Spikevax: Periodic safety update report assessment

18 December 2023 to 17 December 2024

This document consists of:

1. The PRAC assessment report of the Spikevax periodic safety update report (PSUR) covering the period 18 December 2023 to 17 December 2024, 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.

EMADOC-1700519818-1986468
Pharmacovigilance Risk Assessment Committee (PRAC)
Case number: EMA/PSUR/0000257883

PRAC PSUR assessment report

EURD list no.: PSUSA/00010897/202412

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), SARS CoV 2 JN.1 mRNA

Period covered by the PSUR: 1 year to 17 December 2024 (18 Dec 2023 to 17 Dec 2024)

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	12 March 2025	12 March 2025
☐	Start date	13 March 2025	13 March 2025
☐	PRAC Rapporteur AR	12 May 2025	07 May 2025
☐	PRAC/MAH comments	11 June 2025	11 June 2025
☐	Updated PRAC Rapporteur AR	26 June 2025	26 June 2025
☐	PRAC outcome	10 July 2025	10 July 2025
☒	Oral explanation at PRAC	n/a	n/a

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), SARS CoV 2 JN.1 mRNA.

2. Assessment conclusions and actions

This report assessed the 7th PSUR on elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-Co-V-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA, summarizing the safety information gathered during a 1-year period covering the interval from 18 Dec 2023 to 17 Dec 2024.

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. As of June of 2023, the MAH discontinued distribution of elasomeran worldwide. As of Nov 2023, the MAH discontinued distribution of elasomeran/imelasomeran and elasomeran/davesomeran worldwide.

SARS-CoV-2 JN.1 mRNA was approved in the EU on 09 September 2024. SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula was granted authorisation by the US FDA on 22 Aug 2024. Therefore, the current PSUR is the first that includes data on SARS-CoV-2 JN.1 mRNA and SARS-Co-V-2 KP.2 mRNA.

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; SARS-CoV-2). Elasomeran was authorised 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 were 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 had previously received at least a primary vaccination course against COVID-19. Andusomeran is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV2 in individuals 6 months of age and older, SARS-CoV-2 JN.1 mRNA is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

The cumulative subject exposure in clinical trials is estimated to 64,409 subjects. Cumulatively, a total of 1,040,373,873 doses of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA are estimated to have been administered. The total interval exposure from marketing experience is estimated as 36,879,106 administered doses.

Literature

The MAH presented four articles with relevant safety information inthe PSUR. The PRAC agrees that no new significant safety information is identified in three of the four presented articles, regarding acute kidney injury, major congenital anomalies, and chronic urticaria. However, the publication regarding vaccine-associated myocarditis, by Jain SS et al. (2024) provides new and significant safety information. Please see section `safety concerns' below.

Signals

The MAH closed and refuted 7 signals during the reporting interval. This is endorsed. However, the MAH is reminded of their obligation to conduct their own signal detection and to present the validated signals in the relevant section of the PSUR, rather than limiting the presented signals to health authority requests during the reporting period. Furthermore, the MAH is reminded not to present already assessed topics as signals in future PSURs.

Safety concerns

New and significant data was presented for the important identified risk myocarditis and pericarditis. A new multicentre study (Jain SS et al. [2024]) of COVID-19 vaccine-associated myocarditis presented new data, of which some results supported the known safety profile, while other results presented new findings of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging at presentation and at follow-up in patients with COVID-19 vaccine-associated myocarditis (C-VAM). This may raise concerns about potential long-term cardiac risks in these patients despite a mild initial clinical course. As part of additional pharmacovigilance activities, the MAH has an ongoing PASS study mRNA-1273-P911 for the evaluation of long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA). The final study report is expected in October 2028.

No new and significant safety information was identified for any of the remaining safety concerns.

Conclusion

There has been no change or re-characterisation in the safety concerns. Based on the evaluation of cumulative safety data and the benefit-risk analysis, no changes to the additional risk minimization activities are warranted.

Considering no new safety or efficacy information has been identified neither in the current nor in the previous reporting periods, the PRAC recommends to extend the PSUR frequency from to 1 year to 2 years.

The benefit-risk balance of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-Co-V-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA remains unchanged in the approved indications.

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 (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5), SARS CoV 2 JN.1 mRNA remains unchanged and therefore recommends the maintenance of the marketing authorisation(s).

4. Issues to be addressed in the next PSUR

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

- Data in summary tabulations

  For future PSURs, the MAH is requested to indicate any relevant annex as not applicable,

if no data has been found in order to avoid further misunderstandings and to ensure transparency.

5. PSUR frequency

☒ Changes of PSUR frequency are proposed

The current frequency of submission should be changed **from 1 year to 2 years** at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is the PSUSA of the 7th PSUR on elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-Co-V-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA, covering the interval from 18 Dec 2023 to 17 Dec 2024.

Currently, the PSUR for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-Co-V-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA, is on an annual submission schedule based on the European Union (EU) reference dates (EURD). The first three PSURs 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 was included; with the PSUR #7, SARS-Co-V-2 KP.2 mRNA and SARS-CoV-2 JN.1 mRNA are also included.

