of events occurred after Doses 1 and 2 with a TTO that ranged from same day to 120 days (median of 2.0 days; mean of 7.6 days). One hundred events (100) reported an outcome of either "resolved", "resolving", or "resolved with sequelae". Two patients were hospitalized for breast swelling / breast oedema associated with a possible vaccination reaction and chest pain. One patient had a positive rechallenge and two patients had a negative rechallenge with subsequent mRNA-1273 vaccines. The WHO causality assessments were "probable" (8), "possible" (65), "unassessable" (238), and "unlikely" (11), and "not applicable" (1 event occurred with another vaccine). Due to a plausible temporal relationship between the events of mastitis and breast swelling/breast oedema/breast enlargement and 4 cases of positive rechallenge after subsequent vaccinations with mRNA-1273, a contributory role of elasomeran could not be excluded. However, there were 3 cases of a negative rechallenge after subsequent vaccinations. Based on the information provided in the cases, the events of mastitis, breast swelling, breast oedema, and breast enlargement are most likely secondary to post-vaccinal lymphadenopathy, which is a labeled event of elasomeran, triggered by the immune response to the vaccine. Since the immune response to the elasomeran vaccine is robust, the degree of lymphadenopathy is more pronounced [57]. The lymphadenopathy is typically observed in the axilla lymph nodes ipsilateral to the vaccination site. Due to the large scale COVID-19 vaccination campaign, there has been a marked increase in the identification of the lymphadenopathy associated with the vaccines [58]. Of note, vaccine-related lymphadenopathy has been reported with other vaccines (e.g., measles, anthrax, H1N1 influenza, human papilloma virus, Bacille Calmette-Guerin [BCG], smallpox) [59-61]. Furthermore, there were two cases of breast swelling that occurred after receiving Tozinameran and TicoVac vaccines; in both cases, the events occurred

Signal evaluation criteria	Summary
	prior to receiving the first dose of elasomeran vaccine. For mastitis, the O/E analysis was only conducted in women due to lack of expected incidence in men. In overall mastitis (lactational and non-lactational), the number of observed cases were lower than expected cases for all age strata. However, the number of observed cases were higher than expected for two age groups (25-39 years old and 40-49 years old) in non-lactational mastitis. Of note, this did not meet the threshold for disproportionality. For breast oedema, the observed to expected analysis was not conducted due to lack of expected incidence of breast oedema. In VAERS, none of PTs for mastitis and breast swelling were disproportionately reported for both elasomeran and elasomeran/davesomeran. In EVDAS, there was disproportionately observed for mastitis and breast swelling PTs for elasomeran. Also, disproportionately was observed for breast swelling for elasomeran/imelasomeran, however, these data should be interpreted with caution due to the low counts. The literature review revealed a small number of articles describing mastitis and/or breast swelling in conjunction with lymphadenopathy as mostly transient events occurring within 14 days following administration of mRNA vaccine against COVID-19. Most articles described the events of mastitis and breast swelling as a secondary manifestation stemming from the presence of axillary lymphadenopathy following vaccination which were detected on imaging studies (e.g., mammogram, ultrasound).
Conclusion	Based on the analysis of all available safety, non-clinical studies, clinical trial, external database, and literature data as of 17 Jun 2023, the MAH considers that events of mastitis, breast oedema, breast swelling, and breast enlargement are most likely secondary to vaccination-related lymphadenopathy which is well-known ADRs observed with all vaccines. In addition, these events have been detected in mammograms and breast ultrasounds in post-COVID-19 vaccinated women. No new or emerging safety concerns were identified since lymphadenopathy is included as a very common ADRs in the SPIKEVAX PI and the current SPIKEVAX PI is considered to adequately reflect the safety profile of elasomeran. ModernaTx, Inc. concludes that no further action is warranted at this time and will continue to monitor events of Mastitis and Breast swelling using routine surveillance. The benefit-risk evaluation remains positive.

16.2.4 Postmenopausal haemorrhage

Table 16-7 Postmenopausal haemorrhage

Signal evaluation criteria	Summary
Source	On 27 Oct 2023, ModernaTx, Inc received a request from the EMA (EPITT No. 20015) as follows: • Having considered the available evidence from literature and post-marketing data, the PRAC has agreed that the MAH of COVID-19 mRNA vaccine (nucleoside-modified) elasomeran (Moderna Biotech Spain, S.L.) should perform a cumulative review of all cases of postmenopausal haemorrhage from all sources including, but not limited to, available data from clinical trials, scientific literature and post marketing exposure. The MAH should use a DLP as

Signal evaluation criteria	Summary
	recent as possible. • The MAH should discuss whether a causal relationship between elasomeran and postmenopausal haemorrhage can be established. • The MAH should also discuss the need for any potential amendment to the PI (Pl) and/ or the RMP (including relevant risk minimization measures) and make accordingly a proposal for the changes to the relevant sections within this discussion
Background	The MAH considered postmenopausal haemorrhage as a validated signal following receipt of PRAC's signal assessment report (EPITT No. 20015) requesting MAH for elasomeran (Moderna Biotech Spain S.L.) to perform a cumulative review of all cases of postmenopausal haemorrhage. Postmenopausal haemorrhage (PMH) is any vaginal hemorrhage/bleeding that occurs 12 months or more after the final menstrual period, in the absence of hormone replacement therapy use or pelvic surgery. PMH can range from light spotting that is pinkish-gray or brown, all the way to a heavy flow, like a regular period (ACOG). The pathophysiology of the post-menopause phase involves disruptions of the hypothalamic- pituitary-ovarian axis. Primary ovarian failure with depletion of ovarian follicles, especially the granulosa cells, the primary source of estrogen and inhibin. The ovary, therefore, is no longer able to respond to the pituitary hormones. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) level increase due to lack of feedback inhibition, and ovarian estrogen, progesterone, and inhibin production cease the major initial change underlying the menopause is a selective, gradual decline in inhibin B, the major regulator of follicular phase FSH. It is produced by the granulosa cells of antral follicles during the early follicular phase. The inhibin B decline leads to increased FSH. However, the androgen production continues in the remaining ovarian theca cells and adrenal gland. This androgen gets converted to estrogen through peripheral aromatization. Lack of estrogen causes atrophy of the vagina and endometrium. Inside the uterus, the collapsed and atrophic surfaces of the endometrium contain scant or no fluid to prevent friction inside the cavity. This leads to the development of micro-erosions of the epithelial surface, with subsequent chronic inflammation. This chronic endometritis is prone to spotting or light bleeding. PMH occurs in approximately 4 to11 % of postmenopausal women. About 1 to 14% of PMH events will be secondary to endometrial cancer (in developed countries) or due to cervical cancer in low to mid income countries (LMIC). Spontaneous recurrence of bleeding is reported to be very common during the first year after the 12 months of final menstrual period, declining afterwards. Lastly, there is an inverse relationship between PMH and postmenopausal years. The most common causes of PMH are benign, including atrophy of the endometrium or vaginal mucosa. Ninety percent (90%) of postmenopausal women diagnosed with endometrial cancer reported vaginal bleeding. Some potential causes for postmenopausal haemorrhage are structural abnormalities (such as endometrial or cervical polyps, endometritis, vaginitis, leiomyomata uteri, and adenomyosis), carcinomas/hyperplasia (including endometrial/cervical cancer, fallopian tube and ovarian malignancies), medications (such as hormone replacement therapy, anticoagulants, antiplatelets, NSAIDs, and glucocorticoids), non-gynecologic factors (disease in adjacent organs,

Signal evaluation criteria	Summary
	post-radiation therapy, sexual assault/ vaginal intercourse), and infection (ex: endometritis, genital Tuberculosis). PMH may also be accompanied by abdominal pain, fever, chills, headache, dizziness, and change in bladder and/or bowel function. PMH diagnosis involves medical judgement based on relevant medical history, physical/pelvic examination, and diagnostic results. Relevant medical history includes breast cancer, history of fibroids or polyps, menstrual period history menarche, final menstrual period, and duration of cycles.; and concomitant medications like hormone replacement therapy, SSRI's, glucocorticoids, anticoagulants, antiplatelets therapies, NSAIDs, and tamoxifen. Diagnostic tests include transvaginal ultrasound, hysteroscopy, cervical biopsy, and endometrial biopsy. The management of postmenopausal bleeding depends on the etiology: Vaginal atrophy: management includes vaginal lubricants, topical hormones, or other medications to reduce vaginal dryness. Polyps or fibroids: Management may include surgery for removal. Hormone therapy: management includes therapy modification or suspension. Infection: management includes medications to treat infection and stop future bleeding. Thick uterine lining (endometrial hyperplasia): management may include progestin therapy to trigger shedding of the uterine lining or dilation and curettage (D&C) procedure which removes the uterine lining surgically. Endometrial cancer: Management may include surgical removal of the uterus (hysterectomy), and possible removal of the ovaries and fallopian tubes; local lymph node biopsy; and if diagnosis warrants, chemotherapy or radiation after surgery [62].
Methodology	The MAH's clinical database and the GSDB were queried for valid case reports of PMH-related events received from HCP, HA, consumers, and literature, worldwide, for Marketed Moderna vaccines targeting SARS-CoV-2, using the MedDRA PT: "Postmenopausal haemorrhage." Two different Medical Dictionary of Regulatory Activities (MedDRA) versions were used. For clinical trials, MedDRA version 23.0 was used (since this was the version in use during the study periods) and for querying the global safety database, cumulative as of 17 Oct 2023, the current updated MedDRA version 26.1 was used: • Clinical Trial Data: The Company clinical database was queried cumulative from 18 Dec 2020 to 17 Oct 2023. Safety data from 3 adult clinical trials was reviewed to identify unsolicited events (serious and non-serious) reported using the MedDRA (version 23.0) PT "Postmenopausal haemorrhage." The topic of Postmenopausal haemorrhage was cumulatively reviewed in the clinical trial datasets, within the following studies. .1. mRNA-1273-P301, data as of 04 May 2021 .2. mRNA-1273-P205-Part H, data as of 23 Sep 2023 .3. mRNA-1273-P205-Part J, Data as of 25 May 2023 • Non-clinical: The Company non-clinical database was queried cumulative through 17 Oct 2023. A combined pre and postnatal developmental and perinatal/postnatal reproductive toxicity study (DART) with female Sprague Dawley rats was conducted to assess the potential effects of mRNA-1273 on fertility and pre and postnatal development. Safety data were reviewed to identified adverse events.

Signal evaluation criteria	Summary
	• External Databases: VAERS and EVDAS was reviewed for the PT: postmenopausal haemorrhage. • Review of the GSDB: The MAH GSDB was queried cumulative as of 17 Oct 2023, for valid case reports of PMH received from HCP, HA, consumers, and literature, worldwide, for Marketed Moderna vaccines targeting SARS-CoV-2, using the MedDRA dictionary, version 26.2 PT: "Postmenopausal haemorrhage". • Postmenopausal haemorrhage was defined as any vaginal haemorrhage/bleeding that occurs 12 months or more after the final menstrual period, in the absence of use of hormone replacement therapy or pelvic surgery (WHO, International Federation of Gynecology and Obstetrics [FIGO] & International Menopause Society). • Per the EMA request (EPITT No. 20015), only medically confirmed cases of PMH and non-medically confirmed cases of PMH with positive rechallenge were requested for focused medical review. • Non-medically confirmed cases of PMH with positive rechallenge were initially assessed to see if they met the criteria for a positive rechallenge. The criteria used to define a positive rechallenge were: • Event of PMH recurred after a second or third dose of the vaccine. • Event of PMH had previously reduced or stopped following last dose then restarted after a subsequent dose. • Once true positive rechallenge was determined, all medically confirmed cases of PMH and non-medically confirmed cases of PMH with positive rechallenge were medical evaluated to determine if they met case definition for postmenopausal haemorrhage. Cases were classified as: • Level 1: the report of postmenopausal haemorrhage occurred 12 months or more after the final menstrual period in the absences of hormone replacement therapy or pelvic surgery. • Level 2: the report did not provide sufficient information to meet the threshold of true case definition. • Level 3: the report was assessed as not a true case of postmenopausal haemorrhage. • The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment tool was used for causality assessment for all medically confirmed cases of PMH and non-medically confirmed positive rechallenge PMH cases which met Level 1 case definition. • Literature search review: A focused cumulative literature search in PubMed as of 18 Dec 2020 through 17 Oct 2023 retrieved 276 articles.
Results	**Non-clinical Data:** A combined pre and postnatal developmental and perinatal/postnatal reproductive toxicity study (DART) with female Sprague Dawley rats, showed there were no mRNA-1273 related effects or changes in the following parameters: mortality, body weight, body weight gain, food consumption macroscopic observation, estrous cycling during pre-cohabitation, mating and fertility, ovarian/uterine examination, or natural delivery or litter observations. Although PMH was not directly studied, the DART study showed no changes to ovary or uterus. **Clinical Trial Data:** **mRNA-1273-P301 Study:**

Signal evaluation criteria	Summary
	Study mRNA-1273-P301 (randomized, stratified, observer-blind, placebo-controlled study) included healthy adults ≥ 18 years of age. 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. There were 6 participants (3 from the placebo group and 3 from the treatment group) in P301, reporting the event of "Postmenopausal haemorrhage." **mRNA-1273-P205-Part H Study**: Study mRNA-1273-P205-Part H (open label, Phase 2/3 study) included adults ≥ 18 years of age. There were approximately 500 participants who received a second booster dose of 50 µg mRNA- 1273.222. No participants in P205-Part H reported the event of "Postmenopausal hemorrhage." **mRNA-1273-P205-Part J Study:** Study mRNA-1273-P205-Part J (randomized 1:1 ratio study) included adults ≥ 18 years of age. There were approximately 100 participants who received a second booster dose of either 50 µg mRNA-1273.815 or 50 µg mRNA-1273.231. No participants in P205-Part J reported the event of "Postmenopausal hemorrhage." **Summary of Clinical Trial Data** No imbalance was observed in any of the 3 studies for the PTs "Postmenopausal haemorrhage." Three participants in the treatment group identified with the event of interest. All 3 cases were considered as "not related to product IP" by the investigator. **External Databases:** VAERS: No disproportionate reporting of events of PMH was observed using EB05 > 2(mRNA-1273 versus All vaccines in adults) in VAERS. EVDAS: The PT for postmenopausal haemorrhage demonstrated disproportionality as the ROR was >1: Events of PMH with mRNA-1273 (Original) [ROR= 4.34; n=911] and events of PMH with mRNA-1273 Bivalent.222 (Original/BA.4/5) [ROR= 9.05; n=53]. While disproportionality is not uncommon in EVDAS, results should be taken with caution given the limitations in EVDAS, as well as the few cases included in the database. **Review of the GSDB:** Cumulatively as of 17 Oct 2023, the MAH received 978 cases (1,016 events) reporting a PMH-related event, of which 631 were serious (661 serious events) and no case reported a fatal outcome. There were 113 medically confirmed cases, and twenty-four (24) cases which were not medically confirmed, reported a positive rechallenge. **Medically Confirmed PMH Cases:** Out of the 113 cases medically confirmed (115 events) reporting PMH-related events, there were 89 serious cases (90 serious events). The majority of cases (99 cases; 87.6%) were from regulatory authorities and most cases (71; 62.8%) were received from the United States. The mean age of patients was 54.7 years (SD: 7.6 years) with a median age of 53.0 years (range: 27 to 81 years). For those reports providing outcome information (85) most of the events reported their outcome as recovered or recovering (43; 50.6%). *Case Classification for Medically Confirmed Cases:*

Signal evaluation criteria	Summary
	Of the 113 medically confirmed PMH cases which underwent medical review: 25 cases met Level 1 definition case of PMH), 83 cases met Level 2 definition (Not enough information), and 5 cases met Level 3 definition (Not a case). Of the 25 medically confirmed PMH cases that met Level 1 definition, 18 cases (72.0%) were serious, 7 cases (28.0%) were non-serious, and no case reported a fatal outcome. The majority of cases (22; 88.0%) were from regulatory authorities and most cases (16; 64.0%) were received from the United States. The median age was 51 years (range: 47 to 73 years). Most cases (16; 64.0%) reported that the Final Menstrual Period occurred less than 5 years from the PMH event onset. Most cases (16; 64.0%) reported events of PMH occurring after Doses 1 and 2 with a reported TTO of 0 to 28 days following vaccination [11 cases (44.0%) reported TTO between 7 to 28 days]. For more details, please refer to Appendix 5.2d. *WHO-UMC Causality Assessment for Level 1 Case Classification Medically Confirmed Cases* Of the 25 medically confirmed PMH cases which met Level 1 case definition: 5 cases were assessed as possible based on temporal association and the presence of alternate etiologies including thyroid disorders (hypothyroidism and Hashimoto's thyroiditis) and concomitant medications including levothyroxine and tamoxifen; 4 cases were assessed as unlikely; and 16 cases were unassessable. **Non-Medically Confirmed Positive Rechallenge PMH Cases**: Out of the 24 non-medically confirmed positive rechallenge PMH cases (36 events), 16 cases were serious (26 serious events). All 24 cases were from regulatory authorities, with most cases reported from either the Netherlands (10; 41.7%) or Norway (9; 37.5%). The mean age of patients was 52.2 years (SD: 7.2) with a median age of 51.0 years (range: 40 to 74 years). *Case Classification for Non-Medically Confirmed cases with a possible rechallenge:* Medical evaluation of the 24 non-medically confirmed, reported 'positive rechallenge' PMH cases showed only 8 cases met the criteria for positive rechallenge. *Assessment of those 8 non-medically confirmed positive rechallenge PMH cases, only 6 cases met Level 1 definition for PMH.* Half of the cases (3; 50.0%) reported that the Final Menstrual Period occurred less than 3 years from the PMH event onset. Most cases (5; 83.3%) did not report dose number. Time to event onset was reported with a wide range of 2 to 46 days. ***WHO-UMC Causality Assessment for Level 1 Cases, Non-Medically Confirmed Positive Rechallenge PMH Cases*** Of the 6 non-medically confirmed positive rechallenge PMH cases which met Level 1 case definition: 1 case was assessed as unlikely, and 5 cases were unassessable. **Literature search review:** Review of these 276 articles did not show any causal association between elasomeran vaccination and postmenopausal haemorrhage. These articles encompassed different types of studies, including case reports (26), observational studies (5), and others were general literature reviews on importance of vaccination or other general menstrual changes. Among these articles, a few were selected as recommended by PRAC [63] [64] [65], for their comprehensive information regarding postmenopausal hemorrhage following mRNA

Signal evaluation criteria	Summary
	COVID-19 vaccination. These articles provided valuable insights into the incidence, clinical presentation, management, and outcomes of this rare adverse event. ***Summary of PRAC requested articles:*** **Suh-Burgmann et al (2022)** described the "association between vaccination against COVID-19 and postmenopausal bleeding." In a large, diverse community cohort, using a self-controlled, risk interval methodology. The authors reported a slight increase in the rate of postmenopausal haemorrhage (PMH), that was of a small magnitude, implying that the clinical impact at the population level is negligible. The findings provided reassurance that COVID-19 vaccination is not associated with a clinically meaningful increase in the incidence of postmenopausal bleeding. The limitation of this descriptive study is the inability to establish a causal relationship, hence results cannot be generalized [63]. **Ljung et al (2023)** evaluated the "Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study" and observed weak and inconsistent associations between SARS-CoV-2 vaccination and healthcare contacts for bleeding in postmenopausal women. The authors concluded that their findings do not provide substantial support for a causal association between SARS-CoV-2 vaccination and healthcare contacts related to menstrual or bleeding disorders. Although this study used a larger population-based cohort, they were limited by insufficient relevant information, including date of final menstrual period, and TTO, making case definition for postmenopausal bleeding and the interpretation of effect of different risk windows challenging [64]. **Blix et al (2023)** conducted a retrospective data analysis to determine "the association between COVID-19 vaccines and of unexpected vagina bleeding in non-menstruating women." The authors observed an increased risk of unexpected vaginal bleeding after COVID-19 vaccination in non- menstruating women across different stages of reproductive aging. The authors postulated that "underlying mechanism for the increased risk might be related to the SARS-CoV-2 spike protein or ACE2 receptors", rather than disruptions of the hypothalamic-pituitary-ovarian axis and proposed further research to confirm their findings. The authors acknowledged the limitation of a retrospective design that was subject to recall bias and noted that the data are not fit to explore biological mechanisms of causality [65]. **Conclusion on Literature Review:** Overall, review of these published articles did not provide sufficient evidence of a direct causal association between postmenopausal hemorrhage (PMH) and elasomeran vaccination. There was no evidence of a plausible biologic mechanism of a causal relationship between PMH and elasomeran. No new safety reports were identified. Further, literature from observational studies suggest instances of PMH post-vaccination were rare and not statistically linked to the vaccine. Further studies are needed to understand the exact mechanisms and implications. **Possible mechanism(s) of action for the occurrence of PMH following administration of elasomeran: Literature Review.** The relationship between PMH and elasomeran has not been established [66]. There are several hypotheses postulating an immune activation caused by the COVID-19 vaccineswith consequent systemic effects on hemostasis, inflammation, and uterine adaptation [66]. The use of hormonal intrauterine device (IUD) and hormone replacement

Signal evaluation criteria	Summary
	therapy (HRT) have been reported to be another confounding factor related to the risk of PMB after vaccination across different stages of reproductive aging. One of the current hypotheses suggest an immune mediated mechanism, rather than a platform or specific vaccine component issue. Other hypotheses suggests that for the mRNA platform vaccines, including elasomeran, a possible mechanism of action for PMB is related to the SARS-CoV-2 spike protein and not to other vaccine components [66]. The authors proposed that local changes in the endometrium from spike-related immune response that cause inflammation could trigger vaginal bleeding or the endometrial expression of angiotensin-converting enzyme 2 (ACE2) receptors may enhance the spike related effect.
Discussion	Postmenopausal haemorrhage occurs in a small proportion of postmenopausal women, with a prevalence of about 4 – 11%. Spontaneous recurrence of bleeding has been reported to be very common during the first year after the 12 months of final menstrual period, declining afterwards. There is an inverse relationship between PMH and postmenopausal years. Although the most common causes of postmenopausal hemorrhage are benign, a high proportion (90%) of postmenopausal women diagnosed with endometrial cancer reported vaginal bleeding as an initial symptom. The pathophysiology of postmenopausal haemorrhage shows that ovarian failure leads to estrogen depletion and associated atrophy of the endometrium and vagina. The collapsed and atrophic surfaces of the endometrium contain scant or no fluid to prevent friction inside the cavity. This leads to the development of micro-erosions of the epithelial surface, with subsequent chronic inflammation. This chronic endometritis is prone to spotting or light bleeding. The review of published articles did not show any causal association between elasomeran vaccination and postmenopausal haemorrhage. Moreover, the article by Suh-Burgmann et al summarized above, provided reassuring findings from a large diverse community-based study of middle-aged women that COVID-19 vaccination was not associated with a clinically meaningful increase in the incidence of postmenopausal bleeding. Ljung et al evaluation of about 3 million women in Sweden showed a weak and inconsistent association between SARS-CoV-2 vaccination and healthcare contacts related to menstrual or bleeding disorders; and Kristine et al retrospective analysis of unexpected vaginal bleeding after COVID-19 vaccination in non-menstruating women in Norway, did not establish a direct causality of PMH in association with mRNA vaccination. In the MAH's sponsored clinical trials, no imbalance was noted with 3 reports of PMH identified with mRNA-1273 arm (n=15,000) comparable to 3 reports on the placebo arm (n=15,000) group. No cases in the vaccination arms were considered related to the investigational product by the investigator. Cumulatively through 17 Oct 2023 in the MAH GSDB, there were 978 reports of postmenopausal haemorrhage (PMH) among an estimated 1.03 billion vaccinees. This represents a reporting rate of <1 of postmenopausal haemorrhage per 1 million administered dose of marketed Moderna vaccines targeting SARS-CoV-2, constituting an extremely rare occurrence that is not higher than the expected number of reported cases of PMH in the general population. Based on EMA request, focused review of the 113 medically confirmed cases of postmenopausal haemorrhage and 24 non-medically confirmed positive rechallenge cases following elasomeran vaccination, showed most of the cases had insufficient information for medical evaluation. Missing information was a major challenge to the evaluation of

Signal evaluation criteria	Summary
	these cases, with only 22% cases (25/113) of medically confirmed cases and 25% (6/24) of non-medically confirmed positive rechallenge cases meeting the case definition of PMH. Among the cases that met the case definition of postmenopausal haemorrhage, no case was assessed as WHO-UMC Certain or Probable. A fifth of the medically confirmed PMH cases were assessed as possible based on temporal association and the presence of alternative association, including thyroid disorder (hypothyroidism, Hashimoto thyroiditis), breast cancer, depression, and concomitant medications with hormone replacement therapy, tamoxifen, levothyroxine, and SSRI (Sertraline) that provide a more plausible explanation for the occurrence of the event. Unfortunately, most of the non-medically confirmed positive rechallenge cases that met the case definition of PMH had sufficient information and could not be assessed. The background incidence of post-menopausal haemorrhage decreases with increase in age, however, for the observed-to-expected (O/E) the same background incidence for all age groups was used due to limited information in published literature. All age stratified O/E analysis rate ratios were less than 1 when assuming 25% of cases were reported. In MAH US PASS P920, no evidence of increased HR of PMH was observed in the cohort exposed to elasomeran bivalent and influenza vaccine during the same time period, for risk windows of 1-21 days, 1-42 days, and 1-90 days; the incidence rates for PMH following medically attended COVID-19 diagnosis were higher than rates following elasomeran bivalent vaccination. Considering the limitations, the results should be interpreted with caution. Since vaginal bleeding is the presenting feature in over 90% of postmenopausal women with endometrial cancer, every postmenopausal haemorrhage/bleeding should be adequately evaluated to diagnose or exclude malignancy
Conclusion	Overall, based on the analysis of all safety data available as of 17 Oct 2023 including literature articles discussed above, the MAH considers that there is no sufficient information to establish a causal relationship between the administration of elasomeran and PMH. The current PI is considered to adequately reflect the safety profile of elasomeran. No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor Postmenopausal Haemorrhage events using routine pharmacovigilance surveillance. The cumulative safety data evaluated do not provide a sufficient basis for new recommendations or product labelling changes and/or RMP, including relevant risk minimization measures with regard to PMH. The signal of PMH is refuted and closed.