The European Union reference date (EURD) and the international birth date (IBD) of elasomeran is 18 Dec 2020. The product is authorised in 47 unique countries, regions, and unions/areas for active immunisation 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 (MHRA) for use in the United Kingdom (UK) on 12 Aug 2022. Elasomeran/davesomeran was granted Emergency Use Authorisation (EUA) status by the US Food & Drug Administration (FDA) on 31 Aug 2022. Andusomeran was granted authorisation for individuals ≥12 years of age and EUA status for individuals 6 months to 11 years of age by the US FDA on 11 Sep 2023. SARS-CoV-2 JN.1 mRNA was granted authorisation for individuals 6 months of age and older by the Pharmaceuticals and Medical Devices Agency (PMDA) for Japan on 23 Aug 2024. SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula was granted authorisation for individuals 12 years of age and older, and EUA for individuals 6 month to 11 years of age by the US FDA on 22 Aug 2024.

As of June of 2023, the MAH discontinued distribution of elasomeran worldwide. As of Nov 2023, the MAH discontinued distribution of elasomeran/imelasomeran and elasomeran/davesomeran worldwide.

Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-Co-V-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has 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 the most recent Company Core Data Sheet (CCDS) (v19.0, dated 13 Jun 2024), elasomeran was authorised 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 were 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 had previously received at least a primary vaccination course against COVID-19. Andusomeran is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV2 in individuals 6 months of age and older, SARS-CoV-2 JN.1 mRNA is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

Elasomeran is a 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 2 proline residues to stabilise the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of 4 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 (PEG) of average molecular weight 2000 (PEG-2000DMG). Imelasomeran contains mRNA, 5'-capped, encoding a full-length, codon optimised prefusion stabilised 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). Andusomeran 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. SARS-CoV-2 JN.1 mRNA 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 JN.1 mRNA and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 50 mcg nucleoside-modified mRNA encoding the pre-fusion stabilised Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage KP.2. Each dose also contains the following ingredients: a total lipid content of 1.01 mg (SM-102, PEG 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.25 mg tromethamine, 1.2 mg tromethamine hydrochloride, 0.021 mg acetic acid, 0.10 mg sodium acetate trihydrate, and 43.5 mg sucrose.

Elasomeran was formulated as a dispersion for injection supplied in a multidose vial or in a prefilled syringe and was administered intramuscularly (IM). Elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, and SARS-CoV-2 JN.1 are formulated as a dispersion for injection supplied in a single dose vial, a multidose vial or a single use pre-filled syringe. SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is formulated as a dispersion for injection supplied in a single use prefilled syringe.

- Elasomeran 0.2 mg/mL dispersion for injection.

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

- Elasomeran 0.1 mg/mL dispersion for injection.

Elasomeran was supplied as a multidose vial that contained 5 doses of 0.5 mL each or a maximum of 10 doses of 0.25 mL each. One dose (0.5 mL) contained 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) containeds 25 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

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

Elasomeran was supplied as single use pre-filled syringe that contained one dose of 0.5 ml. One dose (0.5 mL) contained 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

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

Elasomeran/imelasomeran was supplied as a multidose 2.5 mL vial (blue flip-off cap) that contained 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) contained 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.

Elasomeran/imelasomeran was supplied as a single dose vial which contained one dose of 0.5 mL. One dose (0.5 mL) contained 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 contained one dose of 0.5 mL, for single use only. One dose (0.5 mL) contained 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 was 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) contained 25 µg of elasomeran and 25 µg of davesomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran/davesomeran (25 µg/25 µg)/mL dispersion for injection.

Elasomeran/davesomeran was supplied as a single dose 0.5 mL vial (blue flip-off cap) containing 1 doses of 0.5 mL. One dose (0.5 mL) contained 25 µg of elasomeran and 25 µg of davesomeran, 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) contained 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) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Andusomeran 50 µg dispersion for injection.

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).

- SARS-CoV-2 JN.1 mRNA, 0.1 mg/mL dispersion for injection.

SARS-CoV-2 JN.1 mRNA is supplied as a multi-dose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 50 µg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- SARS-CoV-2 JN.1 mRNA, 50 µg dispersion for injection.

SARS-CoV-2 JN.1 mRNA is supplied as a single dose 0.5 mL vial (blue flip-off cap) and pre-filled syringe. Each contains 1 dose of 0.5 mL for single use. One dose (0.5 mL) contains 50 µg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- SARS-CoV-2 JN.1 mRNA, 25 µg dispersion for injection.

SARS-CoV-2 JN.1 is supplied as a single dose 0.25 mL pre-filled syringe. Each 0.25 mL dose contains 25 mcg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles).

- SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, 50 µg dispersion for injection.

SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is supplied as single dose pre-filled syringes containing either 0.5 mL or 0.25 mL. Each 0.5 mL dose of SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 50 mcg mRNA-1273.712, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles). Each 0.25 mL dose of SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 25 mcg mRNA-1273.712, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles).

Posology is presented in below Table 1-7

Table 1: Elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran Posology

Concentration	Vaccination Type	Age(s)	Dose	Recommendations
Spikevax 0.2 mg/L dispersion for injection	*Primary series*	*Individuals 12 years of age and older*	2 (2) (0.5 mL each, containing 100 micrograms mRNA)	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 through 11 years of age	2 (2) doses (0.25 mL each, containing 50 micrograms 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*	*1 (one) dose of 0.5 mL, containing 100 micrograms mRNA*	A third dose may be given at least 28 days after the second dose.
		Children 6 through 11 years of age	1 (one) dose of 0.25 mL containing 50 micrograms mRNA	
	Booster dose	*Individuals 12 years of age and older*	1 (one) dose of 0.25 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Spikevax 0.1 mg/L dispersion for injection and Spikevax 50 micrograms dispersion for injection in pre-filled syringe*	*Primary series†*	*Children 6 years through 11 years of age*	2 (2) doses (0.5 mL each, containing 50 micrograms mRNA each)	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age	2 (2) doses (0.25 mL each, containing 25 micrograms mRNA each, which is half of the primary dose for children 6 years through 11 years of age)*	
	Third dose in severely immunocompromise‡	*Children 6 years through 11 years of age*	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA	A third dose may be given at least 28 days after the second dose.
		Children 6 months through 5 years of age	1 (one) dose of 0.25 mL, containing 25 micrograms mRNA*	
	Booster dose	*Individuals 12 years of age and older*	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 6 years of age and older who have received a primary series

		Individuals 6 years through 11 years of age	1 (one) dose (0.25 mL each, containing 25 micrograms mRNA)*	with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.

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

† 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 individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.

Table 2: Andusomeran posology

Age(s)	Dose	Additional Recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS-CoV-2 infection	*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 any Spikevax vaccine, one dose of Spikevax XBB.1.5 should be administered to complete the 2 dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly*	Spikevax XBB.1.5 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 3: Andusomeran Posology for immunocompromised individuals

Age(s)	Dose	Additional Recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	*Two doses of 0.25 mL, given intramuscularly**	A third 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 single dose vial or prefilled syringe to deliver a partial volume of 0.25 mL.

Table 4: SARS-CoV-2 JN.1 mRNA Posology

Age(s)	Dose	Additional Recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS-CoV-2 infection	*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 any Spikevax vaccine, one dose of Spikevax JN.1 should be administered to complete the 2 dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly*	Spikevax JN.1 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.

Table 5: SARS-CoV-2 JN.1 mRNA Posology for immunocompromised individuals

Age(s)	Dose	Additional Recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	*Two doses of 0.25 mL, given intramuscularly**	A third 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 single dose vial or prefilled syringe to deliver a partial volume of 0.25 mL.

Table 6: SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Posology. Individuals 6 Months Through 23 Months of Age by Number of Previous Doses of Moderna COVID-19 Vaccine Received

Number of Previous Doses of Moderna COVID-19 Vaccine(s)[a]	SPIKEVAX (2024-2025 Formula) Dosing Regimen, Dose and Schedule
0[b]	*2 doses[c] 0.25 mL each* *Dose 1: month 0* *Dose 2: month 1*
1	*Single dose, 0.25 mL* *One month after receipt of a previous dose of Moderna COVID-19 vaccine[a]*
≥2	*Single dose, 0.25 mL* *≥2 months after receipt of the last previous dose of Moderna COVID-19 vaccine[a]*

[a] Previous dose refers to a dose of any prior Moderna COVID-19 Vaccine that is no longer authorised for use in the United States.

[b] Not previously vaccinated with any COVID-19 vaccine.

[c] Individuals turning from 23 months to 2 years of age during the vaccination series should receive both doses with SPIKEVAX (2024-2025 Formula).

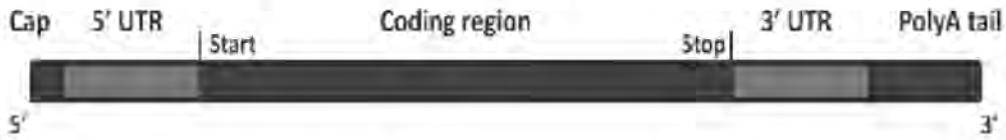
Table 7: SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Posology. Individuals 2 Years of Age and Older Irrespective of COVID-19 Vaccination Status

Age	SPIKEVAX (2024-2025 Formula) Dosing Regimen, Dose and Schedule
2 years through 11 years	*Single dose,* ***0.25 mL***
12 years and older	*Single dose,* ***0.5 mL***

Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA may be used to boost adults who have received a primary series with elasomeran, or a primary series comprised of another SARS-CoV-2 mRNA vaccine or SARS-CoV-2 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 in PSUR appendix 8]. This nucleoside is included in mRNA-1273 drug substance in place of the normal uridine base to minimise the indiscriminate recognition of the mRNA-1273 by pathogen-associated molecular pattern receptors (e.g., toll-like receptors) [3 in PSUR appendix 8]. The cap structure used in the mRNA is identical to the natural mammalian Cap one structure [4,5 in PSUR appendix 8] 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, andusomeran, SARS-CoV-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA contain mRNA encapsulated in LNPs. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat one domain (S-2P) to stabilise 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 stabilised Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5. mRNA-1273.167 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. 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 neutralising antibodies, which may contribute to protection against COVID-19.