16.2.5 Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the United States

Table 16-8 Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age in the United States

Signal evaluation criteria	Summary
Source	The Signal Management Team (SMT) identified an increase in the number of reports from the United States only related to medication errors and/or overfilling of the SDV of the Moderna COVID-19 Vaccine (2023-2024 Formula) for children 6 months to 11 years of age. In some cases, this overfilling has led to overdosing, without concerning adverse events reported to date. Regarding safety, the issue is the potential for overdose (as much as 0.65 mL instead of 0.25 mL) if the total volume is administered to a child aged 6 months to 11 yrs. During the routine signal detection reviews, the review of medication error reports for mRNA-1273.815 on 12 Oct 2023, the signaling team flagged the issue of overfill for discussion at SMT meeting and during the SMT, this topic was escalated to discuss with product quality compliance team and perform a detailed analysis.
Background	Moderna COVID-19 Vaccine (2023-2024 Formula) was developed by ModernaTx, Inc, as a monovalent vaccine encoding the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5. The Moderna COVID-19 Vaccine is made in the same way as the Moderna COVID-19 Vaccine (Original monovalent) and Moderna COVID-19 Vaccine, Bivalent, but it encodes the spike protein of SARS-CoV-2 Omicron variant lineage XBB.1.5 (Omicron XBB.1.5). Moderna COVID-19 Vaccine (2023-2024 Formula) is authorized by the FDA, under an EUA for ages 6 months through 11 years is supplied in SDV. SPIKEVAX (2023-2024) Formula approved for ages 12 years and older is supplied in SDV and single dose pre-filled syringes. Overdose in children in the context of overfill of the SDV mRNA-1273.815 indicated for individuals 6 months through 11 years of age.
Methodology	The assessment of Overdose in children in the context of overfill of the SDV mRNA-1273.815 indicated for individuals 6 months through 11 years of age was performed using the company's GSDB. The methods of evaluation used in the analysed data is described below. There is no clinical data related to use of the mRNA-1273.815 vaccines at the various doses for individuals 6 months through 11 years of age: Review of data from VAERS IDs provided by FDA: A cumulative search in VAERS, through 27 Oct 2023 using the family names mRNA-1273.815 was conducted with the following search strategies: • Product name: andusomeran • Family name: mRNA-1273.815 • MedDRA PT: Incorrect dose administered. • Date: 27 Oct 2023 (FAD cut-off date was 30 Oct 2023). Review of the Pharmacovigilance Database: A cumulative search in GSDB, through 29 Oct 2023 using the family names mRNA-1273.815 was conducted with the following search strategies:

Signal evaluation criteria	Summary
	• Product name: andusomeran • Family name: mRNA-1273.815 • MedDRA PTs: Accidental overdose, Overdose, Circumstance or information capable of leading to medication error, Intercepted medication error, Product packaging quantity issue, Product packaging issue, Incorrect dose administered, Incorrect dosage administered, Extra dose administered. • Cut-off date: 29 Oct 2023. Literature search review: General review of the PubMed literature database as of 27 Oct 2023 was performed
Results	*VAERS Database Review:* There were 237 VAERS reports ID numbers that involved the PT "incorrect dose administered" in the information provided by the FDA on 03 Nov 2023. Ten reports were not yet available in CDC Wonder as of the DLP 27 Oct 2023. Overall, review of these 227 reports of medication error with PT 'Incorrect dose administered' showed 5 reports with additional adverse events. All these 5 reports were non-serious. Here ae the details of these five (5) VAERS reports: VAERS ID [redacted] This non-serious report, involved a female age 8 years who was "on the tail end of antibiotics for sinusitis." After concurrent vaccination for COVID-19 and influenza, it was reported that the child was "dizzy when she showered" and that it "hurt to breathe", which was reported as resolving. Patient was afebrile with pulse oximetry 98-100%. Also, it was reported that she had 1" injection site reactions to both vaccines." The information was reported after an office visit. VAERS ID [redacted] This non-serious report, involved a male patient with a medical history of recurrent otitis media and acute bilateral bacterial conjunctivitis, who developed otitis media again 2 days after vaccination. Office visit. No additional information was provided. VAERS ID [redacted] This non-serious report, is from a consumer that involves a 15-month-old male who the same day after receiving 0.5 mL of the vaccine experienced pyrexia and swelling at the injection site. He was administered paracetamol, and the outcome of the events was reported as not resolved. VAERS ID [redacted] This non-serious report shows redness/swelling/fatigue; events resolved, involved standard vaccine reactogenicity. VAERS ID [redacted] This non-serious report shows pain and fatigue, involved standard vaccine reactogenicity. Review of Data from Product Quality Compliance (PQC) Team Product Quality complaints team have identified 134 complaints related to overfill of the SDV, including one complaint involving 200 patients. All these reports from PQC are sent to case processing team and individual case safety report are created as appropriate. All these ICSRs are reviewed within the ModernaTx, Inc Pharmacovigilance Database Review. Review of the Pharmacovigilance Database: Review of the GSDB with the MedDRA PTs identified 252 reports. All were spontaneously reported (no regulatory agency, literature, or solicited reports). These 252 reports were individually reviewed to identify a true case of medication error. The

Signal evaluation criteria	Summary
	review was conducted to verify if there was any incidence of overfill in these cases and any such case was marked as true medication error case. The review of these 252 reports, identified 127 reports of true overfill medication error from united states. Of these 127 reports, one was a consumer report, and the rest all were from healthcare professionals. Overall, review of these 128 medication error reports identified one clinical adverse event report ([redacted]) that noted Pyrexia (non-serious). Summary of this case is provided below. *Summary of case with Additional Adverse Event:* [redacted] (WWID#[redacted]): This spontaneous report was submitted by health care professional concerning infants (7 to 15 months) of unknown age and gender. The infants received mRNA-1273.815 (andusomeran; batch no. AU5509B), on an unknown date for COVID-19 prophylaxis. No relevant concomitant medications or medical history were reported. On an unknown date they experienced Pyrexia (*fever*), also had medication errors such as, Product Packaging Quantity Issue (*there is significant overfill in the single dose vials*) and Accidental Overdose (*HCP states that a few patients [maybe 8 or 9] received over the 0.25 mL recommended dosage*). The case report was considered invalid due to involvement of multiple patients without identifiers. The reporter did not provide any causality assessments and no treatment medication were reported. Outcome of these events were unknown. Literature search review: General review of the PubMed literature database as of 27 Oct 2023, identified one article that reported an extensive and comprehensive VAERS review of excess dose of vaccination by Moro et al. 2019. Article Summary: The study examined the VAERS for reports of excess vaccine doses administered from 2007-2018. Out of 5067 reports, 76.9% did not describe an adverse health event (AHE). The most common vaccines reported were trivalent inactivated influenza, varicella, hepatitis A, and measles, mumps, rubella, varicella. The most common AHEs reported were pyrexia, injection site erythema, injection site pain, and headache. Of the 5067 reports, 3898 (76.9%) did not describe an AE or any sign or symptom and 1169 reported excess dose, and a clinical review of these 1,169 reports, determined that 64 cases involved an excess vaccine dose, but no specific pattern of adverse events was found. The most common reactions reported were local or systemic reactions, with no increased risk of adverse events or birth outcomes found in a study of women who received Tdap during pregnancy. In conclusion, the study found that the administration of excess doses of vaccines, did not result in any new or unexpected safety issues. No specific pattern of adverse events was found in cases involving an excess vaccine dose. This suggests that administering excess doses of vaccines does not generally lead to serious health risks. However, the study highlights the importance of careful record-keeping and adherence to vaccine recommendations to avoid administration of unnecessary excess doses [67].
Discussion	This safety signal issue is restricted to the US. The MAH conducted a signal evaluation of the potential signal of Overdose in children in the context of overfill of the single dose vial. The signal evaluation included a cumulative review of the MAH safety database

Signal evaluation criteria	Summary
	with a DLP of 29 Oct 2023 and VAERS data as of 27 Oct 2023. Analysis of the MAH global safety database related to overfill of vials as of 29 Oct 2023, retrieved 128 reports. All but one was reported from HCPs. All reports were non-serious, and mainly concerned individuals aged 6 months to 11 years. Apart from one overdose report describing pyrexia, none of the remaining overdose reports indicated any associated clinical adverse events. Additionally, the Product Quality complaints team identified 134 complaints related to overfill of the SDV, including one complaint involving 200 patients; these complaints led to the creation of individual case safety reports if the information in the complaint merited this, and such reports were included in our analysis. In summary, the review of the safety information received as of 29 Oct 2023, showing that events of medication errors associated with the risk of overdose related to pediatric single dose vials indicated for individuals 6 months through 11 years of age distributed in the US, did not find that these medication errors have led to clinical harm in any individual. This clinical finding agrees with a large retrospective 2007-2017 CDC/FDA VAERS study that concluded "More than three-fourths of reports of an excess dose of vaccine did not describe an AHE. Among reports where an AHE event was reported, we did not observe any unexpected conditions or clustering of AEs [67]" The MAH considered Overdose in children aged 6 months to 11 years in the context of overfill of SDV in the US as an important potential risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified, it is considered a potential risk.
Conclusion	This safety signal issue is restricted to the US. Based on the findings of the safety assessment evaluation regarding Overdose in children in the context of overfill of the single dose vial indicated for individuals 6 months through 11 years of age, the MAH considered that this was an Important Potential Risk because the risk of overdose in vaccinated children is important; and as clinical harm has not been identified, it is considered a potential risk. This topic was classified as Priority 2 High Priority Safety Issue: Issues which may impact the product's benefit / risk profile, but which do not require urgent action. The MAH decided on the following risk minimization actions: • Update of the current Fact Sheet, to clarify the dosage and administration instructions to providers. • Update of corresponding websites to clarify dosage and administration information. • Communication of the findings to the appropriate health authorities, including CDC • Distribution of a DHCP letter in the US only. In addition, the MAH is closely monitoring overdose in children in the context of overfill of the SDV and associated harms as part of signal detection activities and pharmacovigilance.

16.3 Evaluation of Risks and New Information

16.3.1 New Information on Important Identified Risks

16.3.1.1 Anaphylaxis (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the known identified risk of Anaphylaxis, has not identified any additional clinically relevant new safety information for this topic. The characterization of this important risk as described in Section 16.4, remains valid.

16.3.1.2 Myocarditis and Pericarditis

Evaluation of information received during the PBRER reporting interval relating to the known important identified risks of myocarditis and pericarditis, has not identified any additional clinically relevant new safety information for these topics. The characterization of these important risks as described in the current RMP and in Section 16.4, below, remains valid.

ModernaTx, Inc. Supplemental Follow-up Questionnaire for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of a marketed Moderna vaccine targeting SARS-CoV-2

During the reporting period of this PBRER a total of 165 follow-up questionnaires (FUQs) for collecting supplementary information on cases of potential/confirmed Myocarditis/Pericarditis were sent by the MAH to the reporters, of which 0 FUQ responses were received. The response rate to this questionnaire was 0%. Cumulatively, a total of 730 Myocarditis/ Pericarditis FUQs have been sent to reporters, of which only 25 FUQs were received, for a response rate of 3%.

This very low response rate may be an indicator of the reporter's difficulties to address all the requested follow-up information. The length of the questionnaire and the redundancy of certain information already provided by the reporter may also discourage reporting. In addition, reporters may not understand the importance of documenting cases to inform and further characterize these already known risks.

Since its implementation in Jul 2021, the cumulative review of FUQs experience, shows an extremely low reporting rate. Hence, ModernaTx, Inc. concludes that the current format of the FUQ included in Annex 4 of the SPIKEVAX RMP is not adequate. In order to improve data collection for these 2 important identified risks, ModernaTx, Inc. proposes an updated version of the FUQ streamlining the information requested in the form and avoiding duplication of the information related to patients' demographic.

The proposed updated questionnaire is included in Annex 4 of the updated EU-RMP version 8.3 submitted with this PBRER.

Table 16-9 Myocarditis and Pericarditis

Important Identified Risk	Myocarditis and Pericarditis
Source of New Information	• ModernaTX, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 120 o New and Significant Safety Information: None (0).
Background	An association between myocarditis and pericarditis and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events, particularly among adolescent and young-adult males within 14 days after Dose 2.
Methods	Cases are classified using both the BC Myocarditis/ Pericarditis case definition [68,69], and the CDC working case definition [70] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	It is important to note a considerable decrease in the number of reported cases of myocarditis/pericarditis during this reporting period. Many of the case reports received from consumers lack important information including medical history, concomitant medications, as well as dose number and TTO; information that is critical for medical review and informed causality assessment. *Myocarditis and Pericarditis Cases Involving elasomeran* During the review period, the MAH received 63 serious cases (64 events) of myocarditis and pericarditis with all cases considered serious cases. There were 3 cases reporting a fatal outcome (See Appendix 12.11). There were 46 medically confirmed cases involving elasomeran. A total of 41 (65.1%) cases involved males and 15 cases (23.8%) involved females; 7 cases (11.1%) were missing gender information. The mean age of the patients was 37.7 (SD:15.4), with a median 35.0 years (range 14.0 to 87.0 years); 12 cases were missing age data. A total of 21 events (32.8%) were reported as "Recovered/Recovering." Limitations exist in capturing follow-up information about individual events from spontaneous reports, such that the category of "Not recovered/Not resolved" likely represents an over-estimate for this category of outcome, as the assessment is based on the reporting date rather than a prescribed interval following symptom onset (i.e., it should not be interpreted as representing the entire episode of care). According to the BC case definition for myocarditis and pericarditis, 5 cases met

Important Identified Risk	Myocarditis and Pericarditis
	Level 1 definition, 13 cases met Level 2 definition, 3 cases met Level 3 definition, 39 cases met Level 4 definition, and 3 cases met Level 5 definition. Appendix 12.11. According to the CDC working definition [70] 2 cases were classified as "Confirmed"; 18 cases were classified as "Probable"; 40 cases were classified as "Unassessable"; and 3 cases were considered "Not a case" of myocarditis or pericarditis. (See Appendix 12.11). According to the WHO causality assessment, there was 1 case considered "Probable"; 18 cases considered "Possible"; 40 cases considered "Unassessable", 1 case considered "Unlikely" related to the vaccine, and 3 cases were not assessed as they were not considered a case of myocarditis or pericarditis. (Appendix 12.11). The 3 cases with fatal outcomes are summarized below: [redacted] *(WWID:* [redacted] This is a spontaneous case concerning a 50-year-old female patient, with no medical history reported (however autopsy findings confirmed chronic conditions), received elasomeran vaccine (first dose). One day after vaccination the patient complained of chest pain and nausea, vomited multiple times. The patient was taken to the hospital. She was treated with amiodarone and epinephrine for atrial fibrillation. The patient suffered from a circulatory arrest. Resuscitation measures failed and she died. The autopsy was performed. The reported cause of death was acute left heart failure/circulatory arrest with acute blocked lung with serious alveolar pulmonary edema. On autopsy, myocarditis was suspected; additional findings revealed past liver injury, chronic pancreatitis, emphysema (chronic nicotine use), chronic bronchitis, moderate to serious condensate pneumopathy, arteriosclerosis and shocked kidney were also determined. This case confounded by medical history (per autopsy): Moderate biventricular myocardial hypertrophy, arteriosclerosis coronary artery, chronic bronchitis, emphysema, liver injury, chronic pancreatitis. This case was considered Level 1 according to BC case definition, probable according to CDC case definition and possible case of myocarditis according to WHO causality assessment. [redacted] *(WWID:* [redacted] : This is a spontaneous fatal case concerning a male patient of an unknown age with no reported medical history. It was reported that the patient fainted and died approximately 20 days after receiving a dose of elasomeran vaccine, received as the first dose of COVID-19 vaccination schedule. Myocarditis was reported as the cause of death, and it is unknown if an autopsy was performed. No further information was disclosed. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment. [redacted] *(WWID:* [redacted] This is a fatal report from regulatory authority reported by consumer (subsequently medically confirmed) on a

Important Identified Risk	Myocarditis and Pericarditis
	30-year-old male patient with the relevant medical history of COVID-19, extrasystoles and heart pounding, who experienced loss of consciousness, circulatory collapse, cardiac arrest, unexpected events of hypersensitivity, palpitations (2 episodes), malaise, nausea, chest discomfort, anxiety, and dizziness, which occurred 18-23 days after the first dose of elasomeran vaccine. Patient died 23 days after vaccination and causes of death were reported as acute circulatory failure and myocarditis. An autopsy was performed, but no results were provided. No further clinical information was provided. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment. *Myocarditis and Pericarditis Cases involving elasomeran/imelasomeran* During the review period, the MAH received 13 serious cases (13 events) of myocarditis and pericarditis involving elasomeran/imelasomeran. All cases were considered serious, and 6 cases were medically confirmed. There was 1 case with a fatal outcome. A total of 8 cases (61.5%) involved males and 3 cases (23.1%) involved females; 2 cases (15.4 %) was missing gender information. The mean age of the patients was 64.2 (SD: 19.7), with a median 63.0 years (range 26.0 to 90.0 years); 4 cases were missing age data. There were 3 events (23.1%) reporting an outcome of "Recovered/ Recovering." According to the BC case definition for myocarditis and pericarditis, 1 case met Level 2 definition, 2 cases met Level 3 definition, and 10 cases met Level 4 definition. According to the CDC working definition (Gargano 2021), 1 case was considered "Acute pericarditis", 2 cases were considered "Probable"; and 10 cases were considered "Unassessable." According to the WHO causality assessment, there were 2 cases considered "Possible", 8 cases considered "Unassessable", and 3 cases considered "Unlikely" related to the vaccine. The one case with fatal outcomes is summarized below: [redacted] *(WWID:* [redacted]: This is a spontaneous fatal case concerning a 26-year-old male patient with medical history of bradycardia, syncope, and suicidal ideation, who experienced dizziness and myocarditis 2 days after the 4th dose with elasomeran/imelasomeran vaccine. Patient died 3 days after vaccine was given. It is unknown if an autopsy was performed. No further details were provided for medical review. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment. *Myocarditis and Pericarditis Cases involving elasomeran/davesomeran* During the review period, the MAH received 2 serious medically confirmed cases

Important Identified Risk	Myocarditis and Pericarditis
	(2 events) of myocarditis and pericarditis involving elasomeran/imelasomeran. There was 1 case with a fatal outcome. Both cases (100%) involved males, the mean age of the patients was 37.0 (SD: 12.7), with a median 37.0 years (range 28.0 to 46.0 years). One event was reported as "Fatal", and the other event was reported as "Recovered/Recovering". According to the BC case definition for myocarditis and pericarditis in patients, 1 case met Level 3 definition, and 1 case met Level 4 definition. According to the CDC working definition [70], 1 case was considered "Probable" and the other case was considered "Unassessable." According to the WHO causality assessment, 1 case was considered "Possible", and the other case was considered "Unassessable." The one case with fatal outcomes is summarized below: [redacted] *(WWID: [redacted]):* This case was received from Regulatory Authority: A 46-year-old male with medical history of hyperlipidemia and hepatitis received elasomeran/davesomeran vaccine, third dose. Approximately 25 days after the third dose of vaccine, the patient experienced syncope and heart arrest. After resuscitation measures the heart function was recovered, however the patient remained in coma. Acute heart failure and multiple organ failure followed. The reported cause of death was Myocarditis. No information disclosed about diagnostic tests performed or treatments received. There was no autopsy performed. This case was considered a Level 4 according to the BC case definition; unassessable according to CDC case definition, and an unassessable case of myocarditis according to WHO causality assessment. *Myocarditis and Pericarditis Cases involving andusomeran* It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant andusomeran. Since its approval, the MAH has received 6 serious cases (7 events) of myocarditis and pericarditis involving andusomeran. All cases were considered serious, and 4 cases were medically confirmed. There were no cases with a fatal outcome. A total of 4 cases (66.7%) involved males and 2 cases (33.3%) involved females. The mean age of the patients was 49.5 (SD: 33.2), with a median 48.5 years (range 13.0 to 91.0 years). There were 5 events (71.5%) reporting an outcome of "Recovered/ Recovering." According to the BC case definition for myocarditis and pericarditis in patients, 1 case met Level 1 definition, 1 case met Level 2 definition, 3 cases met Level 4 definition, and 1 case met Level 5 definition. According to the CDC working definition [70], 2 cases were considered "Probable", 3 cases were considered "Unassessable" and 1 case was considered "Not a case" of

Important Identified Risk	Myocarditis and Pericarditis
	myocarditis. According to the WHO causality assessment, 1 case was considered "Possible", 3 cases were considered "Unassessable", 1 case was considered "Unlikely", and 1 case was not assessed as it was not considered a case of myocarditis or pericarditis. *Myocarditis and Pericarditis Cases Involving SPIKEVAX (NOS)* It is important to note that during the reporting period for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran). During the review period, the MAH received 10 serious cases (10 events) of myocarditis and pericarditis under the SPIKEVAX (NOS) classification. All cases were considered serious, and 4 cases were medically confirmed. There were no cases with a fatal outcome. A total of 6 cases (60.0%) involved males and 3 cases (30.0%) involved females; 1 case (10.0%) was missing gender information. The mean age of the patients was 43.6 (SD: 24.8), with a median 27.0 years (range 25.0 to 78.0 years); 4 cases were missing gender information. There were 2 events (20%) reporting an outcome of "Recovered/ Resolved." According to the BC case definition for myocarditis and pericarditis in patients, 1 case met Level 1 definition, and 9 cases met Level 4 definition. According to the CDC working definition [75], 1 case was considered "Confirmed", and 9 cases were considered "Unassessable." According to the WHO causality assessment, 1 case was considered "Possible", 8 cases were considered "Unassessable", and 1 case was considered "Unlikely" a case myocarditis or pericarditis. See Appendix 12.11 for additional information.
Discussion	A review of the data received during this reporting period showed no meaningful changes in the characteristics of the events of myocarditis and pericarditis reported after vaccination with marketed Moderna vaccines targeting SARS-CoV-2. To date, the safety profile of those reports of myocarditis and pericarditis after vaccination does not differ from the known safety profile of all marketed Moderna vaccines targeting SARS-CoV-2. Please refer to Section 8 for results from the PASS study on the evaluation of myocarditis and pericarditis. Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of myocarditis and pericarditis to be consistent with the known

Important Identified Risk	Myocarditis and Pericarditis
	safety profile of marketed Moderna vaccines targeting SARS-CoV-2 and the benefits of vaccination far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. A review of the data received cumulatively and during this reporting period showed a continuous decreasing trend in the number of reported cases and that events of myocarditis and pericarditis continue to primarily occur in young males shortly after the second dose of the vaccine with a reported TTO less than 7 days. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including PASS to further characterize them. The benefit-risk evaluation remains positive.

16.3.2 New Information on Important Potential Risks

16.3.2.1 IgA Nephropathy (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the known important potential risks of IgA Nephropathy for marketed Moderna vaccines targeting SARS-CoV-2 has not identified any additional clinically relevant new safety information for this topic. The characterization of this important risk as described in Section 16.4, remains valid. IgA Nephropathy is monitored in accordance with a request from a Health Authority.

Table 16-10 IgA Nephropathy (Safety concern in PBRER only)

Important Potential Risk	IgA Nephropathy
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 129 o New and Significant Safety Information: None (0).
Background	Following review of PBRER#4, a Health Authority requested the following information on IgAN: • *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 or bivalent. Thus, the MAH should maintain IgAN as an important*

Important Potential Risk	IgA Nephropathy
	potential risk in the future PBRERs. In the next PBRER, it is therefore expected that the MAH will present new information on IgA nephropathy and risk characterization in PBRER section 16.3 and 16.4, respectively.
Methods	Neither the BC nor CDC has established a case definition for IgA nephropathy. The MAH has 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. The Company case causality assessment is provided utilizing the WHO-UMC standard causality categories and criteria.
Results	Refer to Appendix 12.12 for information about the medical topic. During the review period, the MAH received 18 reports (19 events) that had PTs within the HLT of Glomerulonephritis and Nephrotic Syndrome (note: the following case [redacted] was captured for elasomeran and for those reports under the SPIKEVAX [NOS]) classification. Of these 18 cases, 15 cases involved elasomeran, and 1 case each involved elasomeran/imelasomeran, elasomeran/davesomeran, and SPIKEVAX (NOS). There were no reports involving andusomeran. All the 18 reports were medically reviewed. Four cases were classified as confirmed IgA nephropathy; the remaining 14 cases involved other types of nephropathy or other conditions (e.g., glomerulonephritis minimal lesion, glomerulonephritis membranous, nephrotic syndrome, glomerulonephritis rapidly progressive, and C3 glomerulopathy). Out of the 4 cases involving IgA nephropathy, no cases involved fatal outcomes. All 4 cases involved elasomeran and considered were serious. Three (3) cases were new onset (de novo) of IgA nephropathy, and 1 case was considered IgA nephropathy flares because the patient was reported to have experienced exacerbation of IgA nephropathy that had been diagnosed prior to vaccination. Equal numbers of cases in females (2 cases; 50.0%) and males (2 cases; 50.0%) were reported. The mean age was 20.8 years (SD: 1.7) and median age was 20.5 years (range: 19.0 to 23.0 years). Time to onset was missing in 3 cases and in 1 case TTO was on Day-1.
Discussion	During the reporting period in the MAH's GSDB, there were 4 cases of IgA nephropathy that were identified through medical review, all these 4 cases involved elasomeran. Of the 4 cases of IgA nephropathy, 3 cases involved new onset (de novo) IgA nephropathy, of these 3 cases WHO causality assessment was considered possible for 2 due to positive biopsy, but important information was missing including medical history. Additionally for one of the cases, IgAN was detected within 24 hours of vaccination with elasomeran which is not biologically plausible. The other report is also confounded by previous administration of Comirnaty 6 months before vaccination with a booster dose of elasomeran. The third case was considered Unlikely as the event occurred almost 3 months post vaccine with no biopsy. The fourth case was reported as

Important Potential Risk	IgA Nephropathy
	IgA nephropathy flare which was assessed Possible according to WHO causality assessment due to temporal relationship as the biopsy showed chronic GN and the patient presented in chronic RF. No new patterns were observed with regard to IgA nephropathy-related data for marketed Moderna vaccines targeting SARS-CoV-2. Renal patients are at increased risk of serious illness and death due to COVID-19 disease; thus, vaccination is of great benefit to them. Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of IgA nephropathy to be consistent with the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The benefits for vaccination far outweigh any possible vaccine-associated risks.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2. Information presented in those reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to monitor events for IgA Nephropathy using routine surveillance. The benefit-risk evaluation remains positive.

16.3.3 New Information on Other Potential Risks Not Categorised as Important (if applicable)

Not applicable.

16.3.4 New Information on Other Identified Risks Not Categorised as Important (if applicable)

Not applicable.

16.3.5 Update on Missing Information (if applicable)

16.3.5.1 Use in pregnancy

Evaluation of information received during the PBRER reporting interval relating to missing information of marketed Moderna vaccines targeting SARS-CoV-2 of "Use in pregnancy" has not identified any additional clinically relevant new safety information for this topic. The characterization of these important risks as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, remains valid.

Table 16-11 Use in pregnancy

Missing Information	Use in pregnancy
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 563 o New and Significant Safety Information: None (0).
Background	Use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy is an area of missing information in the RMP; no clinical trials 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. The use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy is embedded in clinical practice and included in relevant health guidelines. No specific safety concerns for pregnancy have been identified.
Methods	Refer to Appendix 12.13 for Methods of Evaluation
Results	Refer to Appendix 12.13 for additional information. **Overview of Pregnancy Cases Who Received elasomeran** It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide after Jun 2023. Therefore, during this review period, there was a considerable decrease in the number of reported pregnancy cases for elasomeran vaccine. During the review period, the MAH received 53 pregnancy cases (246 events) with 42 serious cases (115 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. One (1) case reported a fatal outcome, and a total of 26 cases were medically confirmed. During the review period, a higher proportion (79.2%) of cases were reported as "serious" compared to the cumulative period (35.2%). Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" in addition to known reactogenicity events and are reported as "serious" cases; See below in the Serious and Fatal Cases and Serious Pregnancy-related events-elasomeran 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 all events as serious in a given serious case. Most (22; 48.9%) pregnancy-specific cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been seen in previous review periods.

Missing Information	Use in pregnancy
	During the review period, the most frequently reported PTs (3 events or more) indicating an adverse event/outcome for pregnancy cases were fatigue, myalgia, malaise, injection site pain, arthralgia, COVID-19, injection site swelling, abortion spontaneous, chills, nausea, headache, pain in extremity, vomiting, and dizziness. Most events were reactogenicity events, consistent with the product safety profile and similar between the reporting period and the cumulative periods. During the review period, there were no pregnancy cases reporting events of myocarditis and/or pericarditis after receipt of elasomeran. *Pregnancy-specific events – elasomeran* During the review period, of the 53 pregnancy cases received by the MAH, 45 pregnancy cases reported a pregnancy-specific adverse event/outcome in individuals who received or had a medical history of maternal exposure to elasomeran. (Please note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ). These 45 cases reported 59 pregnancy-specific events with 35 serious cases (44 serious events). No cases with pregnancy-specific adverse events reported a fatal outcome, and 20 cases were medically confirmed. After the exclusion of PTs that did not indicate an adverse pregnancy-specific event/outcome, "Abortion spontaneous" remained the most frequently reported adverse pregnancy event/outcome for both the reporting and cumulative periods. (Refer to Spontaneous abortions, Stillbirths, and Foetal 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 12.13. *Serious Pregnancy-specific Events and Fatal Cases– elasomeran* During the review period, of the 32 reported serious pregnancy cases, when restricted to pregnancy cases reporting only pregnancy-specific events/outcomes, 27 serious cases were identified as including serious pregnancy-specific events (34 events). No cases reported a fatal outcome, and 11 cases were medically confirmed. 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, gestational age 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, concomitant medications, comorbidities (such as chronic hepatitis, autoimmune thyroiditis, substance abuse) and previous

Missing Information	Use in pregnancy
	relevant obstetric history including fetal loss] were present. *Fatal Pregnancy Cases– elasomeran* During the review period, 1 pregnancy case was coded as fatal following receipt of elasomeran. This case of maternal death is summarized below: [redacted]): This literature non-study case concerns a 38-year-old pregnant (reported as 20 weeks gestational age) female with concurrent medical conditions of chronic hepatitis B and autoimmune thyroiditis (under treatment with prednisolone), who experienced hepatitis B reactivation, antiphospholipid syndrome, multi-organ failure, hepatic failure, lactic acidosis, vaginal haemorrhage, and hypotension 8 days after receiving the first dose of elasomeran [vaccine date and event date were not provided]. Five days after vaccination, the patient presented with icteric sclera and yellowish skin discoloration. Hepatitis B flare was detected and tenofovir disoproxil fumarate was prescribed. Nonetheless, the patient developed progressive hepatic decompensation, vaginal bleeding, profound hypotension, and lactic acidosis and was admitted to the intensive care unit. Vaccine-related catastrophic anti-phospholipid syndrome with multi-organ failure was suspected by a rheumatologist. Treatment for the events included plasma exchange, continuous venovenous hemodiafiltration, belimumab, cyclosporin, abatacept, leflunomide, and methylprednisolone. Relevant diagnostic tests included alanine aminotransferase at baseline was 14 U/L, onset/peak of 1745/1860 U/L (no reference ranges provided); aspartate aminotransferase at onset/peak of 1387/1387 U/L (no reference ranges provided); no baseline HBV DNA was tracible, peak of HBV DNA of > 1,000,000,000 IU/mL (no reference ranges provided); total bilirubin of 4.1 mg/dL (no reference ranges provided); international normalized ratio of 1.74 >10 on Day 12 and >10 on Day 13 (no reference ranges provided). Unfortunately, the patient died on Day 26. The reported causes of death were hepatitis B reactivation, catastrophic anti-phospholipid syndrome, multi-organ failure, vaginal bleeding, hypotension, hepatic decompensation and lactic acidosis. It is unknown if an autopsy was performed. The outcome of the fetus was not reported. MAH Comment: Catastrophic antiphospholipid syndrome is most often associated with thrombosis risk factors such as infection, surgery, or pregnancy, in an individual with pre-existing antiphospholipid antibodies or a genetic complement abnormality. This pregnant woman had pre-existing autoimmune disease and chronic hepatitis B infection which became reactivated, which may provide an alternative explanation for the events. This case was assessed as "Unlikely" given the limited information provided regarding obstetric history, complete diagnostic evaluation, and clinical course; and the concurrent medical conditions that provided an alternate etiology.

	Fetal Deaths– elasomeran The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth." Fetal deaths are classified as spontaneous abortion if they occur before 20 weeks gestational age (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 [71]. *Spontaneous and Missed Abortions – elasomeran* During the review period, 6 serious pregnancy cases with a medical history of maternal exposure to elasomeran reported spontaneous abortion with 6 serious events. Of the 6 cases, 2 cases were medically confirmed, and no cases were coded as fatal. The mean age of the cases was 35.4 years (SD: 3.4) with a median age of 36.0 years (range 30-39 years). Analysis of event clustering by dose number and TTO was not meaningful as 4 of the 6 events (66.7%) did not report dose number or TTO. Of the 2 remaining cases, 1 case reported dose number (Dose 3) and TTO (4 days) and the other case reported TTO (443 days) but not dose number. *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 stillbirth as fetal death after 20 weeks gestational age [71]. 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 are 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. During the review period, no pregnancy cases reported stillbirth following maternal exposure to elasomeran. 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. *Congenital Anomaly– elasomeran* During the review period, 13 pregnancy cases that reported a PT from the Congenital, familial, and genetic disorder SOC were identified. After medical review, no reporting patterns or safety concerns were identified. Of the 13 pregnancy cases, 7 cases occurred among foetuses and neonates who were maternally exposed to elasomeran in utero and 6 cases were determined to be "non-pregnancy cases" as they either represented medical history miscoded as an adverse event, or a pre-existing congenital anomaly detected in a

Missing Information	Use in pregnancy
	non-pregnant person. Of the 7 pregnancy cases, 3 cases reported a live birth at delivery. One case ([redacted]) reported the event outcome as "Resolved", 1 case ([redacted]) reported the event outcome as "Resolved with sequelae", and 1 case ([redacted]) reported the event outcome as "Unknown." Further review of the congenital anomalies, considering the GA at vaccination and fetal development, contributed to the assessment of causality. Many cases lacked GA at the time of vaccination and thus causality was considered "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. Even when considering the cumulative data, there were no significant patterns or safety concerns identified. **Subpopulation Analyzes-elasomeran:** *Children <6 years of Age with a medical history of maternal exposure to elasomeran during pregnancy* During the review period, the MAH received 2 serious cases (3 events) among children under 6 years of age with a medical history of maternal exposure to elasomeran during pregnancy. Neither case reported a fatal outcome nor was medically confirmed. [redacted] was previously reported in the prior PBRER review period but had event updates made to the case narrative during this reporting period. The PT "Maternal exposure during pregnancy" was removed from the list of reported PTs and was then captured in infant's medical history. This update did not affect the MAH's original causality assessment. [redacted]: This regulatory authority case reported by a consumer, concerns a 1-year-old female infant, with no medical history reported, who experienced the serious (due to medically significant) event of Foetal growth restriction (reported as stunted intrauterine growth due to poor placental blood flow), which occurred on an unknown date related to elasomeran vaccine. This vaccine was administered to the mother as the second dose within the COVID-19 vaccination schedule. No information was disclosed regarding diagnostic tests performed or treatments received. At the time of the report, the event had not resolved. MAH Comment: Causality was considered "Unassessable" given the limited information provided regarding obstetric history, diagnostic evaluation, and clinical course that precludes a meaningful causality assessment. No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period. *Pregnancy Cases Among Adolescents (12-17 Years of Age – elasomeran* During the review period, no pregnancy cases were received by the MAH among adolescents (12-17 years of age) who received elasomeran.

Missing Information	Use in pregnancy
	Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified cumulative. **Pregnancy Cases After Receiving a Booster Dose with elasomeran/imelasomeran** During the review period, the MAH received 1 serious pregnancy case (2 events) for an individual who received a booster dose of elasomeran/imelasomeran. This case is summarized below: [redacted]: this regulatory authority retrospective pregnancy case reported by a consumer concerns the occurrence of Abortion spontaneous in a 35-year-old female following receipt of elasomeran/imelasomeran. This vaccination was reported as the fourth dose in the COVID-19 vaccine series. The report indicated that vaccination occurred when the mother "was 11 weeks pregnant and had miscarried 3 days later." However, no dates confirming last menstrual period or estimated date of delivery to confirm GA were reported. Concomitant medication included Folic acid. MAH Comment: Causality was considered "Unassessable" given the limited information provided; including missing data regarding maternal medical, family, and obstetric history, diagnostic evaluation, and clinical course that precludes an informed case and a meaningful causality assessment. Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified during the reporting and cumulative periods. **Pregnancy Cases After Receiving a Booster Dose with elasomeran/davesomeran** During the review period, the MAH received 7 pregnancy cases (13 events) with 1 serious case among individuals who received a booster dose of elasomeran/davesomeran. No case reported a fatal outcome, and 5 cases were medically confirmed. Cumulatively and during the review period, there have been no pregnancy cases reporting a fatal outcome, stillbirth, or foetus/infant with congenital anomalies following exposure to a dose of elasomeran/davesomeran. The most frequently reported events/PTs represent expected reactogenicity for elasomeran. The only pregnancy-specific PTs reported have been "Maternal exposure during pregnancy" and "Gestational hypertension." The one serious case reported during the review period is summarized below: [redacted]: This regulatory case concerns a 28-year-old female patient, pregnancy reported, who experienced the serious (hospitalization) event of Gestational hypertension, approximately 3 months after a dose of elasomeran/davesomeran. This vaccination was reported as the fourth dose in the COVID-19 vaccination series. Last menstrual period and estimated date of delivery were not provided. No details of previous doses were provided. No treatment information was provided. No further clinical information was available for medical

Missing Information	Use in pregnancy
	review. Company causality assessed the event of gestational hypertension as not related due to long latency and that the pathophysiology of the reported pregnancy was considered the main risk factor for the event. MAH Comment: Causality was considered "Unassessable" given the limited information provided; including missing data regarding maternal medical, family, and obstetric history, diagnostic evaluation, and clinical course that precludes an informed case and a meaningful causality assessment. Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified during the reporting and cumulative periods. **Pregnancy Cases After Receiving a Booster Dose with andusomeran** It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant XBB 1.5. Therefore, this will be the first PBRER review period where pregnancy cases following andusomeran vaccination will be reviewed. Since its approval, the MAH has received 24 pregnancy cases (75 events) with 3 serious cases (3 events) among individuals who received a booster dose of andusomeran. No cases have reported a fatal outcome, and 22 cases were medically confirmed. Most (14; 58.3%) pregnancy cases reported after receipt of andusomeran occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been seen with elasomeran-containing vaccines in previous review periods. The most frequently reported PTs have been predominantly reactogenicity events, consistent with the product safety profile for elasomeran-containing vaccines and consistent with events reported for elasomeran-containing vaccines in prior review periods. No pregnancy cases after receipt of andusomeran have reported events of myocarditis and/or pericarditis. *Pregnancy-specific Events –andusomeran* Of the 24 pregnancy cases received by the MAH, 23 pregnancy cases reported a pregnancy-specific adverse event/outcome in individuals who received or had a medical history of maternal exposure to andusomeran. (Please note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ). These 23 cases reported 25 pregnancy-specific events with 3 serious cases (2 events). No cases with pregnancy-specific adverse events reported a fatal outcome, and 22 cases were medically confirmed. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome the only PTs reported were "Abortion spontaneous," "Haemorrhage in pregnancy," and "Morning sickness." [Note: Case [redacted] reported the pregnancy-specific event of "Morning sickness." However, assuming the age of the

Missing Information	Use in pregnancy
	patient was reported correctly, it appears this case may have been incorrectly coded as a pregnancy case given the individual's age (75 years)]. 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 12.13. *Serious Pregnancy-specific Events– andusomeran* Of the 3 serious pregnancy cases reported, when restricted to pregnancy cases reporting only pregnancy-specific events, 2 serious cases were identified as including serious pregnancy-specific events (2 events). No cases reported a fatal outcome, and both cases were medically confirmed. The 2 serious cases are summarized below: [redacted]: This spontaneous prospective pregnancy case concerns a 36-year-old female with relevant medical history of retroplacental haematoma in the first trimester and concomitant receipt of the flu vaccine who experienced the serious event of "haemorrhage in pregnancy." The event occurred 2 days following receipt of andusomeran. This vaccination was reported as the sixth dose within the COVID-19 vaccination series. The event duration was 2 days, and the outcome was reported as "Recovered." Vaccination occurred at 17 weeks GA, and it was reported that "baby's heartbeat was heard" upon visit to the hospital. No further clinical information was reported. MAH Comment: Causality was assessed as "Unassessable" given limited data provided; including missing data regarding maternal medical/surgical, family, and obstetric history; diagnostic evaluation; and clinical course that precludes a meaningful causality assessment. Medical history of retroplacental haematoma in the first trimester and concomitant receipt of flu vaccine on the same day as andusomeran are also potential confounders for this event. [redacted]: This spontaneous retrospective pregnancy case concerns the occurrence of Abortion spontaneous in a 34-year-old female with the relevant medical history of a recent flu vaccination ["Flu Shot (1 week ago)"]. The event occurred approximately 1 month after receipt of andusomeran. Vaccination was reported as the fifth dose within the COVID-19 vaccination series. No information was disclosed regarding GA of the fetus, diagnostic tests performed, or treatments received. MAH Comment: Causality was assessed as "Unassessable" given the limited data provided; including missing data regarding maternal medical, family, and obstetric history, diagnostic evaluation and clinical course that precludes an informed case and a meaningful causality assessment. The receipt of a flu vaccination 1 week prior to the report of the event also confounds this case.

	Fatal Pregnancy Cases– andusomeran No pregnancy cases have reported a fatal outcome following receipt of andusomeran. *Fetal Deaths– andusomeran* The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth." Fetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA, and as stillbirth if they occur after 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [71]. *Spontaneous and Missed Abortions – andusomeran* Since its' approval, 1 serious pregnancy case with a medical history of maternal exposure to andusomeran reported spontaneous abortion with 1 serious event. Case [redacted] is summarized in the Serious Pregnancy-specific Events-andusomeran section above. *Stillbirth – andusomeran* No pregnancy cases have reported stillbirth following maternal exposure to andusomeran. *Congenital Anomaly– andusomeran* No pregnancy cases have reported congenital anomaly following maternal exposure to andusomeran. **Subpopulation Analyses-Andusomeran:** No pregnancy cases have been reported for the following subpopulations during the review period: • Children <6 years of Age with a medical history of maternal exposure to andusomeran during pregnancy • Children 6 to 11 years of age • Adolescents (12-17 Years of Age) Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified during the reporting and cumulative periods. **Pregnancy Cases Receiving a vaccine under the SPIKEVAX (NOS) classification** During the reporting period of this PBRER, for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran). During the review period, the MAH received 5 pregnancy cases (9 events) with 2 serious cases (2 serious events) among individuals under the SPIKEVAX (NOS) classification. No cases reported a fatal outcome, and 4 cases were medically confirmed. Most (3; 60.0%) pregnancy cases occurred in the 18 to 39-year age group which is consistent with typical childbearing age. *Pregnancy-specific Events – SPIKEVAX (NOS)*

Missing Information	Use in pregnancy
	After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome the only PTs reported were "Abortion spontaneous," and "Fanconi syndrome." 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 12.13. *Serious Pregnancy-specific Events– SPIKEVAX (NOS)* During the review period, 2 serious pregnancy cases (2 events) were reported following receipt or maternal exposure to a vaccine under the SPIKEVAX (NOS) classification. No cases reported a fatal outcome, and 1 case was medically confirmed. **Case** [redacted] concerned a 42-year-old female who experienced the medically significant event of Fanconi syndrome at an unspecified time following SPIKEVAX (NOS). This report appears to be misclassified as a pregnancy case as there is no indication within the case narrative that the patient was pregnant (i.e., no mention of last menstrual period, estimated delivery date, or obstetric medical history). The remaining serious pregnancy case is summarized below: [redacted]: This spontaneous case concerns an occurrence of abortion spontaneous in a 33-year-old female with medical history of miscarriage, which occurred in context administration of a vaccine under the SPIKEVAX -NOS classificatio. This vaccination was reported as the second dose in the COVID-19 series. It was reported that the event occurred approximately 1 month after becoming pregnant. Last menstrual period and estimated date of delivery were not reported. It was reported that the patient was vaccinated approximately 1 month before becoming pregnant. The PT "Maternal exposure before pregnancy" was also noted in the case. The only concomitant medication reported was folic acid for an unspecified indication. No further details regarding maternal medical, family, and obstetric history, diagnostic evaluation and clinical course were provided for review. The event outcome was reported as "Unknown" at the time of report. MAH Comment: Causality was assessed as "Unlikely" given the patient was vaccinated 1 month prior to pregnancy (second dose of the COVID-19 series) and miscarried approximately 2 months after vaccination (approximately 1 month after becoming pregnant). The patient's medical history of miscarriage is also a potential confounder as history of past miscarriage may represent an increased risk of spontaneous abortion for future pregnancies. *Fatal Pregnancy Cases– SPIKEVAX (NOS)* No pregnancy cases have reported a fatal outcome following receipt a vaccine under the SPIKEVAX (NOS) classification. *Fetal Deaths– SPIKEVAX (NOS)* The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth." Fetal deaths are classified as spontaneous abortion if they occur before

Missing Information	Use in pregnancy
	20 weeks GA, and as stillbirth if they occur after 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [71]. *Spontaneous and Missed Abortions – SPIKEVAX (NOS)* During the review period, 1 serious pregnancy case with a medical history of maternal exposure to a vaccine under the SPIKEVAX (NOS) classification. reported spontaneous abortion with 1 serious event. **Case** [redacted] is summarized in the Serious Pregnancy-specific Events-SPIKEVAX (NOS) section above. *Stillbirth –SPIKEVAX (NOS)* During the review period, no pregnancy cases reported stillbirth following maternal exposure to a vaccine under the SPIKEVAX (NOS) classification. *Congenital Anomaly*– SPIKEVAX (NOS) During the review period, 1 serious case (1 event) reported congenital anomaly following receipt of a vaccine under the SPIKEVAX (NOS) classification. Case [redacted] concerned a 42-year-old female who experienced the medically significant event of Fanconi syndrome at an unspecified time following exposure to a vaccine under the SPIKEVAX (NOS) classification. This report appears to be misclassified as a pregnancy case as there is no indication within the case narrative that the patient was pregnant (i.e., no mention of last menstrual period, estimated delivery date, or obstetric medical history). **Subpopulation Analyses-SPIKEVAX (NOS):** During the review period, no pregnancy cases were reported for the following subpopulations: • Children <6 years of age with a medical history of maternal exposure to vaccination during pregnancy • Children 6 to 11 years of age • Adolescents (12-17 years of age) Based on current available information, no unusual patterns or pregnancy-specific safety concerns were identified during the reporting period.
Discussion	During the reporting period, the MAH received a total of 90 pregnancy cases (345 events) among individuals who received a marketed Moderna vaccine targeting SARS-CoV-2 during pregnancy. The pattern of the reports remained generally consistent when compared with the cumulative data. While there was a higher proportion of serious cases reported following receipt of elasomeran vaccine, review of serious pregnancy-specific events and non-pregnancy-specific events for all marketed Moderna vaccines targeting SARS-CoV-2 during the review period did not identify any new safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of marketed Moderna vaccines targeting SARS-CoV-2 with no other causal association to vaccination.

Missing Information	Use in pregnancy
	Reported cases reflect obstetric events observed after administration of marketed Moderna vaccines targeting SARS-CoV-2. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of adverse event(s), diagnostics, treatment and/or outcome. Where data were available, noted confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy included advanced maternal age, concomitant medications, comorbidities, underlying medical conditions, previous relevant obstetric history, and congenital anomalies which predated the vaccination. Spontaneous abortion remained the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster has been identified during the reporting and cumulative periods. During the review period, no cases reported stillbirth. Cases of stillbirth from the cumulative period had clear alternate etiologies, with 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 marketed Moderna vaccines targeting SARS-CoV-2 and stillbirth. The MAH will continue to review and evaluate cases of spontaneous abortion, fetal death, and stillbirth, using routine surveillance as well as PASS. Review of the cases reporting congenital anomalies following maternal exposure to any marketed Moderna vaccine targeting SARS-CoV-2 during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. After approval of andusomeran, it was observed that reports predominantly represent reactogenicity events, which is consistent with the product safety profile for elasomeran-containing vaccines and consistent with events reported for elasomeran-containing vaccines in prior review periods. The only pregnancy-specific events indicating an adverse clinical outcome following andusomeran vaccination have been “Abortion spontaneous” and “Haemorrhage in Pregnancy.” No pregnancy cases following andusomeran vaccination have reported a fatal outcome, stillbirth, or congenital anomaly. No pregnancy cases have been reported in children or adolescents under 18 years of age. In-depth literature reviews performed have not identified any new safety concerns for the use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy. Thus far, published literature has not identified any evidence of an increased risk of fetal or neonatal complications related to maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. Furthermore, published literature has reported that there is transfer of maternal antibodies, reduction in SAR-CoV-2 infection in vaccinated pregnant women and early evidence that infants benefit from passive protection from SARS-CoV-2 infection and severe disease following maternal COVID-19 vaccination. It is acknowledged that SAR-CoV-2 infection may be more serious and cause

Missing Information	Use in pregnancy
	complications for both the mother and the fetus and published literature supports the favourable benefit/risk profile of maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. Data continues to provide supporting evidence for the use of marketed Moderna vaccines targeting SARS-CoV-2 before and during pregnancy. After careful review of all new safety data received during the reporting period for the safety topic of Use in Pregnancy, the benefit-risk profile for marketed Moderna vaccines targeting SARS-CoV-2 remains favourable.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the safety topic of Pregnancy reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any new safety concern. The MAH will continue to monitor events for pregnancy using routine surveillance and ongoing post authorization studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation remains positive.

16.3.5.2 Use while Breastfeeding

Evaluation of information received during the PBRER reporting interval relating to the known missing information of marketed Moderna vaccines targeting SARS-CoV-2 of "Use while breastfeeding" has not identified any additional clinically relevant new safety information for this topic. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, remains valid.