Modified, variant-matched bivalent COVID-19 mRNA vaccines were developed containing equal amounts of 2 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 2 distinct spike protomers, each of which represents one of the 3 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 stabilised Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5 (andusomeran) and SARS-CoV-2 JN.1 mRNA. 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 programme (See Table 8).

Table 8: Variants and World Health Organisation (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)
mRNA-1273.167	SARS-CoV-2 JN.1 mRNA
mRNA-1273.712	SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

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

The expressed Spike protein of SARS-CoV-2 is then recognised 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 v19 dated 13 Jun 2024) 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 international birth date (IBD) of elasomeran is 18 Dec 2020. The product was authorised in 47 unique countries, regions, and unions/areas for active immunisation 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 (MHRA) for use in the United Kingdom (UK) on 12 Aug 2022. Elasomeran/davesomeran was granted Emergency Use Authorisation (EUA) status by the US Food & Drug Administration (FDA) on 31 Aug 2022. Andusomeran was granted authorisation for individuals >12 years of age and EUA status for individuals 6 months to 11 years of age by the US FDA on 11 Sep 2023. SARS-CoV-2 JN.1 mRNA was granted authorisation for individuals 6 months of age and older by the Pharmaceuticals and Medical Devices Agency (PMDA) for Japan on 23 Aug 2024. SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula was granted authorisation for individuals 12 years of age and older, and EUA for individuals 6 month to 11 years of age by the US FDA on 22 Aug 2024.

As of June of 2023, the MAH discontinued distribution of elasomeran worldwide. As of Nov 2023, the MAH discontinued distribution of elasomeran/imelasomeran and elasomeran/davesomeran worldwide.

Marketed Moderna vaccines targeting SARS-CoV are 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 2 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 3 bivalent vaccines (elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran) as well as additional periodic doses against circulating SARS-CoV-2 variants (SARS-CoV-2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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 Data Lock Point (DLP), elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA is authorised in 47 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, no safety-related actions were taken.

Rapporteur assessment comment:

This section is acknowledged.

1.3.2. 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 2024) and used for this report is the CCDS v19.0 (dated 13 Jun 2024). 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 v18.0 (dated 12 Oct 2023) to v19.0 (dated 13 Jun 2024). The safety-related changes are summarised below in Table 9.

Table 9: CCDS safety-related changes during the reporting period

Version	Date	Summary of changes
19.0	*13 Jun 2024*	**Sections 1, 2, 4.1, 4.2, 5.1, 6.3 and 6.6:** Addition of JN.1 variant particulars and addition of paperboard PFS and 25 mcg PFS SKUs. **Section 6.6:** Deletion of statements on 15-minute wait time per Revenue Operating Committee (ROC) request.

Rapporteur assessment comment:

The RSI used by the MAH for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA in effect at the end of the reporting period (DLP 17 Dec 2024) and used for this report is the CCDS v19.0 (dated 13 Jun 2024).

The MAH reports that the RSI (CCDS) was updated during the reporting period from v18.0 (dated 12 Oct 2023) to v19.0 (dated 13 Jun 2024), with the following safety-related changes:

Addition of JN.1 variant particulars and addition of paperboard PFS and 25 mcg PFS SKUs (sections 1, 2, 4.1, 4.2, 5.1, 6.3 and 6.6).

Deletion of statements on 15-minute wait time per Revenue Operating Committee (ROC) request. (section 6.6). This statement relates to thawing instructions for single-dose vials and cartons before use. The deletion is in line with the information available in the current Spikevax EU SmPC.

The listed change to the CCDS concerns the active substance and the preparation of the vaccine and the MAH is therefore reminded to only list changes to the CCDS that impacts safety in this section in the PSUR.

This section is acknowledged.

1.3.3. Estimated exposure and use patterns

1.3.3.1. Cumulative exposure in clinical trials

Cumulatively, 64,409 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, mRNA-1273.617.2, mRNA-1273.529, mRNA-1273.231, mRNA-1273.712, and mRNA-1273.815), and participants exposed to mRNA-1273 (including its variants) in CTs using the fixed combination compound mRNA-1283 (including its variant mRNA-1283.211); also in CTs in which mRNA-1273 was co-administered with mRNA-1010 or mRNA-1345; and in CTs in which mRN-1273 was co-administered with active licensed sFLU vaccines (Fluzone High-Dose or Fluarix) in clinical development programmes sponsored by ModernaTx, Inc. The total count of 64,409 represents unique subjects (Subjects enrolled in both trials mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total).

During the reporting period, 4,601 subjects were estimated to be exposed to either mRNA-1273, or its variants (mRNA-1273.167, mRNA-1273.214, mRNA-1273.222, SPIKEVAX KP.2, and mRNA-1273.815), and subjects exposed to mRNA-1273 (or its variants) co-administered active licensed sFLU vaccines in the mRNA clinical development programme sponsored by ModernaTx, Inc.

As of DLP, 12,946 subjects were exposed to mRNA-1273 and its variants from ongoing CTs sponsored by licensing partners. Out of 12,946 subjects, 423 subjects were exposed to mRNA-1273 in CTs sponsored by DMID, 19 subjects from a CT sponsored by NCI, 12,342 subjects from a CT sponsored by SAMRC, 162 subjects from CTs sponsored by MSD. Cumulatively, 493 subjects were enrolled in ongoing investigator-initiated trials.