Table 16-12 Use while Breastfeeding

Missing Information	Use in Breastfeeding

Source of New Information	• ModernaTx, Inc. GSDB
	• Literature Sources
	  o Search Criteria Applied: Appendix 13.4
	  o Retrieved: 563
	  o New and Significant Safety Information: None (0)

Background	The topic of Breastfeeding is summarized because the use of marketed Moderna vaccines targeting SARS-CoV-2 among breastfeeding women is an area of missing information in the currently approved RMP. Real world evidence and literature demonstrate that marketed Moderna vaccines targeting SARS-CoV-2 are well tolerated by lactating women and their children, and side-effects experienced are similar to side-effects in the general population. No specific safety concerns for breastfeeding have been identified.
Methods	Refer to Appendix 12.14 for Methods of Evaluation

Missing Information	Use in Breastfeeding
Results	**Overview of Lactation Cases Who Received elasomeran** It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide after Jun 2023. Therefore, during this review period, there was a considerable decrease in the number of reported pregnancy cases for elasomeran vaccine. During the review period, the MAH received 7 lactation cases (54 events) with 1 serious case among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran. Two (2) of the 7 lactation cases were medically confirmed. No lactation cases reported a fatal outcome. A higher percentage (6 cases; 85.7%) of the cases reported during this reporting period were non-serious compared to the prior review period (74.3%). During the reporting period, no meaningful changes were observed in the age distribution of the cases of lactating women and their breastfeeding children and are consistent with the expected age of lactating women and their breastfeeding children. Please note cases coded as males likely represent children who were exposed to breastmilk from mothers who had been vaccinated with elasomeran vaccine. During the review period, the most frequently reported PTs were consistent with reactogenicity events and common breastfeeding issues such as lactation insufficiency. When restricted to lactation-specific adverse events/outcomes, the only PTs reported were "Lactation insufficiency" (1 event), and "Galactostasis" (1 event). There was not a significant change in the pattern of PTs reported during the reporting period when compared to cumulative data. Most of the lactation-related events were transient and occurred within 2 days of vaccination. Medical review of the HLT "Lactation Disorders" was performed and the data for the review period are similar to the previous cumulative experience; no concerning patterns or notable trends were identified. During the reporting period 1 serious lactation case was received. Case [redacted] described the serious event of Guillain-Barre syndrome in a 39-year-old female. This case was reported in the previous review period but added the non-serious concurrent event of COVID-19 infection and other updates to the narrative (reporter information, patient details, medical history, lab data, and event information) during this review period. The only lactation-specific PT reported was "Exposure via breast milk." There were no lactation-specific events reported indicating a clinical adverse event/outcome for an infant/child or lactating woman in this case. **Subpopulation Analyses** *Lactation Cases Under 6 Years of Age–elasomeran* During the review period, the MAH received 3 non-serious cases (11 events) 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). No cases reported a fatal outcome and 1 case was medically confirmed.

Missing Information	Use in Breastfeeding
	Similar to the previous review period, the most frequently reported clinical events reported among children under the age of 6 years of age were fatigue, pyrexia, diarrhoea, vomiting, rash, malaise, and body temperature increased which are consistent with reactogenicity events expected for elasomeran. When restricted to only lactation-specific PTs, the most frequently reported lactation-specific PT continued to be "Exposure via breast milk." During the reporting period, the mean age of lactation cases among children under 6 years was 0.4 years (SD: 0.3) and median age was 0.4 years (range: 0.0 to 0.7 years). The sample size was small so there was no meaningful difference in the number of reports involving males (1; 33.3%) and females (1; 33.3%); with 1 case (33.3%) not reporting gender. When TTO was known, most of the lactation-related events were transient and all events occurred within two days after vaccination. During the review period, no lactation cases reporting seizure were received. Cumulatively, all serious cases with lactation specific events have been medically reviewed and summarized. Many cases lack information on clinical course, outcome, pediatric medical history, or alternate etiologies/concurrent clinical events. Thus, based on the temporal relationship, causality cannot be excluded. To date, no concerning patterns or notable trends have been identified to suggest a vaccine-associated safety concern. *Lactation Cases Among Adolescents (12-17 years of Age)- elasomeran* No lactation cases were reported among adolescents during this review period. Cumulatively and during the reporting period, no unusual patterns or lactation specific safety concerns have been identified after receipt of elasomeran. **Lactation Cases After Receiving Booster Dose with elasomeran/imelasomeran** During the review period, no lactation cases were reported among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with a booster dose of elasomeran/imelasomeran. **Lactation Cases After Receiving Booster Dose with elasomeran/davesomeran** During the review period, the MAH received 2 non-serious lactation cases (4 events) among individuals who received elasomeran/davesomeran. No cases reported a fatal outcome, and both cases were medically confirmed. During the review period, when restricted to lactation-specific events, the only PT reported was "Maternal exposure during breastfeeding." **Lactation Cases Among Adolescents (12-17 years of Age)- elasomeran/davesomeran** No lactation cases were reported among adolescents during this review. Cumulatively and during the reporting period, no unusual patterns or lactation specific safety concerns have been identified after receipt of a booster dose with elasomeran/davesomeran.

Missing Information	Use in Breastfeeding
	Lactation Cases After Receiving Booster Dose with andusomeran It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant XBB 1.5. Therefore, this will be the first PBRER review period where lactation cases among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with a booster dose of andusomeran will be reviewed. Since the approval of andusomeran, the MAH has not received any fatal or serious cases. The MAH has received 5 non-serious lactation cases (17 events) among individuals who received a booster dose of andusomeran. Four (4) of the 5 cases were medically confirmed and 3 cases did not report an adverse clinical event/outcome. When restricted to lactation-specific events, the only PTs reported were "Maternal exposure during breast-feeding" and "Exposure via breast milk." Assuming that the age of the patients was reported correctly, it is important to note that cases [redacted] and [redacted] may have been incorrectly coded as lactation cases given the patient's age (56 years and 70 years, respectively). **Lactation Cases Among Adolescents (12-17 years of Age)- andusomeran** No lactation cases were reported among adolescents during this review. No unusual patterns or lactation-specific safety concerns were identified after receipt of a booster dose with andusomeran. **Lactation Cases After Receiving SPIKEVAX (NOS)** During the reporting period, no lactation cases were reported that were classified as exposed to a vaccine under the SPIKEVAX (NOS) classification.
Discussion	During the reporting period, ModernaTx, Inc. received a total of 14 lactation cases (75 events) among individuals who received or were exposed to breast milk from mothers who had been vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2; of which 3 cases were among children under 6 years of age with exposure to elasomeran via breast milk and the remaining cases (11) were reported for adult females older than 18 years of age. There were no lactation cases reported among adolescents (12-17 years age group) during this reporting period. There was 1 serious lactation case received (reporting the serious event of Guillain-Barre syndrome) for an adult female, however no serious lactation-specific events were reported, and the case was heavily confounded by concurrent medical history of COVID-19 infection. No cases reporting a fatal outcome were received. While vaccination can induce cytokines, which can be passed via breast milk, vaccination while breastfeeding has not been linked to adverse events in infants. In fact, women with fever and illness are encouraged to continue breastfeeding 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 [72] [73] [74].

Missing Information	Use in Breastfeeding
	The most frequently reported terms were exposure during breast-feeding or maternal exposure during breast-feeding. 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 were available, many of the events occurred within 2 days after vaccination, and most events were mild/moderate, transient events. 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 marketed Moderna vaccines targeting SARS-CoV-2 or what is expected in the general population [75] [76] [75]. No specific safety concerns were identified after receipt of a booster dose with andusomeran by breastfeeding women and their children who are exposed to this vaccine through breast milk. The current safety profile of andusomeran is consistent with the safety profile of the other marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to review cases that received the andusomeran vaccines using routine surveillance. Review of the literature to date has not identified any safety concerns related to marketed Moderna vaccines targeting SARS-CoV-2 during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated breastfeeding 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 favourable benefit/risk profile of COVID vaccination during lactation which continues to provide supporting evidence for HA recommendations for the use of COVID-19 vaccines including marketed Moderna vaccines targeting SARS-CoV-2 during lactation. The MAH is closely monitoring the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in this population through routine pharmacovigilance [77-79]. After careful review of all new safety data received during the reporting period for the safety topic of Use while Breastfeeding, the benefit-risk profile for marketed Moderna vaccines targeting SARS-CoV-2 remains favourable.
Conclusion	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Use while Breastfeeding reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any safety concern. The MAH will continue to monitor events associated with breastfeeding women who receive marketed Moderna vaccines targeting SARS-CoV-2 and their children who are exposed to these vaccines through breast milk using routine surveillance and ongoing post-authorization studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation for this sub-population continues to remain positive.

16.3.5.3 Long-term Safety

Evaluation of information received during the PBRER reporting interval relating to the missing information risks of long-term safety, has not identified any additional clinically relevant new safety information for these topics. The characterization of these important risks as described in the current RMP and in Section 16.4, below, remains valid.

Table 16-13 Long-term Safety

Missing Information	Long-term Safety
Source of New Information	As of the DLP of this PBRER, 26 CTs were ongoing 16 of which are sponsored by ModernaTx, Inc. Cumulatively, 59,907 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, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 (including its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administered with mRNA-1010 or co-administered with mRNA-1345, or co-administered active licensed sFLU vaccines (Fluzone HD or Fluarix) in the mRNA-1083 clinical development program sponsored by ModernaTx, Inc.
Background	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-P203, mRNA-1273-P204, mRNA-1273-P205 (Parts A.1, B, C, D, F, and G), and the completed studies mRNA-1273-P101 (DMID 20-0003), and mRNA-1273-P201. Per protocols, safety follow-up period for mRNA-1273-P205 (Parts A.2, H and J) is 6 months and for the competed study mRNA-1273-P301 was 24 months. Post-authorization safety studies in real world that evaluate long-term safety include ongoing studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911.
Methods	The long-term safety profile remains to be characterized through continued trial follow-up, routine pharmacovigilance, and PASS as indicated in the current RMP. The Phase 3 study mRNA-1273-P301, completed during the current review period of this PBRER, included a total of 24 months follow-up; no long-term safety concerns were identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days).
Results	No long-term safety concerns were identified after completion of the clinical pivotal study mRNA-1273-P301.

Missing Information	Long-term Safety
	Post-authorization safety studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911 are ongoing, and no findings related to long-term safety have yet been identified. As of the DLP of this PBRER, no clinically important safety concerns have been identified upon review of long-term follow-up data in CTs.
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 Marketed Moderna vaccines targeting SARS-CoV-2. **Ongoing Studies**: • Study mRNA-1273-P904 (final CSR: 31 Sep 2024) • Study mRNA-1273-P910 (final CSR: 30 Jun 2025) • Study mRNA-1273-P911 (final CSR: 31 Oct 2028) • Study mRNA-1273-P203 (final CSR: 15 Jul 2025) • Study mRNA-1273-P204 (final CSR; 31 Dec 2024) • Study mRNA-1273-P205 (final CSR: 07 Nov 2024) • **Completed Studies**: • Study mRNA-1273-P301 (final CSR: 20 Oct 2023)
Conclusion	As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor the 1 completed study (mRNA-1273-P301) which are being assessed to characterize long-term safety of Marketed Moderna vaccines targeting SARS-CoV-2.

16.3.5.4 Use in immunocompromised subjects (Safety concern in PBRER only)

Evaluation of information received during this PBRER reporting period relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in relation to immunocompromised individuals, has not identified any additional clinically relevant new safety information for this subpopulation.

Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

The characterization of the missing information within the PSUR on Use in Immunocompromised Individuals, as of the DLP of this PBRER, and in Section 16.4, remains valid. The number of fatal

cases received during this reporting period and the associated MAH comment are presented by product in Appendix 12.15.

Table 16-14 Use in immunocompromised subjects (Safety concern in PBRER only)

Missing Information	**Use in immunocompromised subjects**
Source of New Information	• ModernaTx, Inc GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 53 o New and Significant Safety Information: There was no new and significant safety information identified for the immunocompromised population.
Background	The topic of Immunocompromised is summarized because it is considered missing information in the PBRER. No specific safety concerns for immunocompromised individuals have been identified. It is important to note that the use of marketed Moderna vaccines targeting SARS-Cov-2 in immunocompromised individuals is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a request from the PRAC.
Methods	For the purposes of this PBRER reporting period, the following search criteria 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 haematological malignant tumors SMQ, transplantation, primary/innate and acquired immunodeficiency syndromes (including Human Immunodeficiency Virus) and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs. The "General Population" (all marketed Moderna vaccines targeting SARS-CoV-2 data) in the ModernaTx, Inc's. 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.
Results	Refer to Appendix 12.15 for additional information. **Overview of Cases for Immunocompromised Individuals Who Received elasomeran** It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide after Jun 2023. Therefore, during this review period, there was a considerable decrease in the number of reported cases for immunocompromised individuals who received elasomeran vaccine.

Missing Information	Use in immunocompromised subjects
	During this review period, the MAH received 91 cases (360 events) with 54 (59.3%) serious cases (179 serious events) among immunocompromised individuals who received elasomeran. A total of 51 (56.0%) cases were medically confirmed, and 2 cases (2.2%) reported a fatal outcome. Similar to the prior reporting period, there were more cases involving females (45; 49.5%) compared to males (43; 47.3%), with 3 cases (3.3%) that did not report gender information. The median age of patients was 58.0 years (range: 23.0 -83.0 years). Similar to the previous review period, the most frequently reported MedDRA PTs in the immunocompromised subpopulation included headache, fatigue, pyrexia, chest pain, myalgia, and dyspnoea. These PTs were comparable to those reported in the general population and reflected expected reactogenicity. Events of COVID-19 infection were the most frequently reported event during this review period (17; 4.7%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. Note that during the review period, 25 cases (including 15 serious and 1 fatal case) overlapped 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. **Subpopulation Analyzes:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – elasomeran)* During the review period, no cases were reported among immunocompromised individuals in these age groups who received elasomeran. *Fatal Cases in Immunocompromised Individuals – elasomeran* Evaluation of the 2 cases reporting fatal outcome showed that both cases concerned males; one was 75 years of age and the other was 53 years of age. Both cases had comorbidities including malignancies that were chronic conditions, and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Using the WHO-UMC causality assessment tool, both cases were assessed as "Unlikely" (due to long TTO outside the risk window/unspecified latency and concurrent medical conditions that provided an alternate etiology). Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran. **Overview of Cases for Immunocompromised Individuals Who Received elasomeran/imelasomeran** During the review period, the MAH received 15 cases (49 events) with 14 (93.3%)

Missing Information	Use in immunocompromised subjects
	serious cases (46 serious events) for immunocompromised individuals who received a booster dose of elasomeran/imelasomeran. One (1) case (6.7%) was medically confirmed, and no cases reported a fatal outcome. A higher proportion of cases were reported for females (9; 60.0%) than males (5; 33.3%) with 1 case (6.7%) that did not report gender information. The median age of patients was 56.0 years (range: 20.0 to 75.0 years). During the review period, the most frequently reported PTs (>4.0%) in immunocompromised individuals who received elasomeran/imelasomeran were pain in extremity, headache, fatigue, pyrexia, dyspnoea, and palpitations. These events reflect expected reactogenicity and were comparable to events reported in the general population receiving elasomeran/imelasomeran. Events of COVID-19 infection were also frequently reported during this review period (2; 4.1%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. Note that during the review period, 6 cases (including 5 serious cases) overlapped 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. **Subpopulation Analyses:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – elasomeran/imelasomeran* During the review period, no cases were reported among immunocompromised individuals in these age groups who received elasomeran/imelasomeran. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran/imelasomeran. **Overview of Cases for Immunocompromised Individuals Who Received elasomeran/davesomeran** During the review period, the MAH received 12 cases (28 events) with 1 (8.3%) serious case (1 serious event) for immunocompromised individuals who received elasomeran/davesomeran. All 12 cases were medically confirmed, and no case reported a fatal outcome. Similar to the previous review period, there were no meaningful changes in the gender distribution of reports as a slightly higher proportion of cases continued to be reported in females (7; 58.3%) than males (5; 41.7%). The median patient age was 70.5 years

Missing Information	Use in immunocompromised subjects
	(range: 14.0 to 86.0 years). During the review period, the most frequently reported events were issues related to product expiration, medication error (extra dose administered), or product storage error. These events reflect similar events observed during the reporting period in the general population receiving elasomeran/davesomeran. Additionally, during the review period, there was 1 case with a serious event of cerebrovascular accident in a person living with HIV, that was treated with antihypertensives and recovered. The case was assessed as unlikely related to the use of the product due to the short latency period and concurrent hypertension and HIV that provide alternate etiologies. Note that during the review period, 3 non-serious cases overlapped 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. **Subpopulation Analyses:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – elasomeran-davesomeran* During the review period, 1 non-serious case was reported for a 14-year-old immunocompromised female following receipt of elasomeran/davesomeran. Case [redacted] reported the events of product expiration and product storage error with no resulting clinical adverse event/outcome. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran/davesomeran. **Overview of Cases for Immunocompromised Individuals Who Received andusomeran** It is important to note that during the review period, on 11 Sep 2023, the US FDA approved a new formulation for elasomeran against COVID-19 variants, including the new Omicron variant XBB 1.5. Therefore, this will be the first PBRER review period where cases for immunocompromised individuals who received andusomeran will be reviewed. During the review period, the MAH received 58 cases (179 events) with 26 (44.8%) serious cases (75 serious events) for immunocompromised individuals who received andusomeran. A total of 24 (41.4%) cases were medically confirmed, and 1 case (1.7%) reported a fatal outcome. There were more cases reported for females (36; 62.1%) compared to males (16; 27.6%),

Missing Information	Use in immunocompromised subjects
	with 6 cases (10.3%) that did not report gender information. The median age of patients was 64.0 years (range: 23.0 – 93.0 years). The most frequently reported events (>2.0%) included headache, fatigue, pain in the extremity, pyrexia, arthralgia, diarrhoea, dizziness, and product expiration issues. These PTs were comparable to those reported in the general population that received andusomeran and predominantly reflected expected reactogenicity. Events of COVID-19 infection were also frequently reported during this review period (5; 2.8%). This may be due to an already exiting COVID-19 infection prior to vaccination, and the susceptibility to constantly changing variants. Note that during the review period, 10 cases (4 serious) overlapped 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. **Subpopulation Analyses:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – andusomeran)* No cases have been reported among immunocompromised individuals in these age groups who received andusomeran. *Fatal Cases in Immunocompromised Individuals –andusomeran* One (1) case reported a fatal outcome in an immunocompromised individual who received andusomeran. This regulatory authority case concerned an individual of unspecified age and gender with a medical history of immunodeficiency. The patient died on an unknown date and an unspecified latency period following vaccination with andusomeran. The cause of death was not reported, and no autopsy was performed. Using the WHO-UMC causality assessment tool, this case was evaluated as "Unassessable" given limited data provided; including missing data regarding age, gender, dose number, TTO, medical history, concomitant medications, clinical course of events, diagnostic evaluation, and clinical course that precludes a meaningful causality assessment. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received andusomeran. **Overview of Cases for Immunocompromised Individuals Who Received a vaccine under the SPIKEVAX (NOS) classification.** It is important to note that during the reporting period for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to

Missing Information	Use in immunocompromised subjects
	attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, or andusomeran). During this review period, the MAH received 6 cases (13 events) with 1 (16.7%) serious case (1 serious event) among immunocompromised individuals who received a vaccine under the SPIKEVAX (NOS) classification. A total of 5 (83.3%) cases were medically confirmed, and no cases reported a fatal outcome. All cases reporting gender involved females (4; 66.7%), with 2 cases (33.3%) that did not report gender information. The median age of patients was 45.5 years (range: 33.0- 58.0 years). The most frequently reported MedDRA PTs were anaemia, leukaemia, and weight decreased. Events of COVID-19 infection were the most reported event for this subpopulation (4; 30.8%) and the general population (62; 10.1%) during this review period. This may be due to an already exiting COVID-19 infection prior to vaccination, and the susceptibility to constantly changing variants. Note that during the review period, 1 non-serious case overlapped 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. **Subpopulation Analyzes:** *Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – SPIKEVAX (NOS)* During the review period, no cases were reported among immunocompromised individuals in these age groups who received a vaccine under the SPIKEVAX (NOS) classification. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received a vaccine under the SPIKEVAX (NOS) classification.
Discussion	As of the DLP date of this PBRER, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in immunocompromised individuals. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, the general pattern of commonly reported AEs in those considered immunocompromised individuals is comparable to the general population. Evaluation showed that the most frequently reported AEs in the immunocompromised population were representative of expected reactogenicity and were consistent with those

Missing Information	Use in immunocompromised subjects
	seen in the general population. There were no clustering or trends observed after any dose. The adverse events observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population was generally similar. Epidemiological studies have not indicated any increased risk of AEs in immunocompromised individuals after vaccination with a marketed Moderna vaccine targeting SARS-CoV-2. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. During the review period, there was 1 case reported in a 14-year-old adolescent. No cases were reported for children under 12 years of age. Review of cumulative cases for these subpopulations have not revealed any new or unusual pattern of events or safety concerns. Cases with a fatal outcome in immunocompromised individuals during the reporting period (1.7%) were strongly confounded by long or unspecified latency and multiple comorbidities that provided alternate etiologies.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of a marketed Moderna vaccine targeting SARS-CoV-2 in immunocompromised individuals. Information presented in those reports does not differ from the known safety profile of the marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important safety information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Immunocompromised, reported in temporal association with the administration of a marketed Moderna vaccine targeting SARS-CoV-2 did not raise any new safety concerns. The MAH will continue to monitor events for immunocompromised individuals using routine surveillance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904. The benefit-risk evaluation remains positive.

16.3.5.5 Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in the frail subpopulation has not identified any additional clinically relevant new safety information for this subpopulation. Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category

of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran). The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, remains valid.

Table 16-15 Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)

Missing Information	**Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)**
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Retrieved: Appendix 13.4 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	Frail patients are considered at higher risk for 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 co-morbidities were excluded from the registration CTs, the MAH is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Safety reports for frail subpopulation is summarized because it is an area of missing information in the PBRER, but it was removed from the RMP during the previous PBRER reporting period. No specific safety concerns have been identified.
Methods	The ModernaTx, Inc. GSDB was queried for reports of frail individuals using "Frail" custom search as defined in the Moderna Signalling Strategy plan (see Appendix 12.16), which included subjects of all ages with unstable health conditions and comorbidities (including COPD, HIV, diabetes, chronic neurological disease, cardiovascular disorders).
Results	Refer to Appendix 12.16 for more information. **Overview of Frail Cases Reported for elasomeran:** It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide. Therefore, during this review period, there was a considerable decrease in the number of reported cases for frail individuals who received elasomeran vaccine. During the review period, the MAH received 641 cases (3,077 events) reported in Frail subpopulation with 352 (54.9 %) serious cases (1,061 serious events), 279 cases (43.5%) were medically confirmed cases, and 17 (2.7%) cases with fatal outcome involving elasomeran. The majority of cases were reported in females (398, 62.1%) compared to males (225, 35.1%). The median patient age was 55.0 years (range: 0.4 to 97.0 years). A high proportion of reported cases in frail was among the elderly (192, 29.9%).

Missing Information	Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
	The most frequently reported events (>2%) were fatigue, headache, pyrexia, myalgia, and vaccination site pains. These events were comparable to that reported in the general population that received elasomeran and reflected expected reactogenicity. Evaluation of the 17 cases (26.5%) with fatal outcomes showed that majority (10; 58.8%) were elderly above 65 years, and all 17 cases had comorbidities that were confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, most of the cases (13; 76.5%) were assessed as unlikely, due to TTO that was outside the risk window and concurrent medical conditions that provided alternate etiologies. Four cases were assessed as possible, due to temporal association. However, these 4 cases were confounded by concurrent polymorbid conditions. **Overview of Frail Cases reported for elasomeran/imelasomeran:** During the review period, the MAH received 64 cases (207 events) reported in Frail subpopulation, with 51 serious cases (154 serious events), 19 medically confirmed cases, and 4 cases with fatal outcome involving elasomeran/imelasomeran. Cases were almost equally distributed across gender, females (31 cases, 48.4%) compared to males (28 cases, 43.8%). The median patient age was 64.0 years (range: 22.0 to 91.0 years). The most frequently reported MedDRA PTs were fatigue, dyspnoea, headache, arthralgia, pain in extremity, dizziness, chest pain, injection site reaction, syncope, myocarditis and palpitations. The majority of these events were comparable to that reported in the general population that received elasomeran/imelasomeran and reflected expected reactogenicity. Myocarditis is an identified risk for elasomeran. Evaluation of the 4 cases with fatal outcomes showed that half (2; 50.0%) were elderly above 75 years, 1 was in a 25-39 year-old range, and 1 was missing information on age. All 4 cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, 3 of the cases were assessed as unlikely (due to TTO outside the risk window and concurrent medical conditions that provided alternate etiologies); and 1 case was assessed as possible, based on temporal association. However, concurrent comorbidities of bradycardia and syncope provide alternate etiology. **Overview of Frail Cases Reported for elasomeran/davesomeran:** During the review period, the MAH received 93 cases (260 events) reported in the frail subpopulation, with 36 serious cases (76 serious events), 77 medically confirmed cases, and 5 cases with fatal outcome involving elasomeran/davesomeran. A slightly higher proportion of cases were reported in females (51; 54.8%) compared to males (41; 44.1%). The median patient age was 71.0 years (range: 4.0 to 98.0 years) with highest cases seen in the elderly >65+ (62.6%).