Estimates of cumulative subject exposure, based upon actual exposure data from completed CTs and the enrolment/randomisation schemes for ongoing and blinded trials is provided in Table 10 below. Further details on cumulative subject exposure categorised by age, gender, racial group and ethnicity is provided in Table 11 below, Table 5-3 (please see PSUR), Table 5-4 (please see PSUR), and Table 5-5 (please see PSUR), respectively.

Table 10: 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]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	135[a]
mRNA-1273-P205	mRNA-1273.213 Booster	952[a]
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	423[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	5[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	1759[a]
mRNA-1273-P305	mRNA-1273.214 Booster	1422[a]
mRNA-1273-P305	mRNA-1273.529 Booster	367[a]
mRNA-1273-P306	mRNA-1273.214	391[a]
mRNA-1273-P306	mRNA-1273.815	598[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1273-P306	mRNA-1273.815 Booster	249[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P401	Spikevax	109[a]
mRNA-1273-P401	mRNA-1273.815	106[a]
mRNA-1273-P403	mRNA-1273.167	50[a]
mRNA-1273-P403	SPIKEVAX KP.2	50[a]
mRNA-1273-P404	Overall (SPIKEVAX KP.2 - Placebo Crossover or Placebo - SPIKEVAX KP.2 Crossover)	997[a]
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	Overall (mRNA-1273.222 or mRNA-1273.815)	7,106[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	107[a]
mRNA-1083-P101	mRNA-1273.815	41[a, b]
mRNA-1083-P301	Fluarix + Spikevax co-administration	2009[a]
mRNA-1083-P301	Fluzone HD + Spikevax co-administration	2009[a]
mRNA-1083-P302	Licensed influenza vaccine + Spikevax	1007[a, b]
mRNA-1230-P101	mRNA-1273.214	43[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1345-P302	Overall (mRNA-1273.214, or mRNA-1345 + mRNA-1273.214 co-administration)	1,710[a]

[a]= These numbers were counted for the total subject exposure in each study.
[b]= Estimated numbers per randomisation scheme as the study is currently blinded.

Table 11: Cumulative Subject Exposure to Investigational Drug from Completed or Ongoing Unblined/Open-label Clinical Trials by Age[a]

Age Range	mRNA-1273											mRNA-1283		mRNA-CRID	mRNA-1073	mRNA-1083		mRNA-1230	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P401	P403	P101	P201	001	P101	P101 Part 1	P301	P101	
<2 years	0	0	2,606	0	68	0	0	0	667	0	0	0	0	0	0	0	0	0	3,227
2 to <6 years	0	0	3,877	0	0	0	0	0	1,016	0	0	0	0	0	0	0	0	0	4,437
6 to <12 years	0	0	4,549	0	0	0	0	0	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	0	0	0	0	0	2,397
16 to <18 years	0	780	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	781
18 to <65 years	475	0	0	3,868	0	20,679	184	2,349	0	178	64	27	51	56	127	53	2,007	32	27,153
65 to <75 years	120	0	0	1,035	0	5,825	43	1,118	0	28	29	0	5	4	22	47	1,595	11	9,052
75 to <85 years	20	0	0	236	0	1,256	7	75	0	9	7	0	1	0	1	7	399	0	1,837
>=85 years	3	0	0	22	0	83	0	5	0	0	0	0	0	0	0	0	17	0	115
Total	618	3,177	11,032	5,161	68	27,843	234	3,548	1,683	215	100	27	57	60	150	107	4,018	43	53,548[b]

[a]Data from Completed or Unblinded/Open-label trials till 17 Dec 2024.
[b]The Subjects enrolled in both mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total number.

1.3.3.2. Cumulative and interval exposure from marketing experience

Cumulatively, a total of 1,850,065,554 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered to countries worldwide. North America, Europe, and Asia accounted for approximately 85% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed (Table 12).

For the current reporting period (18 Dec 2023 to 17 Dec 2024), a total of 73,758,211 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered and an estimated total of 36,879,106 doses had been administered. North America, Latin America, Europe, and Asia accounted for approximately 95% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed (Table 12).

Given that elasomeran, distribution was discontinued worldwide after second quarter of 2023, no new doses were distributed during this PBRER reporting period. Additionally, elasomeran/imelasomeran and elasomeran/davesomeran were discontinued in Nov 2023, there were no doses distributed between 18 Dec 2023 and 17 Dec 2024.

A total of 25,369,142 doses of andusomeran had been delivered to 23 countries and an estimated total of 12,684,571 doses had been administered. Latin America, North America, and Asia accounted for approximately 93% of doses distributed and approximately 93% of doses

administered. A total of 24,771,589 doses of SARS-CoV-2 JN.1 mRNA had been delivered to 15 countries and an estimated total of 12,385,795 doses had been administered. Europe, and Asia accounted for approximately 90% of all doses delivered and administered. A total of 23,617,480 doses of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula had been distributed to USA, Canada and Japan and an estimated total of 11,808,740 doses had been administered (Table 13-15).

Table 12: Total Doses Distributed and Administered for All Marketed Moderna Vaccines Targeting SARS-CoV-2 as of 17 Dec 2024

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	1,850,065,554	100.0	1,040,373,873	100.0	73,758,211	100.0	36,879,106	100.0
North America	699,828,236	37.83	377,606,869	36.30	26,783,092	36.31	13,391,546	36.31
US	626,478,906	33.86	338,507,107	32.54	22,184,452	30.08	11,092,226	30.08
All Europe	525,182,137	28.39	279,643,099	26.88	16,466,944	22.33	8,233,473	22.33
European Economic Area	422,443,266	22.83	226,294,318	21.75	1,418,923	1.92	709,462	1.92
Asia	436,143,821	23.57	232,191,602	22.32	8,503,205	11.53	4,251,603	11.53
Latin America	95,305,500	5.15	50,762,130	4.88	18,180,550	24.65	9,090,275	24.65
Africa	32,474,530	1.76	17,855,749	1.72	0	0.0	0	0.0
Oceania	29,568,000	1.60	15,967,830	1.53	499,920	0.68	249,960	0.68
Middle East	31,563,330	1.71	16,914,697	1.63	3,324,500	4.51	1,662,250	4.51
International donations	.	.	49,431,898	4.75	.	.	0	0.0

*The international donations were restricted only to Spikevax original (Elasomeran). Based on data shared by the Centres for Disease Control (CDC) for the US, the MAH had estimated that approximately 15% of all Moderna doses distributed may be part of such agreements. As tracking data on the administration of doses donated after initial distribution was not available, the MAH had conservatively assumed that only 25% of these doses have been administered globally.

Doses Distributed and Administered for Andusomeran, SARS-CoV2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula as of 17 Dec 2024

Table 13: Andusomeran

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	108,692,842	100.0	54,346,421	100.0	25,369,142	100.0	12,684,571	100.0
North America	42,487,162	39.09	21,243,581	39.09	3,165,712	12.48	1,582,856	12.48
US	34,238,612	31.50	17,119,306	31.50	3,165,712	12.48	1,582,856	12.48
All Europe	18,731,190	17.23	9,365,595	17.23	110,120	0.43	55,060	0.43
European Economic Area	1,683,620	1.55	841,810	1.55	109,870	0.43	54,935	0.43
Asia	24,639,370	22.67	12,319,685	22.67	2,618,740	10.32	1,309,370	10 32
Latin America	18,840,550	17.33	9,420,275	17.33	17,830,150	70.28	8,915,075	70 28
Africa	0	0.00	0	0.00	0	0.0	0	0.0
Oceania	1,000,030	0.92	500,015	0.92	499,920	1.97	249,960	1.97
Middle East	2,994,540	2.76	1,497,270	2.76	1,144,500	4.51	572,250	4.51

Table 14: SARS-CoV-2 JN.1 mRNA

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	24,771,589	100.0	12,385,795	100.0	24,771,589	100.0	12,385,795	100.0
North America	0	0.00	0	0.00	0	0.00	0	0.00
US	0	0.00	0	0.00	0	0.00	0	0.00
All Europe	16,356,824	66.03	8,178,413	66.03	16,356,824	66.03	8,178,413	66.03
European Economic Area	1,309,053	5.28	654,527	5.28	1,309,053	5.28	654,527	5.28
Asia	5,884,365	23.75	2,942,183	23.75	5,884,365	23.75	2,942,183	23.75
Latin America	350,400	1.41	175,200	1.41	350,400	1.41	175,200	1.41
Africa	0	0.00	0	0.00	0	0.00	0	0.00
Oceania	0	0.00	0	0.00	0	0.00	0	0.00
Middle East	2,180,000	8.80	1,090,000	8.80	2,180,000	8.80	1,090,000	8.80

Table 15: SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	23,617,480	100.0	11,808,740	100.0	23,617,480	100.0	11,808,740	100.0
North America	23,617,380	100.0	11,808,690	100.0	23,617,380	100.0	11,808,690	100.0
US	19,018,740	80.53	9,509,370	80.53	19,018,740	80.53	9,509,370	80.53
All Europe	0	0.00	0	0.00	0	0.00	0	0.00
European Economic Area	0	0.00	0	0.00	0	0.00	0	0.00
Asia	100	0.00	50	0.00	100	0.00	50	0.00
Latin America	0	0.00	0	0.00	0	0.00	0	0.00
Africa	0	0.00	0	0.00	0	0.00	0	0.00
Oceania	0	0.00	0	0.00	0	0.00	0	0.00
Middle East	0	0.00	0	0.00	0	0.00	0	0.00

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, Isle of Man, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Ukraine, Switzerland, UK
Asia: Bangladesh, Bhutan, Cambodia, 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.

Rapporteur assessment comment:

Exposure from Clinical trials

The cumulative subject exposure in clinical trials is estimated to 64,409 subjects.

Exposure from Post-marketing

Cumulative exposure

Cumulatively, a total of 1,040,373,873 doses of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA are estimated to have been administered.

Interval exposure

The total interval exposure from marketing experience is estimated as 36,879,106 administered doses.

Given that elasomeran distribution was discontinued worldwide after second quarter of 2023, no new doses were distributed during this reporting period. Additionally, as elasomeran/imelasomeran and elasomeran/davesomeran were discontinued in Nov 2023, there were no doses distributed between 18 Dec 2023 and 17 Dec 2024.