Missing Information	Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
	The most frequently reported MedDRA PTs in frail subpopulation receiving elasomeran/davesomeran were pyrexia, myalgia, pain in extremity, fatigue, vaccination site pain, headache, arthralgia, and malaise. These events are expected reactogenicity and consistent with reports in the general population that received elasomeran/davesomeran. Evaluation of the 57 frail/elderly cases showed a higher proportion of case in females (33; 57.9%) compared to males (24; 42.1%), with over half (31; 54.4%) reported in 75+-year age group. Evaluation of the 5 cases with fatal outcomes showed a higher number of cases reported in females (3; 60.0%). All of the cases were from Japan and 4 of the 5 were over 75 years of age. All cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Using the WHO-UMC causality assessment tool, all 5 cases were assessed as unlikely, due to TTO outside the risk window, and concurrent polymorbid medical conditions that provide alternate etiologies. **Overview of Frail Cases Reported for andusomeran:** During the review period, the MAH received 228 cases (811 events) reported in the frail subpopulation, with 94 serious cases (223 serious events), 129 medically confirmed cases, and 8 cases with fatal outcome involving andusomeran. A slightly higher proportion of cases were reported in females (129; 56.6%) compared to males (88; 38.6%). The median patient age was 70.0 years (range: 5.0 to 98.0 years) with the highest cases seen in the elderly >65+ (63.2%). The most frequently reported MedDRA PTs in frail subpopulation receiving andusomeran were fatigue, headache, pyrexia, chills, chest pain, nausea, myalgia, diarrhoea, seizure, and loss of consciousness. Most of these events are expected reactogenicity (except for seizure, loss of consciousness, and chest pain) and were consistent with reports in the general population that received andusomeran. Over half of the cases (57.0%) were from the US. Evaluation of the 144 frail/elderly cases showed a higher proportion of case in females (75; 52.1%) compared to males (63; 43.8%). with over half (77; 53.5%) reported in 65-74 year age group. Most of the deaths were reported in females (5; 62.5%). Four cases were from Japan. All 8 cases had significant comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Seven of the individuals were over 80 years of age. Using the WHO-UMC causality assessment tool, 5 cases were assessed as unlikely, due to concurrent polymorbid conditions that provided alternated etiologies. Three cases were assessed as possible, based on temporal association, and reported clinical features of myocarditis and anaphylaxis. However,

Missing Information	Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
	there were underlying cardiovascular, respiratory, and chronic renal disease confounders/risk factors. Myocarditis and anaphylaxis are identified risk for elasomeran. **Overview of Frail Cases Reported Involving a Vaccine Under the SPIKEVAX (NOS) Classification.:** During the review period, the MAH received 19 cases (50 events) reported in the frail subpopulation, with 6 serious cases (8 serious events), 14 medically confirmed cases, and 1 case with a fatal outcome involving a vaccine under the SPIKEVAX (NOS) classification. Cases were similarly reported in females (8; 42.1%) and males (9; 47.4%). The median patient age was 67.5 years (range: 23.0 to 83.0 years) with the highest events seen in the elderly >65+ years (42.1%) followed by the 50-64-year age group (21.1%). Most cases were non-serious (68.4%) with the most frequently reported MedDRA PTs in frail subpopulation receiving a vaccine under the SPIKEVAX (NOS) classification were fatigue, pyrexia, arthralgia, pain in extremity, and weight decreased. Most of these events are expected reactogenicity (except for weight decreased) and consistent with reports in the general population. COVID-19 infection was reported as a clinical event. The majority of cases (84.2%) were from the United States. Evaluation of the 8 frail/elderly cases showed equal distribution across gender (4 cases each; 50%) with the majority (6; 75.0%) reported in 65-74 year age group. Among serious cases, the majority had missing outcome. There was 1 case with fatal outcome in a 23-year-old male with a medical history of chronic asthma, who experienced respiratory distress, dyspnoea, and chest pain after vaccination of a dose of a vaccine under the SPIKEVAX (NOS) classification, with an unknown TTO. There was no report of concomitant medications, clinical course of events, and diagnostic results, The cause of death was not reported nor was an autopsy performed. Using the WHO-UMC causality assessment tool, the case was assessed as unassessable due to insufficient information on TTO, clinical course of events, diagnostic results. This case is confounded by concurrent asthma.
Discussion	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. Most of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, 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. Evaluation showed that the most frequently reported AEs in the frail population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The pattern of events observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population was generally similar. Epidemiological studies have not indicated any

Missing Information	Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
	significantly increased risk of side-effects in frail individuals after vaccination with elasomeran. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events or safety concern. Cases with fatal outcome in the frail subpopulation in the reporting period (3.2%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiologies.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2 in the frail subpopulation. Information presented in those reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important safety information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in the frail subpopulation. Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Frail, reported in temporal association with the administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any new safety concern. The MAH will continue to monitor events for Frail using routine surveillance. The benefit-risk evaluation remains positive.

16.3.5.6 Use in subjects with autoimmune or inflammatory disorders (AI/ID) (Safety concern in PBRER only)

Evaluation of information received during the present PBRER reporting interval relating to individuals with known history of autoimmune and inflammatory disorders (MedHx AI/ID) and vaccination with a marketed Moderna vaccine targeting SARS-CoV-2, has not identified any additional clinically relevant new safety information for this population. Please note that for better attribution of case reports to SPIKEVAX products, the MAH created a dosing category of SPIKEVAX (NOS) (i.e., not otherwise specified) for cases reported without sufficient information to attribute the relationship of the case and events to a specific SPIKEVAX product (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran).

The characterization of this missing information within this PSUR as of the DLP of this PBRER and in Section 16.4, remains valid. The number of cases received during reporting period are

presented by product in Table 16-16. Refer to Appendix 12.17 for further information on fatal cases.

Table 16-16 Use in subjects with Autoimmune or Inflammatory Disorders (AI/ID) (Safety concern in PBRER only)

Missing Information	Use in subjects with autoimmune or inflammatory disorders (AI/ID)
Source of New Information	• ModernaTx, Inc. GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 73 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	To date, clinical trials have not identified any specific safety risks in individuals with AI/AD. Because there was limited data from CTs on the use of elasomeran COVID-19 vaccines, in individuals with AI/ID, the MAH has been closely monitoring the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in this population through routine Pharmacovigilance. Important to note that use of these vaccines in individuals with AI/ID is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a request from the PRAC. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in AI/ID 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. Furthermore, some countries are suggesting additional doses after primary series in individuals with MedHx of AI/ID. Thus far, there have been no specific safety concerns for individuals with MedHx of AI/ID. Epidemiological studies have not indicated any increased risk of side-effects in individuals with AI/ID after vaccination with marketed Moderna vaccines targeting SARS-CoV-2 and have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general population receiving marketed Moderna vaccines targeting SARS-CoV-2.
Methods	The ModernaTx, Inc GSDB was queried for valid clinical and spontaneous reports for marketed Moderna vaccines targeting SARS-CoV-2 in people with a medical history of autoimmune and/or inflammatory disease, received for review period (18 Jun 2023 to 17 Dec 2023). Reports from individuals with a MedHx AI/ID were identified from MAH GSDB using Immune-mediated/autoimmune disorder SMQ "Immune-mediated/autoimmune

Missing Information	Use in subjects with autoimmune or inflammatory disorders (AI/ID)
	disorders SMQ" PTs identified in past medical history. Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	Refer to Appendix 12.17 for additional information. **Overview of MedHx AI/ID Cases Reported for elasomeran** During this reporting period, 367 cases (209 serious, 147 medically confirmed, 5 fatal cases) with 1,700 events (663 serious) were reported in individuals with a known MedHx AI/ID after receiving elasomeran. Majority of cases (264; 71.9%) were reported in females compared to males (88 cases; 24.0%), with a small proportion of cases (15; 4.1%) having no gender reported. The mean patient age was 51.4 years (SD: 15.8) and median age was 51.0 years (range: 16.0 to 97.0 years). Of note, 36 cases (9.8%) were missing age-related information. The most frequently reported serious events during this reporting period were headache, fatigue, and multiple sclerosis pseudo relapse. Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (elasomeran) During this reporting period, there was 1 non-serious case reported in a 16-year-old male. Fatal Cases in Individuals with MedHx AI/ID (elasomeran) During this reporting period, 5 cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran. Refer to Appendix 12.17 for further information. **Overview of MedHx AI/ID Cases Reported for elasomeran/imelasomeran:** During the reporting period, 22 cases (19 serious, 3 medically confirmed, 0 fatal) with 78 events (68 serious) reported in individuals with a known MedHx AI/ID after receiving elasomeran/imelasomeran. When gender was known, no important differences were noted in reports involving females (11 cases; 50.0%) and males (10 cases; 45.5%), with 1 case (4.5%) having no gender reported. The mean patient age was 56.9 years (SD:14.2) and median age was 62.0 years (range: 27.0 to76.0). Of note, 1 case (4.5%) was missing age-related information. The most frequently reported serious events were fatigue, diarrhoea, pain in extremity, syncope, and COVID-19 in individuals with known MedHx AI/ID who received elasomeran/imelasomeran. Subpopulation Analysis: Use in Children <18 years of Age with MedHx AI/ID (elasomeran/imelasomeran) During this reporting period, no cases were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (elasomeran/imelasomeran) During this reporting period, no cases with fatal outcome were reported in individuals

Missing Information	Use in subjects with autoimmune or inflammatory disorders (AI/ID)
	with known MedHx AI/ID who received elasomeran/imelasomeran. **Overview of MedHx AI/ID Cases Reported for elasomeran/davesomeran:** During the reporting period, 25 cases (6 serious, 21 medically confirmed, 0 fatal) with 72 events (9 serious) reported in individuals with known MedHx of AI/ID after receiving elasomeran/davesomeran. The majority of cases were reported in females (17 cases; 68.0%) compared to males (7 cases; 28.0%), with 1 case (4.0%) having no gender reported. The mean patient age was 64.8 years (SD:14.4) and median age was 68.0 years (range: 28.0 to 92.0 years). Of note, 3 cases (12.0%) did not report age-related information. During this reporting period, anaphylactic reaction was reported in 2 cases, (22.2%), and all other serious events, each were reported once (11.1%) in individuals each with known MedHx AI/ID receiving elasomeran/davesomeran. Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (elasomeran/davesomeran) During this reporting period, no cases involving elasomeran/davesomeran were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (elasomeran/davesomeran) During this reporting period, no cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran/imelasomeran. **Overview of AI/ID Cases Reported for andusomeran:** During this reporting period, 62 cases (26 serious, 27 medically confirmed, 1 fatal case) with 248 events (84 serious) were reported in individuals with a known MedHx AI/ID after receiving andusomeran. The majority of cases (44; 71.0%) were reported in females compared to males (14 cases; 22.6%), with a small proportion of cases (4; 6.5%) having no gender reported. The mean patient age was 57.0 years (SD: 17.7) and median age was 57.0 years (range: 24.0 to 89.0 years). Of note, 8 cases (12.9%) did not provide age-related information. The most frequently reported serious events during this reporting period often reflected expected reactogenicity events, such as pyrexia, headache, and fatigue. These are consistent with cumulative reporting. Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (andusomeran) During this review period, no cases involving andusomeran were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (andusomeran) During this reporting period, 1 case with fatal outcome was reported in an individual with known MedHx AI/ID who received andusomeran. Refer to Appendix 12.17 for further information.

Missing Information	Use in subjects with autoimmune or inflammatory disorders (AI/ID)
	Overview of MedHx AI/ID Cases Reported for a vaccine under the SPIKEVAX (NOS) classification: During this reporting period, 14 cases (3 serious, 9 medically confirmed, 0 fatal) with 33 events (9 serious) were reported in individuals with a known MedHx AI/ID after receiving a vaccine under the SPIKEVAX (NOS) classification. When gender was known, no important differences were noted in reports involving females (6 cases, 42.9%) and males (4 cases, 28.6%), and 4 cases (28.6%) had no gender information reported. The mean patient age was 57.5 years (SD: 10.6) and median age was 59.0 years (range: 37.0 to 74.0 years). Of note, 6 cases (42.9%) did not provide age-related information. During this reporting period, all serious events (haematuria, pyrexia, axillary mass, cardiogenic shock, diarrhoea, influenza, lymphadenopathy, stress cardiomyopathy and vomiting) each were reported once (11.1%). Subpopulation Analysis: Use in Children <18 Years of Age with MedHx AI/ID (SPIKEVAX [NOS]) During this review period, no cases involving a vaccine under the SPIKEVAX (NOS) classification. were reported in children <18 years of age. Fatal Cases in Individuals with MedHx AI/ID (SPIKEVAX [NOS]) During this reporting period, no cases with fatal outcome were reported in individual with known MedHx AI/ID who received a vaccine under the SPIKEVAX (NOS) classification.
Discussion	Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers the cases of MedHx AI/ID to be consistent with the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2 and the benefits for elasomeran far outweigh any possible vaccine-associated risks. No new safety concerns were identified in the literature review concerning marketed Moderna vaccines targeting SARS-CoV-2. The safety and benefit/risk profile of COVID vaccination in individuals with AI/ID remains acceptable. In AI/ID patients with disease flares, there is a natural waxing and waning course, and there are no reliable referenced data on the background rates of respective flares especially given the number of various AI/ID diseases and how to accurately measure a flare. The identified flare cases did not demonstrate a safety concern for this reporting period. 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 marketed Moderna vaccines

Missing Information	Use in subjects with autoimmune or inflammatory disorders (AI/ID)
	targeting SARS-CoV-2. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving marketed Moderna vaccines targeting SARS-CoV-2. For the fatal AI/ID cases, common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, and hyperlipidemia, are similar to those reported in the general population fatal reports.
Conclusion	Evaluation of the data during this reporting period did not identify any new safety information that would suggest a possible association between the evaluated events and administration of marketed Moderna vaccines targeting SARS-CoV-2. Information presented in those reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important information on the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Autoimmune/ inflammatory Disorders reported in temporal association with the administration of marketed Moderna vaccine targeting SARS-CoV-2 did not raise any new safety concern. The MAH will continue to monitor events in individuals with known MedHx AI/ID using routine surveillance. The benefit-risk evaluation remains positive.

16.4 Characterization of Risks

Table 16-17 Important Identified/Important Potential Risks

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
Potential Mechanism	Immediate type (Type 1), hypersensitivity mediated by immunoglobulin (Ig) E. Naturally existing IgM and IgG can bind to various components commonly present in nanomedicines, (cholesterol, phospholipids and polyethylene glycol).
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and the post-authorization safety information, including PASS, as well as published literature information.
Characterization of risk	The Phase 3 study mRNA-1273-P301, completed during the current review period of this PBRER, included a total of 24 months follow-up; no long-term safety concerns were identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days). In study mRNA-1273-P301 (Part A), in the anaphylaxis SMQ, 9 events were reported for 5 participants in the elasomeran group, and 18 events were reported for 8 participants in the placebo group. Anaphylactic reaction of unknown cause was reported for 2 participants in the elasomeran group as nonserious, moderate severity events approximately 2 months after the second dose; both were considered not related to investigational product and resolved on the same day with concomitant

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	medications. Among the other terms in the SMQ, reported events in the elasomeran group were all nonserious and described as follows: mild cough and mild eye pruritus for one participant on Day 47 after the second dose (not considered related); mild tachypnea on Day 29 after the first dose (which was reported on the day of the second dose), severe tachypnea on Day 1 after the second dose (which was the same day; event resolved on Day 64), and moderate urticaria beginning 30 minutes after the second dose and resolved in 1 hour with concomitant medication (all events considered related); and moderate dyspnea (considered related; reported as resolving) and severe swelling face (not considered related; resolving with prednisone) beginning on Day 34 after the second dose. In Part B of mRNA-1273-301, amongst the SAEs, a grade 3 anaphylaxis was reported in 2 participants in the placebo-elasomeran group, both of which were considered unrelated to elasomeran. These 2 participants had history of asthma. The first participant was a 50s' years old female who experienced anaphylaxis 19 days after the first injection which resolved the same day; the participant did not receive the second dose. The second participant was a 50s' year old female who experienced anaphylaxis a few months after receiving the second dose of vaccine; however, it was not temporally related to elasomeran and considered associated to a steroid injection per the investigator. In the placebo group, no anaphylaxis was reported. In the elasomeran group, 1 participant experienced anaphylaxis due to antigen challenge allergy testing (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B]). In Part C, a review of the anaphylaxis SMQ revealed no events of anaphylaxis or that suggest anaphylaxis to the study vaccine (mRNA-1273-P301-addendum 3-Section 7.3.2.3.2.3). Cumulatively, in the global safety database a total of 24 cases (24 events), with 22 serious cases (22 serious events) with no reported fatal outcomes, of anaphylaxis-related events in patients < 18 years were received after elasomeran. Twenty (20) cases were medically confirmed. Of the 24 cases, 11 were male (45.8%) and 13 were female (54.2%) with a mean age of 15.3 [SD:1.6], and a median: 16.0. There is only one case of anaphylaxis reported in a 9-month-old child who the same day after the dose 1 of elasomeran experienced an anaphylaxis reaction. The events were reported to occur after having dinner. 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. Cumulative a total of 2 cases, both serious (2 events) with no reported fatal outcome, of anaphylaxis-related events in patients <18 years of age, were received after the administration of elasomeran/davesomeran. Both patients were females; one was 16 years old, and the second one was 7 years old. Cumulatively as of 17 Dec 2023, 36 cases (36 events), of which (35 serious events) have been reported in adults 18 years of age or older after administration of elasomeran/imelasomeran and elasomeran/davesomeran. Of these 36 cases, 29 were medically confirmed, and none of the cases had a fatal outcome. The event outcomes were resolved/resolving in the majority of cases. These cases were reported mostly in females (26; 72.2%), nine (25.0%) in males, and one case (2.8%) had missing gender information. The median age was 62 years (ranging from 23.0 to 94 years). Most of

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	the cases were reported via regulatory authority (24; 66.7%), with 11 (30.6%) cases reported spontaneously and one (1) case (2.8%) from literature. Cases were reported in Japan (20; 55.6%), the UK (12; 33.3%), the US (3; 8.3%) and Netherlands (1; 2.8%). Andusomeran was newly added to the product profile of marketed Moderna vaccines targeting SARS-CoV-2 during the PBRER#6 review period and review of these cumulative cases as of 17 Dec 2023, period. There were 8 cases (8 events) reported, with 6 cases that were medically confirmed, and there was 1 case that had a fatal outcome. All events were serious. The majority of the cases reported event outcomes as resolved/resolving (6; 75.0%). Most of the cases were reported in females (7; 87.5%) with 1 case (12.5%) in a male. The median age was 59.0 years (ranging from 42.0 to 90.0 years). Most of the cases were reported via regulatory authority (7; 87.5%). The majority of cases were reported from Japan (7 cases; 87.5%) and 1 case (11.1%) was reported from UK. The case reporting a fatal outcome was in a frail patient with multiple co-morbidities (cardiac valve disease, arrhythmia, aortic surgery, chronic kidney disease and dialysis) that may provide a more plausible explanation for the fatal outcome. For the case (WWID#[redacted] that involved a fatal outcome in a frail patient on andusomeran, the patient had multiple co-morbidities (cardiac valve disease, arrhythmia, aortic surgery, chronic kidney disease and dialysis) that provide a more plausible explanation for the fatal outcome. For additional details on fatal case see Appendix 12.10. See Appendix 12.10, for list of reports received for the review period with MAH comments. Review of the data received cumulatively as of 17 Dec 2023, does not suggest any new identifiable pattern or trend in reports of anaphylaxis in children <18 years of age, or adults > 18 years and above, that may differ from already known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. In most of the cases where the relevant information was available, these cases where it was 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 patient's 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 marketed Moderna vaccines targeting SARS-CoV-2 appear to be generally consistent in nature and severity to those reported with elasomeran. For the cases (one in children and another in adults) that involved a fatal outcome, the alternative etiology (emphysema, COPD, and diabetes) and multiple co-morbidities provides a plausible explanation for the fatal outcome.
Risk factors and risk groups	Any participant receiving the vaccine. However, participants with a known history of hypersensitivity to any component of the vaccine may be at risk of hypersensitivity reactions.
Preventability	All marketed Moderna vaccines targeting SARS-CoV-2 are contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any

Important Identified Risk	**Anaphylaxis (Safety concern in PBRER only)**
	component of the vaccine or to a previous dose of the vaccine. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation is recommended following vaccination for 30 minutes for people with a history of an immediate allergic reaction of any severity to another vaccine or injectable therapy, and/or people with a history of anaphylaxis due to any cause. All other persons should be observed for 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of the vaccine.
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 anaphylaxis occurring after vaccination with any marketed Moderna vaccine targeting SARS-CoV-2. Causal association between any of these vaccines and anaphylaxis is considered of at least a reasonable possibility. In Jun 2022, elasomeran RMP v4.0 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 any of the marketed Moderna vaccines targeting SARS-CoV-2. As per request from the PRAC, in their final assessment report for PBRER#4, anaphylaxis is retained as an important identified risk within the PBRER.
Public health impact	Anaphylaxis associated with vaccines typically occurs at a low incidence, which results in a low public health impact. Although the potential clinical consequences of an anaphylactic reaction are serious, this is a risk known to healthcare professionals.

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 [80]. 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.

Important Identified Risk	Myocarditis
	Important to note that cases of myocarditis and pericarditis have been identified in clinical trials of Novavax COVID-19 Vaccine (a protein subunit vaccine) and have also been reported during post-authorization use outside the United States. These findings suggest that an increased risk for these conditions may be present after receiving Novavax COVID-19 vaccine. These observations strongly suggest that the risk is not specific to the mRNA platform but is related to spike protein antigens. One leading 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. In a prospective pilot study [81] of 13 healthcare workers (HCW), 18 years and older, with no known history of SARS-CoV-2 infection was conducted from Dec 2020 to Mar 2021. Out of the 13 HCW, according to the authors, 11 participants exhibit S1 antigen in plasma after the first injection, while nucleocapsid concentrations are insignificant in all participants, confirming that the detected S1 originates from vaccination and not natural infection. The presence of S1 the authors concluded, 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 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 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 is produced.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and post-authorization safety information, including PASS, as well as published literature information.
Characterization of risk	The Phase 3 study mRNA-1273-P301, completed during the current review period of this PBRER, included a total of 24 months follow-up; no long-term safety concerns were identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days). In Part A and Part B of the study, no cases of myocarditis were reported. In Part C, an SAE of myocarditis was reported in a 42-year-old mixed race male BD-Day 1 and adjudicated as probable acute myocarditis. Two other cases of suspected myocarditis were reported but were not adjudicated as myocarditis. The CMQ including a medical review of events or symptoms that might indicate potential myocarditis or pericarditis was conducted and no additional cases were identified. Using post-authorization safety data, cases are classified using both the BC Myocarditis/ Pericarditis case definition [68-70] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment. Evaluation of the data during this reporting period did not provide any new safety information that would differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2 and continued to show a decreasing trend in the number of reported cases. The cumulative review of the GSDB showed no changes in the demographic

Important Identified Risk	Myocarditis
	characteristics of the cases reporting an event of myocarditis and pericarditis after vaccination any marketed Moderna vaccine targeting SARS-CoV-2. Cases of myocarditis/pericarditis continue to occur at a greater frequency in males aged 18 to 39 years, with an acute onset, within 2 to 4 days after dose 2 of the vaccine. A lower reporting of cases has been observed after subsequent doses of elasomeran-containing vaccines, and andusomeran, as shown by the analysis of the observed cases vs. expected cases. Analysis of safety data housed in the MAH's GSDB, as well as review of the literature, continued to show that most of the individuals who experienced an event of myocarditis after vaccination with any marketed Moderna vaccines targeting SARS-CoV-2 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 [82]. The characterization of myocarditis and pericarditis in the Special Warnings and Precautions section of the PI was revised during this PBRER reporting period for use with elasomeran or any of its variant formulations, including andusomeran. The revisions were based on post-marketing surveillance and analysis, prompted by requests from health authorities to re-evaluate the statements in the original PI, as elasomeran has been authorized for use for >2 years. Important revisions to the PI included: • Information regarding cases of myocarditis/pericarditis with a fatal outcome in ModernaTx, Inc GSDB: "Although causality has not been established, fatal events have been rarely reported." • Updating information related to dose-related frequency as well as severity of such cases: "Post-authorisation data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than viral infectious myocarditis or pericarditis." Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of myocarditis to be consistent with the known safety profile of all marketed Moderna vaccines targeting SARS-CoV-2 and the benefits for these vaccines far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.
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) [83]. 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

Important Identified Risk	Myocarditis
	reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. 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 [84]. 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. Cases of myocarditis/pericarditis continue to occur at a greater frequency in males aged 18 to 39 years, with an acute onset, within 2 to 4 days and mainly after dose 2 of the vaccine.
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 viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated [85]. 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 [86]. Current SmPC and Package information Leaflet (PIL) adequately covers the information on this risk awareness to the health-care professionals, caregivers and vaccinees. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including post-authorization safety studies to further characterize them. The benefit-risk evaluation remains positive.
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 marketed Moderna vaccines targeting SARS-CoV-2. Causal association between marketed Moderna COVID-19 vaccines and myocarditis is considered of at least a reasonable possibility. Available data indicate that most cases are typically mild, and individuals tend to recover within a short time following standard treatment and rest. Post authorization data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than infectious myocarditis or pericarditis. Information is not yet available about potential long-term sequelae. Healthcare professionals should be alert to the signs and symptoms of myocarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, Intensive care unit admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended [70].

Important Identified Risk	Myocarditis
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 are 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 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 [87]. 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, 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. Important to note that cases of pericarditis have been identified in clinical trials of Novavax COVID-19 Vaccine (a protein subunit vaccine) and have also been reported during post-authorization use outside the United States. These findings suggest that an increased risk for these conditions may be present after receiving Novavax COVID-19 vaccine. These observations strongly suggest that the risk is not specific to the mRNA platform but is related to spike protein antigens. One leading hypothesis for pericarditis 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. In a prospective pilot study [81] of 13 healthcare workers (HCW), 18 years and older, with no known history of SARS-CoV-2 infection was conducted from Dec 2020 to Mar 2021. Out of the 13 HCW, according to the authors, 11 participants exhibit S1 antigen in plasma after the first injection, while nucleocapsid concentrations are insignificant in all participants, confirming that the detected S1 originates from vaccination and not natural infection. The presence of S1 the authors concluded, 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 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 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 is produced.

Important Identified Risk	**Pericarditis**
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and post-authorization safety information, including PASS, as well as published literature information.
Characterization of risk	The Phase 3 study mRNA-1273-P301, completed during the current review period of this PBRER, included a total of 24 months follow-up; no long-term safety concerns were identified for the two-dose mRNA-1273 100 ug primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days). In Part A, 2 participants in the mRNA-1273 group and 2 participants in the placebo group reported pericarditis. Participants in the mRNA-1273 group include a 59-year-old female with pericarditis on Day 68 after Dose 2 and assessed as related to study vaccine by the investigator and a 65-year-old man who experienced pericarditis (Day 73 after Dose 2) resolving in 1 day and occurring 19 days after the SAE of MI. Pericarditis in Part C: • A 68-year-old male reported a nonserious pericarditis on BD-Day 64. The participant had experienced a viral upper respiratory infection 10 days prior. The AE was assessed as unrelated to the study vaccine by the Investigator and Sponsor and more likely related to the upper respiratory infection. The CEAC adjudicated this as a case of acute pericarditis. • A 37-year-old female with history of valvular heart disease and congenital atrioventricular septal defect developed suspected pericarditis on BD-Day 333, 16 days after onset of a severe COVID-19 infection. The event was considered unrelated to the BD and more likely secondary to the COVID-19 infection by the treating physician. The event was adjudicated as undecided by the CEAC as there was not enough information to confirm the diagnosis. • A 60-year-old female with a history of seasonal allergies and restless leg syndrome developed shortness of breath and was hospitalized on BD-Day 304 days with suspected pericarditis. The participant underwent a pericardial window procedure with chest tube placement for management of pleural effusion. She was discharged on BD-Day 315 and readmitted on BD-Day 325 with recurrent pericarditis. The CEAC adjudicated both events as acute pericarditis. Both events were considered unrelated to the study vaccine by the Investigator and Sponsor. Using post-authorization safety data, cases are classified using both the BC Myocarditis/ Pericarditis case definition [68,69], and the CDC working case definition [70] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment. Evaluation of the data during this reporting period did not provide any new safety information that would differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2 and continued to show a decreasing trend in the number of reported cases. The cumulative review of the GSDB showed no changes in the demographic characteristics of the cases reporting an event of pericarditis after vaccination with

Important Identified Risk	Pericarditis
	any marketed Moderna vaccine targeting SARS-CoV-2. Cases of pericarditis continue to occur at a greater frequency in males aged 18 to 39 years, with an acute onset, within 2 to 4 days after dose 2 of the vaccine. A lower reporting of cases has been observed after subsequent doses of elasomeran-containing vaccines, and andusomeran, as shown by the analysis of the observed cases vs. expected cases. To date, the safety profile of those reports of pericarditis after vaccination does not differ from the known safety profile of all marketed Moderna vaccines targeting SARS-CoV-2. 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 pericarditis after vaccination with marketed Moderna vaccines targeting SARS-CoV-2 were considered recovered by health-care providers after at least 90 days following the onset of pericarditis. In addition, their quality-of-life measures were comparable to those in pre-pandemic and early pandemic populations of a similar age [82]. The characterization of myocarditis and pericarditis in the Special Warnings and Precautions section of the PI was revised during this PBRER reporting period for use with elasomeran or any of its variant formulations, including andusomeran. The revisions were based on postmarketing surveillance and analysis, prompted by requests from health authorities to re-evaluate the statements in the original PI, as elasomeran has been authorized for use for >2 years. Important revisions to the PI included: • Information regarding cases of myocarditis/pericarditis with a fatal outcome in ModernaTx's Inc., GSDB: "Although causality has not been established, fatal events have been rarely reported." • Updating information related to dose-related frequency as well as severity of such cases: "Post-authorization data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than viral infectious myocarditis or pericarditis." Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers cases of pericarditis to be consistent with the known safety profile of all marketed Moderna vaccines targeting SARS-CoV-2, and the benefits for these vaccines far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.
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 [88]. 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.

Important Identified Risk	Pericarditis
	A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years [87]. 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 [89]. Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare. Cases of myocarditis/pericarditis continue to occur at a greater frequency in males aged 18 to 39 years, with an acute onset, within 2 to 4 days and mainly after dose 2 of the vaccine.
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 [90]. 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. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. Centre for disease control 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 [86].
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 any marketed Moderna vaccines targeting SARS-CoV-2. Causal association between marketed Moderna COVID-19 vaccines and myocarditis is considered of at least a reasonable possibility. Available data indicate that most cases are typically mild, and individuals tend to recover within a short time following standard treatment and rest. Post authorization data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than infectious myocarditis or pericarditis. Information is not yet available about potential long-term sequelae. 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	**IgA Nephropathy (Safety concern in PBRER only)**
Potential Mechanism	IgA Nephropathy is included as a safety concern in the PSUR only as an important potential risk as per request from the PRAC Rapporteur. Based on the analysis of all available safety data as of 17 Dec 2023, the MAH considers that there is insufficient information to establish a causal relationship between the administration of a marketed Moderna vaccines targeting SARS-CoV-2 and the development of IgA nephropathy; similarly, a signal of IgA Nephropathy Flare-Up based primarily on one literature article [31] was refuted on 22 Jun 2023. There is no known mechanism of action to account for an association of marketed Moderna vaccines targeting SARS-CoV-2 vaccination and IgA nephropathy. IgA Nephropathy (also known as Berger's disease) has been observed following infection with any of several viral pathogens, including SARS-CoV-2. It has been proposed that shared epitopes in the SARS-CoV-2 spike proteins and human proteins resulting in cross-reactive antibodies. Based on a review of literature published before 10 Jul 2022, Ma and Yu [91] identified 32 articles related to COVID-19 vaccination and IgA nephropathy. These articles reported on a total of 48 patients; however, inferences drawn from analyses of these cases, all selected from the literature, may be susceptible to publication bias. With reference to the "multi-hit hypothesis" of IgA nephropathy and to the mucosal origin of hypogalactosylated IgA1 in IgA nephropathy, the authors proposed three hypotheses for the causation of IgA nephropathy by COVID-19 vaccination: 1) production of excess antiglycan antibodies; 2) an increase in pathogenic IgA production; 3) cytokine storm with speculated sharp increases of inflammatory factors such as IL-6, IL-10 and GM-CSF. In their article, Ma and Yu acknowledged multiple limitations in their report, including: there is only a temporal association between symptom onset and COVID-19 vaccination in IgAN patients, and the authors were unable to infer a causal relationship between vaccine and IgAN; the mechanisms that they proposed for the vaccine-IgAN association combine hypotheses from case reports and the literature and are not proven; and due to the small sample size, there may be errors in their statistical analyses. IgA nephropathy is the most common cause of primary (idiopathic) glomerulonephritis in resource-abundant settings; similarly, it is the most common type of glomerulonephritis in the adverse event reports received by the MAH for marketed Moderna vaccines targeting SARS-CoV-2. With regard to IgA nephropathy and subclinical IgA deposits in kidneys, the scientific literature has found that there is a clinically significant cohort of undiagnosed "latent" IgA nephropathy in the general population as seen in native kidney biopsies. It is also noted that the process of mesangial IgA deposition may be separate from the induction of glomerular injury, and IgA deposition does not necessarily result in subsequent nephritis
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from post authorization safety data. Based on the analysis of all available safety data as of 17 Dec 2023, the MAH considers that there is insufficient information to establish a causal relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the development of IgA nephropathy.
Characterization of risk	The MAH conducted an extensive evaluation of the potential signal of IgA nephropathy as signal trigger based on PRAC PSUR assessment report received on 07 Jul 2022. The signal evaluation included a cumulative review of clinical trial data for any terms from HLT of Glomerulonephritis and nephrotic syndrome from

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)
	mRNA-1273 studies (P301, P203 and P204), and review in the MAH GSDB with a DLP of 17 Jun 2022, using the search terms from MedDRA HLT glomerulonephritis and nephrotic syndrome, along with review of the literature. IgA nephropathy is the most common form of primary glomerulopathy, the extent of which is unknown given the predominantly 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 has 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 were no reports from clinical trials in reporting for either between the placebo and mRNA-1273 arms, for events within the terms including MedDRA HLT of Glomerulonephritis and nephrotic syndrome. Overall, cumulatively as of 17 Dec 2023, 58 IgA nephropathy confirmed reports in 1,043,567,281 doses administered, shows an approximate reporting rate < 1 case per 10 million doses. Of these, 37 cases were de novo, and 21 cases were flares/relapses. The number of vaccinees with IgA nephropathy is unknown, and therefore an observed rate of IgA flares cannot be estimated; in addition, there is no established background rate of IgA flares which also precludes an O/E analysis. Persons with IgA nephropathy are already likely to seek medical attention when they have gross hematuria or other signs and symptoms of renal dysfunction.
Risk factors and risk groups	Risk factors and risk groups associated with IgA Nephropathy that have been identified include: • **Sex**: In North America and Western Europe, IgA nephropathy affects at least twice as many men as it does women. • **Ethnicity:** IgA nephropathy is more common in whites and Asians than it is in blacks. • **Age**: IgA nephropathy most often develops between the late teens and late 30s. • **Family history**: In some cases, IgA nephropathy appears to run in families, indicating that genetic factors contribute to the disease. Some studies suggest that genetic factors, immune response to infections in the upper respiratory tract and nutritional imbalance would promote the development of IgAN [92].
Preventability	No data have indicated the value of active screening or additional education of IgA nephropathy patients' post-vaccination. Time to onset data suggest that patients with flares are mostly diagnosed within 2 days of 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, as suggested by The European Renal Association and the European Vasculitis Society who stated in Mar 2022: "COVID-19 vaccines are safe, exhibiting a very low risk of de novo or relapsing immune-mediated kidney disease. Population-based studies will determine whether this is causal or coincidental. Such cases respond to standard management, including the use of immunosuppression. We recommend that patients with immune-mediated kidney diseases follow national guidance on vaccination."

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)
Impact on the benefit-risk balance of the product	Overall, based on the analysis of all available safety data as of 17 Dec 2023, the MAH considers that there is insufficient information to establish a causal relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the development of IgA nephropathy. No new or emerging safety issues of concern were identified. The MAH will continue to monitor events for IgA Nephropathy using routine pharmacovigilance surveillance. The MAH considers, in agreement with the PRAC's Rapporteur's opinion, that the cumulative evidence is not sufficient to warrant amendment of the PI regarding IgA nephropathy at present, nor to include IgA Nephropathy to the list of safety concerns in the RMP for marketed Moderna vaccines targeting SARS-CoV-2.
Public health impact	Independent of vaccination, IgA Nephropathy is the most common cause of the primary glomerular diseases and can lead to end-stage renal disease (ESRD) [93]. Half of patients with IgA Nephropathy may progress to ESRD within 25 years of the disease. Overall, 58 IgA nephropathy confirmed cumulative reports following vaccination with marketed Moderna vaccines targeting SARS-CoV-2 represent an extremely rare occurrence, with a reporting rate of <1 case per 10 million doses administered.

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 RMP; no CTs were conducted among pregnant women. 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. 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

Missing information	Use in Pregnancy and While Breast-Feeding
	1.05, CI: 0.72 to 1.54). Additional studies have not found an increased risk of congenital anomalies among pregnant people who received COVID-19 vaccines including marketed Moderna vaccines targeting SARS-CoV-2 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, 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 a marketed a Moderna vaccine targeting SARS-CoV-2, studies show no increased risk in short-term adverse effects. In the large case series by [94] 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. During the reporting period, the MAH received a total of 90 pregnancy cases (345 events) among individuals who received or were maternally exposed to a marketed Moderna vaccine targeting SARS-CoV-2. The pattern of the reports remained generally consistent when compared with the cumulative data. While there was a higher proportion of serious cases reported following receipt of elasomeran vaccine, review of serious pregnancy-specific events and non-pregnancy-specific events for all marketed Moderna vaccines targeting SARS-CoV-2 during the review period did not identify any new safety concerns. Overall, cases of pregnancy-specific complications are temporally associated with the administration of marketed Moderna vaccines targeting SARS-CoV-2 with no other causal association to vaccination. Reported cases reflect obstetric events observed after administration of marketed Moderna vaccines targeting SARS-CoV-2. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of adverse event(s), diagnostics, treatment and/or outcome. Where data were available, noted confounding factors for spontaneous abortion/foetal deaths and complications of pregnancy included advanced maternal age, concomitant medications, comorbidities, underlying medical conditions, previous relevant obstetric history, and congenital anomalies which predated the vaccination. Spontaneous abortion continued to be the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster has been identified during the reporting and cumulative periods. During the

Missing information	Use in Pregnancy and While Breast-Feeding
	review period, no cases reported stillbirth. Cases of stillbirth from the cumulative period had clear alternate etiologies, with 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 marketed Moderna vaccines targeting SARS-CoV-2 and stillbirth. The MAH will continue to review and evaluate cases of spontaneous abortion, foetal death and stillbirth, using routine surveillance as well as PASS. Review of the 13 cases reporting congenital anomalies following maternal exposure to elasomeran during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. Review of the 2 serious cases received during the reporting period concerning children under 6 years of age exposed to elasomeran during gestation did not identify unusual patterns or safety concerns. No pregnancy cases among adolescents were received during the reporting period. Overall, based on current available information there are no unusual patterns or pregnancy-related safety concerns identified among these subpopulations. On 11 Sep 2023, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new Omicron variant XBB 1.5. Since that approval, the MAH has received 24 pregnancy cases reporting events after exposure to a booster dose of andusomeran. Review of serious pregnancy-specific events and non-pregnancy-specific events for all pregnancy cases received following andusomeran vaccination did not identify any new safety concerns. Overall, cases of pregnancy-specific complications were temporally associated with the administration of andusomeran vaccine with no other causal association to vaccination. No unusual patterns or pregnancy-specific safety concerns have been identified with use during pregnancy. The current safety profile of andusomeran is consistent with the safety profile of elasomeran-containing vaccines. The MAH will continue to review cases that received andusomeran vaccine using routine surveillance. The most frequently reported PTs following andusomeran vaccination have been predominantly reactogenicity events, which is consistent with the product safety profile for elasomeran-containing vaccines and consistent with events reported for elasomeran-containing vaccines in prior review periods. The only pregnancy-specific events indicating an adverse clinical outcome following andusomeran vaccination have been "Abortion spontaneous" and "Haemorrhage in Pregnancy." No pregnancy cases following andusomeran vaccination have reported a fatal outcome, stillbirth, or congenital anomaly. No pregnancy cases have been reported among children or adolescents under 18 years of age. The MAH will continue to review and evaluate cases of spontaneous abortion, foetal death, and stillbirth, using routine surveillance as well as PASS. Routine surveillance of pregnancy cases among children and adolescents will also continue. In-depth literature reviews performed have not identified any new safety concerns for the use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy. Thus far, published literature has not identified any evidence of an increased risk of foetal or neonatal complications related to maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. Furthermore, published literature has reported that

Missing information	Use in Pregnancy and While Breast-Feeding
	there is transfer of maternal antibodies, reduction in SAR-CoV-2 infection in vaccinated pregnant women and early evidence that infants benefit from passive protection from SARS-CoV-2 infection and severe disease following maternal COVID-19 vaccination. It is acknowledged that SAR-CoV-2 infection may be more serious and cause complications for both the mother and the foetus and published literature supports the favourable benefit-risk profile of maternal immunization with marketed Moderna vaccines targeting SARS-CoV-2. Data continues to provide supporting evidence for the use of marketed Moderna vaccines targeting SARS-CoV-2 before and during pregnancy. After careful review of all new safety data received during the reporting period for the safety topic of Use in Pregnancy, the benefit-risk profile for marketed Moderna vaccines targeting SARS-CoV-2 remains favourable. During the reporting period, ModernaTx, Inc. received a total of 14 lactation cases (75 events) among individuals who received or were exposed to breast milk from mothers who had been vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2; of which 3 cases were among children under 6 years of age with exposure to elasomeran via breast milk and the remaining cases (11) were reported for adult females older than 18 years of age. There were no lactation cases reported among adolescents (12-17 years age group) during this reporting period. There was 1 serious lactation case received (reporting the serious event of Guillain-Barre syndrome) for an adult female, however no serious lactation-specific events were reported. No cases reporting a fatal outcome were received. While vaccination can induce cytokines, which can be passed via breast milk, vaccination while breastfeeding has not been linked to adverse events in infants. In fact, women with fever and illness are encouraged to continue breastfeeding 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. The most frequently reported terms were exposure during breast-feeding or maternal exposure during breast-feeding. 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 were available, many of the events occurred within 2 days after vaccination, and most events were mild/moderate, transient events. 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 marketed Moderna vaccines targeting SARS-CoV-2 or what is expected in the general population. Review of the literature to date has not identified any safety concerns related to marketed Moderna vaccines targeting SARS-CoV-2 during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated breastfeeding 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 favourable benefit-risk profile of COVID vaccination during lactation which continues to provide supporting evidence for HA recommendations for the use of COVID-19 vaccines including marketed Moderna vaccines targeting SARS-CoV-2 during lactation.

Missing information	Use in Pregnancy and While Breast-Feeding
	After careful review of all safety data received during the reporting period for the safety topic of Use while Breastfeeding, the benefit-risk profile for marketed Moderna vaccines targeting SARS-CoV-2 remains favourable.
Anticipated risk/consequence of the missing information	Targeted populations of the indication include women of childbearing potential, thus, the use of marketed Moderna vaccines targeting SARS-CoV-2 in pregnant and breastfeeding women is happening. Pregnancy outcome data is collected via routine pharmacovigilance activities. An observational cohort pregnancy study will inform on the risk of adverse outcome in women who were exposed to marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy. Based on the analysis of all the safety data received cumulative and during the reporting period of this PBRER, the MAH considers that cases related to use of any marketed Moderna vaccines targeting SARS-CoV-2 in pregnant women and/or while breastfeeding did not raise any safety concerns and the information provided does not support evidence of causality between the reported events and the exposure to any marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to monitor events associated with pregnancy and breastfeeding women who receive marketed Moderna vaccines targeting SARS-CoV-2 and their children who are exposed to these vaccines through breast milk using routine surveillance. The benefit-risk evaluation remains positive.

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 studies that will assess long-term safety: mRNA1273-P203, mRNA-1273-P204, mRNA-1273-P205 (Parts A.1, B, C, D, F, and G), and the completed studies mRNA-1273-P101 (DMID 20-0003), and mRNA-1273-P201. Per protocols, safety follow-up period for mRNA-1273-P205 (Parts A.2, H and J) is 6 months and that for mRNA-1273-P301 is 24 months. The Phase 3 study mRNA-1273-P301, completed during the current review period of this PBRER, included a total of 24 months follow-up; no long-term safety concerns were identified for the two-dose mRNA-1273 100 mcg primary series based on the final analysis that includes 17,072.8 person-years and at least 6 months of follow-up for over 3,000 participants (a median of 415 days follow-up after completion of the primary series; range 1 to 892 days). Post-authorization safety studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911 are ongoing, and no findings related to long-term safety have yet been identified.
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, PASS, and routine pharmacovigilance.

Missing information	Use in Immunocompromised subjects (Safety concern in PBRER only)
Evidence source	The MAH has been monitoring the safety profile in the subpopulation Immunocompromised and/or Immunosuppressed individuals through routine pharmacovigilance. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose

Missing information	Use in Immunocompromised subjects (Safety concern in PBRER only)
	(3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, countries are recommending variant updated annual doses. Based on the final assessment report for PBRER#4 (Procedure no.: EMEA/H/C/PSUSA/00010897/202212, received after the DLP of this PBRER) the final recommendation regarding removal of Use in immunocompromised subjects as Missing Information from the EU RMP, was endorsed, and as per request from the PRAC "the topic of use in immunocompromised subjects shall remain in the PSUR list of safety concerns and an evaluation of new information on these topics is required with future PSUR."
Anticipated risk/consequence of the missing information	As of the DLP date of this PBRER#6, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in immunocompromised individuals. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, the general pattern of commonly reported AEs in those considered immunocompromised individuals is comparable to the general population. Evaluation showed that the top five most frequently reported AEs in the immunocompromised population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The pattern of events observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in immunocompromised individuals after vaccination with a marketed Moderna vaccines targeting SARS-CoV-2. Furthermore, these studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. Review of cumulative cases for these subpopulations have not revealed any new or unusual pattern of events or safety concerns. Cases with a fatal outcome in immunocompromised individuals during the reporting period (1.7%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiologies. 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 all marketed Moderna vaccines targeting SARS-CoV-2 remains favourable. The MAH will continue to monitor events for immunocompromised individuals using routine surveillance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904. The elasomeran SmPC section 4.4 was updated to reflect that the use of all marketed Moderna vaccines targeting SARS-CoV-2 in immunocompromised individuals is no longer a missing information, and no risk is associated with the use of all marketed Moderna vaccines targeting SARS-CoV-2 in this population.

Missing information	Use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
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. Based on the final assessment report for PBRER#4 (Procedure no.: EMEA/H/C/PSUSA/00010897/202212, received after the DLP of this PBRER) the final recommendation regarding removal of use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as Missing Information from the EU RMP, was endorsed. As per request from the PRAC the topic of use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) shall remain in the PSUR list of safety concerns.
Anticipated risk/consequence of the missing information	As of the DLP of this PBRER#6, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in frail individuals. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, 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. Evaluation showed that the most frequently reported AEs in the frail population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The pattern of events observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals after vaccination with elasomeran. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events or safety concern. Cases with fatal outcome in the frail subpopulation in the reporting period (3.2%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiologies. Evaluation of the data during this reporting period did not provide any new safety information that would suggest a possible association between the evaluated events and administration of all marketed Moderna vaccines targeting SARS-CoV-2 in frail subpopulation. Information presented in those reports does not differ from the known safety profile of all marketed Moderna vaccines targeting SARS-CoV-2. There was no published clinical literature that described new and potentially important safety information on the safety profile of all marketed Moderna vaccines targeting SARS-CoV-2 in frail subpopulation.

Missing information	Use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
	Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Frail, reported in temporal association with the administration of all marketed Moderna vaccines targeting SARS-CoV-2 did not raise any new safety concern. The MAH will continue to monitor events for Frail using routine surveillance. The benefit-risk evaluation remains positive.

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders (Safety concern in PBRER only)
Evidence source	Because there was limited data from CTs on the use of Moderna vaccines targeting SARS-CoV-2 in individuals with AI/ID, the MAH has been closely monitoring the safety profile of Moderna vaccines targeting SARS-CoV-2 in this population through routine Pharmacovigilance. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in AI/ID 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 booster dose in MedHx AI/ID patients to achieve an adequate, more robust immune response to vaccinations. Furthermore, countries are recommending a variant updated annual booster dose. On 11 Sep 2023, US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new omicron variant XBB 1.5. Thus far, there have been no specific safety concerns for individuals with MedHx of AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with Moderna vaccines targeting SARS-CoV-2 and have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general population receiving Moderna vaccines targeting SARS-CoV-2. The safety, reactogenicity, and immunogenicity of elasomeran were evaluated in a two-part Phase 3b open-label study in adult solid organ transplant (SOT) recipients, including kidney and liver transplants (mRNA-1273-P304). A 100 ug (0.5 mL) dose was administered, which was the dose authorized at the time of study conduct. 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.

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders (Safety concern in PBRER only)
	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. Safety evaluation showed that the 3-dose primary series and BD of mRNA-1273 were well tolerated with an acceptable safety profile in this post-transplant population.
Anticipated risk/consequence of the missing information	Based on the analysis of all the safety data available as of 17 Dec 2023, the MAH considers the cases of MedHx AI/ID to be consistent with the known safety profile of the marketed Moderna vaccines targeting SARS-CoV-2, and the benefits far outweigh any possible vaccine-associated risks. No new safety concerns were identified in the literature review concerning Moderna vaccines targeting SARS-CoV-2. The safety and benefit/risk profile of COVID vaccination in individuals with AI/ID remains acceptable. In AI/ID patients with disease flares, there is a natural waxing and waning course, and there are no reliable referenced data on the background rates of respective flares especially given the number of various AI/ID diseases and how to accurately measure a flare. The identified flare cases did not demonstrate a safety concern cumulatively or for this reporting period. 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 the 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 Moderna vaccines targeting SARS-CoV-2. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving Moderna vaccines targeting SARS-CoV-2. For the fatal AI/ID cases, common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, and hyperlipidaemia are similar to those reported in the general population fatal reports. The MAH will continue to monitor events for AI/ID in vaccinated subjects using routine surveillance. The benefit-risk evaluation remains positive.

16.5 Effectiveness of Risk Minimisation (if applicable)

There are no additional risk minimization measures in place for Marketed Moderna vaccines targeting SARS-CoV-2.

17. BENEFIT EVALUATION

17.1 Important Baseline Efficacy and Effectiveness Information

Epidemiology and Natural History of COVID-19 disease

Coronaviruses (CoVs) 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 [95].

An outbreak of the CoV disease (COVID-19) caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) began in Wuhan, Hubei Province, China in Dec 2019, and has spread globally [96] [97]. The WHO declared COVID-19 a pandemic on 11 Mar 2020; however, by that time, there was already widespread community transmission in many locations. As of 17 Dec 2023, over 772 million confirmed cases and nearly seven million deaths have been reported globally [98]. Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [96] [97].

Globally, the number of new cases increased by 52% during the 28-day period of 20 Nov 2023 to 17 Dec 2023 as compared to the previous 28-day period, with over 850 000 new cases reported. The number of new deaths decreased by 8% as compared to the previous 28-day period, with over 3000 new fatalities reported. At the regional level, the number of newly reported 28-day cases increased across four of the six WHO regions: the European Region (+54%), the Western Pacific Region (+67%), the African Region (+77%), and the South-East Asia Region (+388%); while cases decreased in two WHO regions: the Eastern Mediterranean Region (-51%), and the Region of the Americas (-23%). The number of newly reported 28-day deaths decreased across four regions: the Eastern Mediterranean Region (-65%), the African Region (-50%), the Region of the Americas (-48%), and the Western Pacific Region (-32%); while deaths increased in two WHO

regions: the European Region (+14%), and the South-East Asia Region (+317%). As of 17 Dec 2023, over 772 million confirmed cases and nearly seven million deaths have been reported globally [99].

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 [100]. Transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic individuals has also been documented and may account for an estimated 59% of transmission [101]. 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, SOT, and stroke or cerebrovascular disease [102]. Smokers and individuals with substance use disorders are also at increased risk for severe COVID-19 [102].

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. 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 [103,104]. Myocardial injury has reported among patients with severe COVID-19 [105]. Additionally, some patients develop serious medical complications such as myocardial inflammation, ventricular dysfunction, pulmonary function abnormalities, and acute kidney injury [106,107] [108-110]. 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 VOC

and variants of interest (VOI) [111]. 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.

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.

As of 03 March 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 VOC, as these parental lineages are no longer circulating. ECDC will continue to categorize and report on specific SARS-CoV-2 sub-lineages in circulation that are relevant to the epidemiological situation. There are currently no SARS-CoV-2 variants meeting the VOC criteria [112]. Among the nine countries (Austria, Denmark, France, Germany, Italy, Latvia, Luxembourg, the Netherlands, and Sweden) with an adequate volume of sequencing or genotyping for weeks 1 to 2 (2 to 15 Jan 2023), the estimated distribution of VOC or VOI ranged from 48.4-76.0% in seven countries for BQ.1, 11.3-76.9% in nine countries for BA.5, 6.6-27.8% in eight countries for BA.2.75, 1.4-5.6% in six countries for XBB.1.5, 0.9-6.5% in seven countries for XBB, 0.3-15.3% in eight countries for BA.2, and 0.1-0.9% in eight countries for BA.4 [113].

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 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.

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 03 Mar 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 VOC, as these parental lineages are no longer circulating. ECDC will continue to categorize and report on specific SARS-CoV-2 sub-lineages in circulation that are relevant to the epidemiological situation. These additional variants of SARS-CoV-2 have been de-escalated based on at least one the following criteria: (1) the variant is no longer circulating, (2) the variant has been circulating for a long time without any impact on the overall epidemiological situation, (3) scientific evidence demonstrates that the variant is not associated with any concerning properties.

As of 17 Dec 2023, the circulating VOI were recombinant Omicron subvariants XBB.1.5, XBB.1.16, EG.5, BA.2.86, and JN.1. Previously circulating VOCs and current Omicron subvariants under monitoring are [111] 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, Sep 2020	18 Dec 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	G/478K.V1	21A	+S:417N	India, Oct 2020	VOI: 04 Apr 2021

WHO label	Pango lineages*	GISAID clade	Next strain clade	Additional amino acid changes monitored*	Earliest documented samples	Date of designation
	AY.2 AY.3 AY.3.1					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 sub lineage	BA.5 + S:R346T	24 Jan 2022
BQ.1$	GRA	22E	BA.5 sub lineage	BQ.1 and BQ.1.1: BA.5 + S:R346T, S:K444T, S:N460K	07 Feb 2022
BA.2.75§	GRA	22D	BA.2 sub lineage	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 sub lineages, i.e. BJ1 and BM.1.1.1, with a breakpoint in S1	BA.2+ S:V83A, S:Y144-, S:H146Q, S:Q183E, S:V213E, 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)	13 Aug 2022

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

As of 17 Dec 2023, over 773 million confirmed cases and more than seven million deaths have been reported globally [99]. 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 [114]. 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.

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.

Marketed Moderna COVID-19 Vaccines are 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 22 ongoing CTs including 12 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 [115]. 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 HR 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 [115].

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 HR).

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 HR 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 (≥ 18 to < 65 years, ≥ 65 years, ≥ 65 years to < 75 years, and ≥ 75 years); age and health risk (≥ 18 to < 65 years and not at risk, ≥ 18 to < 65 years and at risk, and ≥ 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, CT 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 pseudo virus 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, CT 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). 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)*
	Case (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.

Clinical efficacy in children 6 months through 5 years of age

An ongoing Phase 2/3 study was 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 cutoff 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.

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.

Immunogenicity in children 6 months through 5 years of age

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 ug) to those of young adults (n = 295; 100 ug) 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 $\geq$ 0.67; point estimate $\geq$ 0.8). The GMFR from baseline to Day 57 for these children was 183.3 (95% CI: 164.03, 204.91). The difference in seroresponse rates (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 mcg) to those of young adults (n = 295; 100 mcg) 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 $\geq$ 0.67; point estimate $\geq$ 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 prespecified success criteria for the primary immunogenicity objective were met for both age groups, allowing efficacy of 25 ug 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 LLOQ are replaced by 0.5 x LLOQ.
Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
A The log-transformed antibody levels are analysed 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]**
		1 410.0	1 390.8	1.0	Y

SARS-CoV-2 neutralization assayc	28 days after Dose 2	(1 273.8, 1 560.8)	(1 262.5, 1 532.1)	(0.9, 1.2)	
		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 LLOQ are replaced by 0.5 x LLOQ.
Values greater than the 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 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.

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 BD (0.25 mL) at least 6 months after receiving the second dose in the primary series. A single BD (0.25 mL) was shown to be immunogenic at Day 29 post-BD 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 BD (0.5 mL, 25 µg/25 µg)

The safety, reactogenicity, and immunogenicity of an elasomeran/imelasomeran BD 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 BD, and 377 participants received the elasomeran (original) 50 µg BD.

Study P205 Part G evaluated the safety, reactogenicity and immunogenicity of elasomeran/imelasomeran when administered as a second BD to adults who previously received

2 doses of elasomeran (original) (100 μg) as a primary series and a BD 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 BD 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 6,422.3 (5990.1, 6885.7) and 5,286.6 (4,887.1, 5,718.9) 28 days after the elasomeran/imelasomeran and elasomeran (original) BDs, 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 (2,264.5, 2,715.8) and 1,421.2 (1,283.0, 1,574.4) 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 BD administration as compared to a 50 μg BD of elasomeran [116]. 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 [116] 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 BD [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 BD 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) BD in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous BD) is inferred from immunogenicity data supporting effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) BD administered following completion of a Moderna COVID-19 Vaccine primary series and from immunogenicity data from an independent Phase 1/2 open-label CT (NCT04889209) conducted in the United States that evaluated a heterologous BD (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 BD 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 BD 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 (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) 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.

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 ug) 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 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 17-8 and Table 17-9).

Table 17-8 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 LLOQ are replaced by 0.5 x LLOQ. Values greater than the 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 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 17-9 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		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

		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]**
neutralization assay[c]	28 days after Dose 2	**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 LLOQ are replaced by 0.5 x LLOQ. Values greater than the 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 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

From the study mRNA-1273-P204, 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.

Three-month antibody persistence of elasomeran/imelasomeran booster vaccine against COVID-19.

Participants in Study P205 Part G were sequentially enrolled to receive 50 ug of elasomeran (n = 376) or elasomeran/imelasomeran (n = 437) as second BD. In participants with no pre-booster incidence of SARS-CoV-2, elasomeran/imelasomeran elicited Omicron BA.1-neutralizing antibody titres (observed GMT) that were significantly higher (964.4 [834.4, 1114.7]) than those of elasomeran (624.2 [533.1, 730.9]) and similar between boosters against ancestral SARS-CoV-2 at three months.

Immunogenicity in participants 18 years of age and older–after elasomeran/davesomeran BD (0.5 mL, 25 ug/25 ug)

The safety, reactogenicity, and immunogenicity of an elasomeran/davesomeran BD 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, 511 participants received the elasomeran/davesomeran 50 ug BD, and 376 participants received the elasomeran 50 ug BD.

Study P205 Part H evaluated the safety, reactogenicity and immunogenicity of elasomeran/davesomeran when administered as a second BD to adults who previously received 2 doses of elasomeran (100 ug) as a primary series and a first BD of elasomeran (50 ug). In P205 Part F, study participants received elasomeran (50 ug) as a second BD and the Part F group serves as a within-study, non-contemporaneous comparator group to the elasomeran/davesomeran 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 GMT and corresponding 95% CI was 87.9 (72.2, 107.1) and 2324.6 (1921.2, 2812.7) 28 days after the elasomeran/davesomeran and elasomeran BDs, respectively. The Day 29 GMR for elasomeran Original/Omicron BA.4-5 ug BD versus the elasomeran 50 ug booster dose was 6.29 (5.27, 7.51), meeting the pre-specified criterion for superiority (lower bound of CI >1).

The estimated neutralizing antibody GMTs (95% CI) against Omicron BA.4/BA.5 adjusted for pre-booster titre and age group were 2747.3 (2399.2, 3145.9) and 436.7 (389.1, 490.0) 28 days after elasomeran/davesomeran and elasomeran booster doses, respectively, and the GMR (95% CI) was 6.29 (5.27, 7.51), meeting the pre-specified criterion for non-inferiority (lower bound of CI >0.667).

Primary Series Effectiveness (Study mRNA-1273-P901)

Study P901 is an ongoing observational cohort study conducted within Kaiser Permanente Southern California (a large, integrated health care system serving a diverse population of over 4.5 million members) in the US to estimate the real-world VE of mRNA-1273 in preventing SARS-CoV-2 infection (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality). This study was initiated on 28 Jan 2021 and has resulted in several analyses assessing the real-world effectiveness of mRNA-1273 over time during the SARS-CoV-2 pandemic [117] [7,8].

A test-negative case-control analysis to evaluate mRNA-1273 VE against SARS-CoV-2 variants and assess its effectiveness against the delta variant by time since vaccination was conducted within Study P901 [117]. Individuals with a SARS-CoV-2 positive test sent for whole genome sequencing or a negative test from 1 Mar 2021 to 27 Jul 2021 were included. Test-positive cases were matched 1:5 to test-negative controls. The analysis included 8,153 test-positive cases and their matched controls. The two-dose VE was 86.7% (95% CI: 84.3%, 88.7%) against infection with the delta variant, 98.4% (95% CI: 96.9%, 99.1%) against alpha, 90.4% (95% CI: 73.9%, 96.5%) against mu, 96%-98% against other identified variants, and 79.9% (95% CI: 76.9%, 82.5%) against unidentified variants (that is, specimens that failed sequencing). The VE against hospital admission with the delta variant was 97.5% (95% CI: 92.7%, 99.2%). The VE against infection with the delta variant declined from 94.1% (95% CI: 90.5%, 96.3%) 14-60 days after vaccination to 80.0% (95% CI: 70.2%, 86.6%) 151-180 days after vaccination. Waning was less pronounced for non-delta variants. The VE against delta infection was lower among people aged ≥ 65 years (75.2% [95% CI: 59.6%, 84.8%]) than those aged 18-64 years (87.9% [95% CI: 85.5%, 89.9%]).

Another test-negative case-control analysis to evaluate mRNA-1273 VE against infection and hospitalization with Omicron or Delta was conducted within Study P901 [8]. Individuals with a SARS-CoV-2 positive test sent for whole genome sequencing or a negative test from 06 Dec 2021 to 31 Dec 2021 were included. Test-positive cases were matched 1:2 to test-negative controls. The analysis included 26,683 test-positive cases with variants determined by S gene target failure status (16% Delta and 84% Omicron). The two-dose VE against Omicron infection at 14–90 days was 44.0% (95% CI: 35.1%, 51.6%) but declined quickly.

An analysis conducted within Study P901 estimated the VE of receipt of 2 doses (primary series) of 100 µg mRNA-1273 versus unvaccinated individuals [117]. Individuals receiving 2 doses of mRNA-1273 ≥ 24 days apart (18 Dec 2020 to 31 Mar 2021) were 1:1 matched with randomly selected unvaccinated individuals, with follow-up through 30 Jun 2021. This analysis included 352,878 recipients of 2 doses of mRNA-1273 matched to 352,878 unvaccinated individuals. The VE against COVID-19 diagnosis was 87.4% (99.3% CI: 84.8%, 89.6%). The VE against COVID-19 hospitalization and hospital death was 95.8% (99.3% CI: 90.7%, 98.1%) and 97.9% (99.3% CI: 66.9%, 99.9%), respectively. The VE was higher against symptomatic (88.3% [98.3% CI: 86.1%, 90.2%]) than asymptomatic COVID-19 (72.7% [98.3% CI: 53.4%, 84.0%]), but was generally similar across age, sex, and racial/ethnic subgroups. The VE among individuals with history of COVID-19 ranged from 8.2% to 33.6%. The most prevalent variants were Delta

(47.1%), Alpha (21.4%), Gamma (11.4%), Epsilon (4.3%), and Iota (4.3%) among vaccinated individuals and Alpha (41.2%), Epsilon (18.2%), Delta (11.0%) and Gamma (8.6%) among unvaccinated individuals.

Booster Effectiveness (Study P901)

Tseng et al observed that the three-dose VE was 93.7% (95% CI: 92.2%, 94.9%) and 86.0% (95% CI: 78.1%, 91.1%) against Delta infection and 71.6% (95% CI: 69.7%, 73.4%) and 47.4% (95% CI: 40.5%, 53.5%) against Omicron infection at 14–60 days and >60 days, respectively [8]. The three-dose VE was 29.4% (95% CI: 0.3%, 50.0%) against Omicron infection in immunocompromised individuals. The three-dose VE against hospitalization with Delta or Omicron was >99% across the entire study population. Receipt of three doses of mRNA-1273 demonstrated high, durable VE against Delta infection but lower effectiveness against Omicron infection, particularly among immunocompromised people. However, VE of three doses of mRNA-1273 remained high against hospitalization with Delta and Omicron variants.

An analysis conducted within Study P901 estimated the rVE of receipt of 3 doses (2-dose primary series [100 µg mRNA-1273] plus booster [50 µg mRNA-1273]) versus 2 doses (primary series only) of mRNA-1273 among immunocompetent individuals [7]. Immunocompetent individuals who received a BD of mRNA-1273 from 20 Oct 2021 through 31 Dec 2021 were matched 1:1 to randomly selected 2-dose mRNA-1273 recipients and followed up through 31 Jan 2022. This analysis included 431,328 mRNA-1273 booster dose vaccinated individuals matched to 431,328 2-dose mRNA-1273 vaccinated individuals. In this analysis, IR of symptomatic SARS-CoV-2 infection, COVID-19 hospitalization and COVID-19 related hospital death rates were lower in individuals who had received a BD of mRNA-1273 as compared with individuals who had received only the primary series. The rVE of a 50 µg mRNA-1273 BD was 61.3% (95% CI: 60.5%, 62.2%) for SARS-CoV-2 infection, 89.0% (95% CI: 86.2%, 91.2%) for COVID-19 hospitalization, and 96.0% (95% CI: 68.0%, 99.5%) for COVID-19 hospital death. Relative VE estimates against SARS-CoV-2 infection did not differ substantially by age, sex, race/ethnicity, pregnancy status, chronic disease, and infection history sub-groups (ranging from 55.6% to 66.7%). Relative VE against SARS-CoV-2 infection decreased from 67.1% (0 to <1 month of follow-up) to 30.5% (2 to <3 months). For COVID-19 hospitalization, rVE decreased from 91.2% (0 to <1 month) to 78.7% (2 to <3 months). Results from the analysis for rVE of a BD of mRNA-1273 were consistent with those from Study P301 and demonstrated that SARS-CoV-2 infection rates and COVID-19 rates were lower in boosted versus non-boosted individuals who had received only the 2-dose mRNA-1273 primary series.

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

Vaccine efficacy evaluating real-world effectiveness of elasomeran and elasomeran bivalent variant-containing formulations

This study (mRNA-1273-P901) evaluated the effectiveness of elasomeran (original) administered as a two- or three-dose primary series among immunocompromised individuals against symptomatic SARS-CoV-2 infection, COVID-19-associated hospitalization, and COVID-19 associated death. Incidence of COVID-19-associated outcomes among immunocompromised individuals who received three doses of elasomeran (original) was compared to individuals who received two doses of elasomeran (original) to estimate relative VE (rVE) and absolute VE, respectively. "Immunocompromised" was defined as having a diagnosis of HIV/acquired immunodeficiency syndrome, leukemia, lymphoma, congenital and other rare conditions, organ transplant procedure, or use of immunosuppressant medication prior to receipt of the third dose. There were 21,942 immunocompromised individuals who received a third dose of elasomeran (original) and were matched on age, sex, race/ethnicity, and date of receipt of the third dose to an equal number of individuals who received two doses of elasomeran (original) only.

The adjusted rVE of three doses versus two doses of elasomeran was 55.0% (95% CI: 50.8, 58.9), 83.0% (95% CI: 75.4, 88.3), and 87.1% (95% CI: 30.6, 97.6) against SARS-CoV-2 infection, COVID-19-associated hospitalization, and COVID-19-associated death, respectively.

Following the approval of elasomeran/davesomeran, a follow-up analysis in this study also evaluated the VE of elasomeran/davesomeran administered as a booster dose among individuals (including immunocompromised individuals) who previously received two or more doses of any monovalent mRNA COVID-19 vaccine only in preventing COVID-19-associated hospitalization. Incidence of COVID-19-associated hospitalization among booster-vaccinated individuals was compared to individuals who received a monovalent mRNA COVID-19 vaccine only or no COVID-19 vaccination (i.e., unvaccinated) to estimate rVE and absolute VE, respectively. "Immunocompromised" was defined as having a diagnosis of HIV/acquired immunodeficiency syndrome, leukemia, lymphoma,

congenital and other rare conditions, organ transplant procedure, or use of immunosuppressant medication prior to the date of booster vaccination (or cohort selection for monovalent only and unvaccinated cohorts).

There were 12,338 immunocompromised individuals who received two or more doses of any monovalent mRNA COVID-19 vaccine followed by a booster dose of elasomeran/davesomeran; 19,991 immunocompromised individuals received two or more doses of monovalent mRNA COVID-19 vaccine but no booster dose; and 4,788 immunocompromised individuals did not receive any COVID-19 vaccine (unvaccinated). The rVE (compared to individuals who received a monovalent mRNA COVID-19 vaccine only or were unvaccinated) against COVID-19 associated hospitalization was 64.7% (95% CI: 44.0, 77.7) in immunocompromised individuals compared to 71.3% (95% CI: 64.5, 76.7) in immunocompetent individuals. The absolute VE was 71.8% (95% CI: 48.8, 84.5) in immunocompromised individuals and 84.1% (95% CI: 80.1, 87.4) in immunocompetent individuals.

Immunogenicity in participants 18 years of age and older–after elasomeran/davesomeran booster dose (0.5 mL, 25 ug/25 ug)

The safety, reactogenicity, and immunogenicity of elasomeran/davesomeran booster dose is evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 511 participants received the elasomeran/davesomeran 50 ug booster dose, and 376 participants received the elasomeran 50 ug booster dose.

Study P205 Part H evaluated the safety, reactogenicity and immunogenicity of elasomeran/davesomeran when administered as a second booster dose to adults who previously received 2 doses of elasomeran (original) (100 ug) as a primary series and a first booster dose of elasomeran (original) (50 ug). In P205 Part F, study participants received elasomeran (50 ug) as a second booster dose and the Part F group serves as a within-study, non-contemporaneous comparator group to the elasomeran/davesomeran.

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 GMT and corresponding 95% CI was 87.9 (72.2, 107.1) and 2324.6 (1921.2, 2812.7) 28 days after the elasomeran/davesomeran and elasomeran booster doses, respectively.

The Day 29 GMR for elasomeran/davesomeran 50 ug booster dose versus the elasomeran (original) 50 ug booster dose was 6.29 (5.27, 7.51), meeting the pre-specified criterion for superiority (lower bound of CI >1).

The estimated neutralizing antibody GMTs (95% CI) against Omicron BA.4/BA.5 adjusted for pre-booster titre and age group were 2747.3 (2399.2, 3145.9) and 436.7 (389.1, 490.0) 28 days

after elasomeran/davesomeran and elasomeran (original) booster doses, respectively, and the GMR (95% CI) was 6.29 (5.27, 7.51), meeting the pre-specified criterion for non-inferiority (lower bound of CI >0.667).

Immunogenicity of a single dose of elasomeran/davesomeran in participants 12 years through 17 years of age with evidence of prior SARS-CoV-2 infection

In an open-label phase of this study conducted in the United States and the Dominican Republic, participants 12 years through 17 years of age who were vaccine-naïve received a single dose (50 ug) of elasomeran/davesomeran. Of the 246 participants in the immunogenicity subset, 99.6% were baseline SARS-CoV-2 positive. The primary immunogenicity analysis population included 245 participants who were baseline SARS-CoV-2 positive in this study and a subset of 296 participants 18 through 25 years from the Adult study who were baseline SARS-CoV-2 negative and received two doses (100 ug) of elasomeran 1 month apart. Among participants 12 years through 17 years of age assessed for immunogenicity, 53.5% were male, 46.5% were female, 94.3% were Hispanic or Latino, 14.3% were White, 33.9% were African American or Black, 51.0% were other races, and 0.8% were multiracial.

A comparison of neutralizing antibody titres against a pseudovirus expressing Omicron BA.4-5 and the original SARS-CoV-2 spike protein (D614G) was conducted. The primary immunogenicity analyses of the GMC ratio following the single dose in this study compared to after the primary series in the adult study met the pre-defined immunobridging success criteria.

Secondary endpoints included the difference in seroresponse rates, where seroresponse for a participant was defined as achieving a ≥4-fold rise of neutralizing antibody concentration from baseline (before the first dose of the primary series in this study and the dose in the adult study).

Immunogenicity in adults – after andusomeran (0.5 mL, 50 ug) versus an investigational bivalent andusomeran/ elasomeran/davesomeran dose (0.5 mL, 25 ug/25 ug)

The safety, reactogenicity and immunogenicity of andusomeran (50 ug mRNA of the Omicron XBB.1.5 spike protein) and of a bivalent vaccine that contains equal mRNA amounts of Omicron XBB.1.5 and Omicron BA.4/BA.5 spike proteins (25 ug andusomeran/25 ug elasomeran/davesomeran) are evaluated in a Phase 2/3 open-label study in adults. In his study, 50 participants received andusomeran and 51 participants received the investigational bivalent andusomeran/ elasomeran/davesomeran vaccine (mRNA-1273- P205, Part J). The two groups were randomized 1:1 in an open-label fashion.

The vaccines were administered as a fifth dose to adults who previously received a two-dose primary series of any mRNA COVID-19 vaccine, a booster dose of any mRNA COVID-19 vaccine, and a booster dose of any mRNA bivalent elasomeran/davesomeran vaccine.

Andusomeran and bivalent andusomeran/(elasomeran/davesomeran) elicited potent neutralizing responses at Day 15 against XBB.1.5, XBB.1.16, BA.4/BA.5, BQ.1.1 and D614G. In the per-protocol immunogenicity set that includes all participants, with and without prior SARS-CoV-2 infection (N=49 and N=50 for andusomeran and bivalent andusomeran/(elasomeran/davesomeran) groups, respectively), the Day 15 GMFR (95% CI) for andusomeran and bivalent andusomeran/(elasomeran/davesomeran) was 16.7 (12.8, 21.7) and 11.6 (8.7, 15.4), respectively, against andusomeran and 6.3 (4.8, 8.2) and 5.3 (3.9, 7.1) against elasomeran/davesomeran.

For variants not contained in the vaccines, the Day 15 GMFR (95% CI) for andusomeran and bivalent andusomeran/(elasomeran/davesomeran) was 11.4 (8.5, 15.4) and 9.3 (7.0, 12.3) against andusomeran 16; 5.8 (4.7, 7.3) and 6.1 (4.6, 7.9) against BQ.1.1 and 2.8 (2.2, 3.5) and 2.3 (1.9, 2.8) against D614G.

Effectiveness of elasomeran versus BNT162b2 in immunocompromised individuals

Systematic literature review and pairwise meta-analysis of 17 observational studies compared the effectiveness of elasomeran to BNT162b2 in immunocompromised adults. Evidence in the analysis was evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework.

Evidence from RCTs is limited in immunocompromised individuals; however, many observational studies have reported clinical effectiveness in individuals with SOT, solid and haematological cancers, haemodialysis, poorly controlled HIV infection, and autoimmune conditions requiring immunosuppressive therapy.

A systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 framework (PRISMA) was performed on 19 Dec 2022 and reported 17 observational studies comparing elasomeran (100 ug dose for primary series and 50 ug dose for booster) with BNT162b2 (30 ug/dose) in immunocompromised adults ≥18 years of age. Overall, 178,298 and 170,760 individuals received elasomeran (original) (50 or 100 ug dose) and BNT162b2 (30 ug/dose), respectively.

Compared with BNT162b2, elasomeran (original) was associated with significantly reduced risk of SARS-CoV-2 infection, severe SARS-CoV-2 infection, COVID-19–associated hospitalization,

and COVID-19–associated mortality in immunocompromised individuals ≥18 years of age results were consistent for laboratory-confirmed SARS-CoV-2 infection but did not reach statistical significance.

Concomitant administration of elasomeran and Fluzone high dose quadrivalent influenza vaccine

In a descriptive open-label, randomised clinical study (Study QHD00028, NCT04969276), adults aged 65 years and older received an investigational booster dose of elasomeran (100 ug) at least 5 months after the second dose of the primary series with Fluzone high-dose quadrivalent influenza vaccine alone (n=92) or concomitantly (n=99). A third group received only the investigational booster dose of elasomeran (100 ug) (n=105). There was no evidence of interference in the immune response to high dose quadrivalent influenza vaccine or to elasomeran when administered concomitantly.

Concomitant administration of elasomeran and Fluarix quadrivalent influenza vaccine.

In an open-label, randomised clinical trial (NCT05047770, Study 217670), 988 adults aged 18 years and older received doses of elasomeran (original) (50 ug) and standard quadrivalent flu vaccine either concomitantly (n=498) or sequentially (n=497), administered two weeks apart. The antibody responses to each vaccine were similar, whether administered concomitantly or sequentially. Furthermore, immunological non-inferiority between concomitant and sequential administration was demonstrated for the elasomeran (original) (50 ug) in terms of anti-S protein antibody GMC and for all four strains included in Fluarix quadrivalent in terms of hemagglutination inhibition (HI) antibody GMTs.

Concomitant administration of elasomeran and Shingrix herpes zoster (shingles) vaccine

In an open-label, randomised clinical trial (NCT0504770, Study 217670), 515 adults aged ≥50 years received elasomeran (50 ug) and two doses of Shingrix (56 days apart). Elasomeran was either co-administered with the first dose of Shingrix (n=257) or sequentially administered two weeks apart (n=258). The antibody response to each vaccine was similar, whether co-administered or provided sequentially. Furthermore, immunological non-inferiority between sequential and co-administration was demonstrated for both the anti-S protein antibody GMC for elasomeran (50 ug) and the anti-glycoprotein E antibody GMC for Shingrix.

17.3 Characterization of Benefits

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 1.7 billion doses of elasomeran distributed, and more than 774 million doses estimated to have been administered globally as of 17 Dec 2023. Further, safety for bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran), as well with the 2023-2024 monovalent variant vaccine (andusomeran), has been demonstrated in adults including young adults (18 to < 25 years) in clinical studies and post authorization settings, where approximately more than 251 million doses have been administered.

The efficacy of elasomeran to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273-P301. Data included in the final CSR for P301 showed that elasomeran 100 µg was 98.2% effective in preventing severe COVID-19.

Subgroup analysis 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.

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).

Elasomeran 100 µg also demonstrated protection against asymptomatic SARS-CoV-2 infection. The VE to prevent asymptomatic SARS-CoV-2 infection was 63.0% and VE to prevent COVID-19 or SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0%.

In P301 Part C, BD recipients who received the primary series in Part A demonstrate a) the persistence of the immune response following the 2-dose 100 µg mRNA-1273 primary series, and b) the robust immunogenicity of the mRNA-1273 50 µg BD following the primary series, including in those who had evidence of prior infection preboost. Following Dose 2 of the primary series, nAb levels were increased by 119-fold at Day 57 (28 days after Dose 2). A reduction in nAbs was apparent at Day 209 and at prebooster BD-Day 1.

Data from both P201 Part A and P301 Part A studies support persistence of immunogenicity and effectiveness through at least 6 months.

Across the full paediatric 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 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 [116] 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 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.

Studies conducted for a 50 µg mRNA-1273 booster (including the original mRNA-1273 booster and the variant-containing bivalent vaccines mRNA-1273.222 and mRNA-1273.214) elicits enhanced immune responses against SARS-CoV-2 compared to those elicited by the primary series, and consistent responses were observed across adolescents, younger adults, and older adults. Additionally variant-containing bivalent boosters elicit superior immune responses to the variant in the vaccine compared with the original mRNA-1273 booster, and enhanced responses are observed in both younger and older adults, and regardless of prior SARS-CoV-2 status, and variant-containing bivalent boosters induce immune responses that are durable, and cross neutralize divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted individuals, and rates of COVID-19, hospitalized COVID-19 and hospitalized COVID-19 death are lower in boosted versus non-boosted individuals.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR AUTHORIZED INDICATIONS

18.1 Benefit-Risk Context – Medical Need and Important Alternatives

As a result of the outbreak of COVID-19 caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) that began in Wuhan, Hubei Province, China in Dec 2019, and that soon started to spread globally, the WHO declared COVID-19 a pandemic on 11 Mar 2020. Widespread

community transmission of SARS-CoV-2 was soon reported in the Americas, Europe, Africa, and Southeast Asia. Soon the world mobilized and sustained a historic response to the COVID-19 pandemic as it became a health and an economic crisis that disrupted every single segment of the population shattering lives, business, and our day-to-day life. As of 17 Dec 2023, over 773 million confirmed cases and more than 7 million deaths have been attributed to the COVID-19 pandemic globally [118]. The WHO tracked VOC using a reporting structure that focuses on identifying subvariants with the Omicron lineage. As of 17 Dec 2023, the circulating VOI were recombinant Omicron subvariants XBB.1.5, XBB.1.16, EG.5, BA.2.86, and JN.1 [118].

As of 17 Dec 2023, more than 1.3 billion doses of elasomeran are estimated to have been distributed to 91 countries and more than 774 million doses administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. More than 129 million BDs of elasomeran/imelasomeran are estimated to have been distributed to 42 countries and more than 70 million doses administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. More than 245 million BDs of elasomeran/davesomeran are estimated to have been distributed to 43 countries and more than 135 million doses to have been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses distributed and administered. Low- and middle-income countries [119] are estimated to account for approximately 13% of the doses distributed globally and approximately 13% of doses administered. Andusomeran was introduced as a new marketed Moderna vaccine targeting SARS-CoV-2 in Sep 2023. As of 17 Dec 2023, 83,301,090 doses of andusomeran had been delivered to 19 countries and an estimated total of 45,815,600 doses were administered. North America, Europe, and Asia accounted for approximately >95% of all doses delivered and 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) and andusomeran continue to expand continue to expand.

Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 404,120,202 individuals received a first dose, 311,160,321 received a second dose, 190,540,777 received a third dose, and 78,503,483 received a fourth dose, with third and fourth

doses including both original elasomeran and elasomeran/imelasomeran and elasomeran/davesomeran booster dose formulations.

In Nov 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 [120]. While less pathogenic as compared to the delta variant, the Omicron variant was significantly more transmissible than previous variants [121-123]. As a result, soon after its emergence, Omicron rapidly became the dominant circulating variant worldwide [124]. While incident cases, hospitalizations, and deaths increased in the US during the Omicron wave, individuals who received mRNA-based vaccines, such as mRNA-1273, had lower rates of these outcomes based on data reported to the US CDC. The 2-dose mRNA-1273 primary series, along with the use of a BD, has been shown to be effective against COVID-19 and hospitalization due to COVID-19 caused by SARS-CoV-2 variants, including Alpha, Beta, Delta, Gamma, and Omicron.

Furthermore, after the Omicron (BA.1) variant's discovery, additional subvariants of Omicron had been identified, demonstrating increased transmissibility and immune escape versus the original strain, resulting in additional waves of COVID-19 infection dominated by these new subvariants. The morbidity and mortality associated with COVID-19 caused by antigenically divergent variants such as Omicron and the decreased effectiveness of mRNA-1273 against Omicron infection created the need to develop a booster with enhanced immunogenicity in order to confer improved protection against COVID-19 and help decrease the burden on hospitals and healthcare systems [125,126].

SARS-CoV-2 evolution is complex and remains unpredictable. There is no indication that SARS-CoV-2 evolution is slowing down, though immunity appears to be mitigating severe clinical outcomes. Intrinsic viral factors, including mutation rate and recombination potential, generate possibilities for increased transmissibility and adaptation to the host. At the same time, host immune responses and other factors contribute to selection of variants. Generation of immune escape variants may be further facilitated by chronic infections in immunocompromised hosts or potentially by waning of immunity in immunocompetent hosts. Thus far, the impressive plasticity, especially in spike, suggests that the virus can continue evolving by both incremental (drift-like) and saltatory (shift-like) modes, underscoring the importance of on-going global surveillance [127].

Throughout the first half of 2023, global public health agencies and vaccine regulators met to align the criteria used and the vaccine strain composition recommendations and have generally aligned around a common recommendation for the 2023-2024 COVID-19 vaccine formulation.

On 06 Jun 2023, the ECDC and the EMA issued a statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants. Similar to the WHO TAG-CO-VAC statement, ECDC/EMA recommended a monovalent vaccine composition as suitable to ensure adequate immunogenicity against circulating SARS-CoV-2 variants in both primed and naïve individuals, and XBB.1.5 was considered a reasonable choice to increase the breadth of immunity also against XBB descendent lineages [113].

On 15 Jun 2023, the FDA VRBPAC voted unanimously in favor of recommending an update of the COVID-19 vaccines to a monovalent XBB-lineage for the andusomeran. Based on the totality of evidence, ModernaTx, Inc developed a vaccine with a monovalent XBB.1.5 composition [128].

After more than 2 years of marketed Moderna vaccines targeting SARS-CoV-2 post-authorization use and more than an estimated 1 billion doses (including variant formulations) administered, the previously identified risk of myocarditis and pericarditis following vaccination with a marketed Moderna vaccine targeting SARS-CoV-2 continues to show that it is more common in males (aged 18 to 39 years), especially after dose 2 of the primary series. This is consistent with post-marketing surveillance, results from the PASS (mRNA-1273-P903), and multiple published studies containing real-world safety information. The continuous evaluation of post-authorization safety data and observational studies have allowed for a better understanding of the clinical profile of patients presenting with myocarditis/ pericarditis following vaccination with elasomeran (including variant formulations), including outcomes, and longer follow-up information. This includes rare cases of myocarditis/pericarditis with a fatal outcome though causality has not been established.

As of 17 Dec 2023, the safety profile of reports on myocarditis/pericarditis (after any of the 2 elasomeran bivalent vaccines, as well as andusomeran) does not differ from the safety profile of reports on the elasomeran primary series. There is a continuous decreasing trend in the number of reported cases of myocarditis and pericarditis and events of myocarditis and pericarditis cases continue to occur primarily in young males shortly after dose 2 with a reported TTO of <7 days. The characterization of myocarditis and pericarditis in the Special Warnings and Precautions section of the PI was revised during this PBRER reporting period for use with elasomeran (also referred to as mRNA-1273 or SPIKEVAX™) or any of its variant formulations. The revisions are

based on post marketing surveillance and analysis, prompted by requests from health authorities to re-evaluate the statements in the original PI. Important revisions to the PI included:

- Information regarding cases of myocarditis/pericarditis with a fatal outcome in ModernaTx Inc.'s GSDB: "Although causality has not been established, fatal events have been rarely reported."
- Updating information related to dose-related frequency as well as severity of such cases: "Post-authorisation data also indicate that myocarditis and pericarditis following vaccination is generally of shorter duration and less severe than viral infectious myocarditis or pericarditis."

Myocarditis and pericarditis have been well described as a complication of SARS-CoV-2 infection, and the clinical syndrome of COVID-19 related myocarditis is more severe and clinically meaningful compared to vaccine-associated myocarditis. Almost all individuals with cases of vaccine-associated myocarditis are hospitalized and clinically monitored, however, most cases follow an uncomplicated clinical course with reported resolution of symptoms rapidly achieved within a few days (2 to 4 days) after receiving conservative clinical management. Cases with a reported a fatal outcome were mostly confounded by associated comorbidities that provided a more plausible explanation for the reported fatal outcome. Only a few (4 fatal cases) reports were considered possibly associated with elasomeran vaccination. This new information on the course and outcome of reported cases of myocarditis/ pericarditis justified updating the CCDS for the purpose of providing additional information to health care providers on the risk of myocarditis and pericarditis after vaccination with a marketed Moderna vaccines targeting SARS-CoV-2.

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, persistent anosmia and ageusia, and cardiac palpitations that may persist 6 months or more after infection [129].

As the pandemic continues, it is evident that the vaccination coverage in pediatric and adolescent populations, as well as pregnant women, 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 1.3 billion doses of elasomeran distributed, and more than

774 million doses estimated to have been administered globally as of 17 Dec 2023. Further, bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran) and andusomeran 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.

The efficacy of mRNA-1273 to prevent COVID-19 was confirmed after administration of a primary series to adults 18 years and older in the pivotal Phase 3 study, Study P301 Part A. Data from Part A, the randomized placebo-controlled phase of the study, supported the US EUA (authorization on 18 Dec 2020) and BLA (approval on 31 Jan 2022). Results from P301A demonstrated VE of 93.2% (95% CI: 91.0, 94.8; $p < 0.0001$) for a total of 799 adjudicated COVID-19 cases, confirming persistent, high efficacy with a large case database over a median 5.3-month blinded observation period [130]. P301A results also demonstrated that mRNA-1273 was immunogenic, as indicated by increased nAb and bAb levels 1month after first dose (Day 29) and 1 month after second dose (Day 57). Effectiveness in adolescents and children 6 months and older was inferred by immunobridging, and favorable point estimates also were observed.

While the efficacy of the primary series was previously demonstrated, the emergence of highly transmissible and antigenically divergent SARS-CoV-2 variants such as Delta and Omicron contributed to breakthrough infection among vaccinated individuals [8], thereby prompting the authorization of first and second BDs of 50 μg mRNA-1273 to confer enhanced protection. Immunogenicity and real-world effectiveness studies have demonstrated the ability of boosters to protect against novel variants; however, the ongoing genetic evolution of the SARS-CoV-2 virus necessitated the development of booster vaccine formulations to target immunity to new variants and further enhance clinical effectiveness against circulating variants.

Studies conducted for a 50 μg mRNA-1273 booster (including the original mRNA-1273 booster and the variant-containing bivalent vaccines mRNA-1273.222 and mRNA-1273.214) elicits enhanced immune responses against SARS-CoV-2 compared to those elicited by the primary series, and consistent responses were observed across adolescents, younger adults, and older adults. Additionally variant-containing bivalent boosters elicit superior immune responses to the variant in the vaccine compared with the original mRNA-1273 booster, and enhanced responses are observed in both younger and older adults, and regardless of prior SARS-CoV-2 status, and variant-containing bivalent boosters induce immune responses that are durable, and cross neutralize divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted

individuals, and rates of COVID-19, hospitalized COVID-19 and hospitalized COVID-19 death are lower in boosted versus non-boosted individuals [8,117].

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%) [8] .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 [131-134].

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.

Evaluation of the post-marketing safety information included in the GSDB for children <18 years of age showed that the safety profile for the elasomeran vaccines is comparable to that observed during the clinical studies for the vaccines, and that the safety data evaluated as of 17 Dec 2023 does not indicate any changes in the benefit-risk profile of elasomeran. Overall, most cases were non-serious. When serious, these cases often had serious events reported once that did not demonstrate any unusual patterns or groupings by medical concept. 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. The observed safety profile of the use of elasomeran vaccines in the subpopulation of infants 0-5 months of age and children 6 months to 17 years of age continues to support a positive benefit-risk assessment.

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. Data also indicates 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.

Evaluation of the cumulative information for reports of myocarditis and/or pericarditis following exposure to elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran 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.

Post-authorization safety data collected in the GSDB show that Marketed Moderna vaccines targeting SARS-CoV-2 are well tolerated, and the safety profiles are similar to that observed during the MAH's clinical studies.

Considering the available safety and efficacy data from the 12 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 Marketed Moderna vaccines targeting SARS-CoV-2.

Risks associated with Marketed Moderna vaccines targeting SARS-CoV-2 are considered adequately managed with the product labels. An RMP is in place with ongoing studies 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 [120]. Omicron shares antibody escape site mutations with the Beta variant and it also exhibits transmissibility advantages [135-137]. Globally, the number of new cases increased by 52% during the 28-day period of 20 Nov 2023 to 17 Dec 2023 as compared to the previous 28-day period, with over 850.000 new cases reported. The Omicron variant has become the epidemiologically dominant variant in multiple countries since 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). The European Center for Disease Prevention and Control lists BA.2.75 and its sub-lineages, BQ.1, XBB and its sub-	• 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 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. • On 04 May 2023, the WHO Director-General in agreement with the recommendation provided by the International Health Regulations (2005) (IHR)

Decision Factors	Evidence/ Uncertainties	Conclusions
	lineages (excluding XBB1.5 and its sub-lineages), XBB.1.5 as VOI as of 26 Jan 2023 [113]. Among the nine countries (Austria, Denmark, France, Germany, Italy, Latvia, Luxembourg, the Netherlands, and Sweden) with an adequate volume of sequencing or genotyping for weeks 1 to 2 (2 to 15 Jan 2023), the estimated distribution of VOC or VOI ranged from 48.4-76.0% in seven countries for BQ.1, 11.3-76.9% in nine countries for BA.5, 6.6-27.8% in eight countries for BA.2.75, 1.4-5.6% in six countries for XBB.1.5, 0.9-6.5% in seven countries for XBB, 0.3-15.3% in eight countries for BA.2, and 0.1-0.9% in eight countries for BA.4 [113]. On 04 May 2023, the WHO Director-General in agreement with the recommendation provided by the International Health Regulations (2005) (IHR) Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, announced that "…COVID-19 is now an established and ongoing health issue which no longer constitutes a PHEIC." Additionally, on 09 May 2023, the Department of HHS in the US, stated that "Based on current COVID-19 trends, the Department of HHS is planning for the federal PHE for COVID-19, declared under Section 319 of the PHS Act, to expire at the end of the day on 11 May 2023.	Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, announced that "…COVID-19 is now an established and ongoing health issue which no longer constitutes a PHEIC."
Medical Need for Treatment of Condition/ Disease	As of 17 Dec 2023, over 772 million confirmed cases and nearly seven million deaths have been reported globally. Globally, the number of new cases increased by 52% during the 28-day period of 20 Nov 2023 to 17 Dec 2023 as compared to the previous 28-day period, with over 850.000 new cases reported [99]. Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [97,138]. Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults [98,139,140]. However, COVID-19 can also lead to severe outcomes in children and adolescents [141,142].	• Since Dec 2020, elasomeran and other COVID-19 vaccines have been available under EUA, conditional approvals, and full approval worldwide. • As of 17 Dec 2023, more than 1.3 billion doses of elasomeran are estimated to have been distributed to 91 countries and more than 774 million doses administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. More than 129 million BDs of elasomeran/imelasomeran are

Decision Factors	Evidence/ Uncertainties	Conclusions
	As of 17 Dec 2023, confirmed COVID-19 mortality has surpassed 1.1 million deaths in the US. 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.	estimated to have been distributed to 421 countries and more than 70 million doses administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. More than 245 million BDs of elasomeran/davesomeran are estimated to have been distributed to 4325 countries and more than 135 million doses to have been administered. Andusomeran was introduced as a new marketed Moderna vaccine targeting SARS-CoV-2 in Sep 2023. As of 17 Dec 2023, 83,301,090 doses of andusomeran had been delivered to 19 countries and an estimated total of 45,815,600 doses were administered. North America, Europe, and Asia accounted for approximately >95% of all doses delivered and 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 additional doses in special populations (e.g., immunocompromised) and/or as a BD, including authorization for two bivalent vaccines (elasomeran/imelasomeran, and elasomeran/davesomeran) and andusomeran 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.	• The efficacy of elasomeran to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273

Decision Factors	Evidence/ Uncertainties	Conclusions
	Analysis of the 04 May 2021 dataset showed that elasomeran 100 µg was 98.2% effective in preventing severe COVID-19. Subgroup analysis 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. 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 mRNA-1273-P201 Part A and mRNA-1273-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.	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, and P301, as well as Study DMID 21-0012. • In Studies mRNA-1273-P203 and mRNA-1273-P204 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 mRNA-1273-P301. • 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%) [8]. • Elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior

Decision Factors	Evidence/ Uncertainties	Conclusions
	Across the full pediatric program, the effectiveness of elasomeran was demonstrated from 6 months to 17 years. In Studies mRNA-1273-P203 and mRNA-1273-P204 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 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 [116] 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 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. Studies conducted for a 50 µg mRNA-1273 booster (including the original mRNA-1273 booster and the variant-containing bivalent vaccines mRNA-1273.222 and mRNA-1273.214) elicits enhanced immune responses against SARS-CoV-2 compared to those elicited by the primary series, and consistent responses were observed across adolescents,	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 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. • Variant-containing bivalent boosters elicit superior immune responses to the variant in the vaccine compared with the original elasomeran booster. • Enhanced responses are observed in both younger and older adults, and regardless of prior SARS-CoV-2 status. • Variant-containing bivalent boosters induce immune responses that are durable, and cross neutralize divergent SARS-CoV-2 strains.

Decision Factors	Evidence/ Uncertainties	Conclusions
	younger adults, and older adults. Additionally variant-containing bivalent boosters elicit superior immune responses to the variant in the vaccine compared with the original mRNA-1273 booster, and enhanced responses are observed in both younger and older adults, and regardless of prior SARS-CoV-2 status, and variant-containing bivalent boosters induce immune responses that are durable, and cross neutralize divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted individuals, and rates of COVID-19, hospitalized COVID-19 and hospitalized COVID-19 death are lower in boosted versus non-boosted individuals.	
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, 59,907 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, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administered with mRNA-1010 or co-administered with mRNA-1345, or co-administered active licensed sFLU vaccines (Fluzone HD or Fluarix) in the mRNA clinical development program sponsored by	• 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 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

Decision Factors	Evidence/ Uncertainties	Conclusions
	ModernaTx, Inc. The total count of 59,907 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). As of DLP, 14,848 subjects were exposed to mRNA 1273 and its variants from ongoing CTs sponsored by licensing partners. Out of 14,848 subjects, 1,160 subjects were exposed to mRNA 1273 in CTs sponsored by DMID, 19 subjects from a CT sponsored by NCI, 19 subjects from a CT sponsored by UCLA, 12,340 subjects from a CT sponsored by SAMRC, 1, 005 subjects from CTs sponsored by MSD, and 305 subjects from a CT sponsored by University of Southampton. Cumulatively, 1,573 subjects were enrolled in ongoing investigator-initiated trials. The type, incidence, and severity of ARs and TEAEs reported with elasomeran in CTs were consistent with the CT 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 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	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 pericarditis and is self-limited. • The clinical course of cases of myocarditis and pericarditis appears generally favorable;

Decision Factors	Evidence/ Uncertainties	Conclusions
	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 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	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
	co-existing viral infections. No confirmed cases of myocarditis or pericarditis were reported in Studies mRNA-1273-P203 and mRNA-1273-P204. 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 or elasomeran/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. 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	

Decision Factors	Evidence/ Uncertainties	Conclusions
	consequence [143].	

19. CONCLUSIONS AND ACTIONS

Overall, the cumulative evidence on the safety and efficacy for marketed Moderna vaccines targeting SARS-CoV-2 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.

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, mRNA-1273.222, and mRNA-1273.815.

During the reporting period of this PBRER, six signals were closed by the MAH, five closed signals were refuted by the MAH [IgA nephropathy flare-up, Sensorineural hearing loss, Breast swelling, Mastitis, and Postmenopausal haemorrhage] and one signal restricted to the US and limited to the US EUA of Moderna COVID-19 vaccine (2023-2024 formula) for individuals 6 months through 11 years of age, of "Overdose in children in the context of overfill of the SDV indicated for individuals 6 months through 11 years of age in the United States" was confirmed as important potential risk.

The data included in this PBRER#6 does not indicate any changes in the benefit-risk profile of marketed Moderna vaccines targeting SARS-CoV-2. The safety profile of Marketed Moderna vaccines targeting SARS-CoV-2 is closely monitored on a continuous basis and the analysis of the data contained within this report supports the current RSI (CCDS v18.0, dated 12 Oct 2023) for marketed Moderna vaccines targeting SARS-CoV-2.

Examination of the data contained within this report further supports the conclusion that the overall benefit-risk balance for marketed Moderna vaccines targeting SARS-CoV-2 continues to be positive and remains unchanged.

20. APPENDICES TO THE PBRER

Appendix 1 Reference Safety Information

Appendix 2 Worldwide Marketing Authorization status

Appendix 3 Cumulative Summary Tabulations of Serious AEs from Clinical Trials

Appendix 4 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Reactions from Post-marketing Data Sources

Appendix 5 Tabular Summary of Safety Signals and Signal Evaluation Reports

Appendix 6 Listing of all MAH-Sponsored Interventional Trials with the Primary Aim of Identifying, Characterizing, or Quantifying a Safety Hazard or Confirming the Safety Profile of the Medicinal Product

Appendix 7 Listing of all the MAH-sponsored Non-interventional Studies with the Primary Aim of Identifying, Characterizing, or Quantifying a Safety Hazard; Confirming the Safety Profile of the Medicinal Product; or Measuring the Effectiveness of Risk Management Measures

Appendix 8 List of the Sources of Information Used to Prepare the PBRER

Appendix 9 EU Regional Appendices

Appendix 10 US Regional Appendices

Appendix 11 Canada Regional appendix

Appendix 12 Other Appendices Supporting PBRER

Appendix 13 Literature search strategies