For andusomeran, the estimated interval exposure is 12,684,571 administered doses.

For SARS-CoV-2 JN.1 mRNA, the estimated interval exposure is 12,385,795 administered doses.

For SARS-CoV-2 KP.2 mRNA, the estimated interval exposure is 11,808,740 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 (HCP) to record the name and batch number of the administered vaccine to improve traceability.

The vaccine carton labelling also contains a scannable 2D barcode that provides the batch/lot number and expiry date. In addition, ModernaTx, Inc. also provides stickers (2 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 use in special populations

Use in elderly

Evaluation of information received during this PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in the elderly population has not identified any clinically relevant new safety information for this subpopulation.

This reporting interval is 12 months, which has changed from the last PBRER reporting period of 6 months. The number of cases received during this 12-month reporting period and the MAH medical review of cases are presented by product in Table 16. There was a total of 45 cases with a reported fatal outcome. Most of these cases, irrespective of the variant formulation used, were assessed as unlikely related to the Company product due to concurrent polymorbidities that provided alternative aetiologies.

Refer to PSUR Appendix 12.2 for more information on individual case assessment.

Table 16: case reports and MAH comment by product

Source of New Information	• Moderna Global Safety Database (GSDB) • Literature Sources- See Appendix 13.4 • Retrieved: 555 (1 relevant article reviewed) • New and Significant Safety Information: There was no new and significant safety information identified.		
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	994	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/ Imelasomeran	>65 years of age	76	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/ Davesomeran	>65 years of age	127	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Andusomeran	>65 years of age	2,223	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
SARS-CoV-2 JN.1 mRNA	>65 years of age	225	The observed safety data were generally consistent with the known safety profile of elasomeran. The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation was positive.
SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula	>65 years of age	185	The observed safety data were generally consistent with the known safety profile of elasomeran. The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation was positive.
SPIKEVAX (NOS)	>65 years of age	139	There have been no new safety findings. The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.

<u>Andusomeran</u>

During this 12-month reporting period, the MAH received 2,223 cases (979 serious, 1,241 medically confirmed, 35 fatal) with 6,981 events (2,477 serious) in the elderly population (>65+ years of age) who received andusomeran. When gender was known, cases were disproportionately reported in females (1,174, 52.8%) compared to males (854, 38.4%), with small proportion of cases (195, 8.8%) having no gender reported. The mean patient age was 76.9 years (SD: 7.2) and median age of 76.0 years (range: 65.0 to 116.0 years). During the reporting period, there has been >2-fold increase in the number of case reports with andusomeran use compared to the previous reporting period which was likely reflective of the corresponding increase in the market uptake of andusomeran. This included, a four-fold increase of cases reported in the UK (1,401; 63.0%) and a decline in the US (374, 16.8%) and similar reporting rates in Canada (259, 11.7%)

compared to the previous reporting period. No clustering or trends of any safety concerns were identified following the data review. The most commonly reported events (PTs) were consistent with the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2.

During the reporting period, when dose number and time to onset could be determined, events were most often reported after Dose 2 (1,280, 18.3%) followed by Dose 1 (314, 4.5%) and Dose 6 (186, 2.7%), typically within the first 5 days of vaccination. When outcome was recorded, 20.1% of events had resolved (1,404 events), 14.4% were resolving (1,006 events) and 16.8% of events had not resolved (1,172 events), at the time of report. Of the 35 cases reported with fatal outcomes, the majority of the cases with fatal outcome were evaluated as unlikely related to the use of the product. These cases often involved patients of advanced age and with concurrent polymorbid conditions, the likely progression/ worsening of which or their potential associated complications provided a more likely explanation of the reported fatal event(s). No new safety concerns were identified with the use of Company product in this population subgroup (PSUR Appendix 12.2).

SARS-CoV-2 JN.1 mRNA

Cumulatively, the MAH received 225 cases (61 serious, 156 medically confirmed, 5 fatal) with 605 events (123 serious) in the elderly population (>65+ years of age) who received mRNA-1273.167 formula. When gender was known, the majority of cases were reported in females (132, 58.7%) compared to males (86, 38.2%), with few cases (7, 3.1%) not reporting gender information.

The mean patient age was 77.1 years (SD: 8.3) and median age of 76.0 years (range: 65.0 to 99.0 years), representing the population that is mainly getting vaccinated worldwide. Majority of cases were reported from the UK (209, 92.9%) followed by Denmark (6; 2.7%), and Switzerland (5; 2.2%).

The most frequently reported events (PTs) were generally consistent with reactogenicity events consistent with the marketed Moderna vaccines targeting SARS-CoV-2 safety profile.

Cumulatively, when dose number and time to onset could be determined, events were most often reported after Dose 2 (62; 10.2%) followed by Dose 1 (15, 2.5%) and Dose 6 (9, 1.5%), typically within the first 3 days of vaccination. When outcome was recorded, 16.5% of events had not resolved (100 events), 11.2% were resolved (68 events) and 10.1% of events were resolving (61 events), at the time of report. There were 5 cases with reported fatal outcomes (UK 4 cases; Denmark 1 case). A review of these cases yielded no safety issues of concern (PSUR Appendix 12.2).

SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

Cumulatively, the MAH received 185 cases (18 serious, 144 medically confirmed, no fatal cases) with 695 events (49 serious) in the elderly population (>65+ years of age) who received SARS Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. When gender was known, more cases were reported in females (115, 62.2%) compared to males (62, 33.5%), with small proportion of cases (8, 4.3%) having no gender reported. The mean patient age was 75.1 years (SD: 6.9) and median age of 74.0 years (range: 65.0 to 107.0 years). All cases were from the United States.

The most frequently reported events (PTs) were consistent with reactogenicity events consistent with the known safety profile for marketed Moderna vaccines targeting SARS-CoV-2.

Cumulatively, when dose number and time to onset could be determined, events were most often reported after Dose 4 (37; 5.3%) followed by Dose 6 (33, 4.7%) and Dose 5 and Dose 8 (32, 4.6%), typically within the first 2 days of vaccination. When the outcome was recorded, 29.4% of events had not resolved (204 events), 15.7% were resolving (109 events) and 14.7% of events were resolved (102 events), at the time of report. There were no cases with a reported fatal outcome.

Spikevax NOS

During this reporting period, the MAH received 139 cases (54 serious, 84 medically confirmed) with 362 events (92 serious) in the elderly population (>65+ years of age) who received SPIKEVAX (NOS). When gender was known, more cases were reported in females (79, 56.8%) compared to males (56, 40.3%), with 4 cases (2.9%) having no gender reported. The mean patient age was 74.0 years (SD: 6.6) and median age of 73.0 years (range: 65.0 to 92.0 years). The majority of the cases were reported in United States (83, 59.7%) followed by Asia (20, 14.4%) and the UK (17, 12.2%).

There were 5 cases with a reported fatal outcome. A review of these cases yielded no new safety issues (PSUR Appendix 12.2).

Overall, adverse events (AEs) reported during the review period of this PBRER for this special population reflected reactogenicity or those known to occur following vaccination with marketed Moderna vaccines targeting SARS-CoV-2. The reported events did not show any clustering or trends of safety concerns in this patient population.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the special population of elderly individuals 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 reported for this special population using routine surveillance. The benefit-risk evaluation remains positive.

Use in children

The evaluation of information received during this PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in children has not identified any additional clinically relevant 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 17. Refer to PSUR Appendix 12.3 for additional information.

During the reporting period of this PBRER, the MAH received 636 cases (48 serious, 617 medically confirmed, and 3 fatal) with 1,573 events (100 serious) reported for children under 18 years of age who received marketed Moderna vaccines targeting SARS-CoV-2. When gender was known, more cases were reported in females (284; 44.7%) compared to males (241; 37.9%), with 111 cases (17.5%) lacking gender information. The mean patient age was 7.9 years (standard deviation [SD]: 5.3) and median age of 8.0 (range: 0.0 to 17.0 years). The Majority were spontaneous reports (635; 99.8%), with one (0.2%) literature-non-study report. Most cases were reported in The United States (507; 79.7%), followed by Asia (40; 6.3%) and Latin America (37; 5.8%).

The most frequently reported events in children, by Preferred Term (PT) were "No adverse event" (458; 29.1%), "Expired product administered" (180; 11.4%), "Wrong product administered (137; 8.7%)", "Poor quality product administered" (91; 5.8%) and "Overdose" (85; 5.4%).

Table 17: case reports and MAH comment by age group

Source of New Information	• Moderna Global Safety Database (GSDB). • Literature Sources- 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 (Serious, fatal) • Elasomeran: 7 cases (6 serious, 1 fatal). • Elasomeran/imelasomeran: No cases were reported during this review period. • Elasomeran/davesomeran: No cases were reported during this review period. • Andusomeran:3 serious cases (0 fatal). • SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula: 3 non-serious cases. • SARS-CoV-2 JN.1 mRNA: 1 serious case, 0 fatal. • SPIKEVAX NOS: 1 non-serious case.	Cases ([redacted] (fatal case); [redacted] involved foetal or neonatal outcomes associated with elasomeran vaccine exposure. These cases included serious events such as hydrops fetalis, congenital anomalies (e.g., pulmonary valve stenosis, atrial septal defect, patent ductus arteriosus, and kidney duplex), premature birth, and growth restriction, For detailed information on these cases. Please refer to Section 16.3.5.1 for further details. A review of 4 serious cases [[redacted] (involved andusomeran) and case [redacted] (involved SARS-CoV-2 JN.1 mRNA)] received via UK MHRA suggested that the reported ages of the patients ([redacted]-day-old, [redacted]-day-old, and [redacted]-day old) may have been incorrectly reported. The reported ages suggest a potential inconsistency with the use of andusomeran in individuals under 6 months of age. Additional clarification regarding the correct ages of the patients would be beneficial for the accurate case assessments. At the time of this report, no follow-up information has been received to address these discrepancies. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children (6 months to 5 years)	• Elasomeran: 14 cases (4 serious, 0 fatal), • Elasomeran/imelasomeran: No cases were reported during this review period,	Case [redacted]elasomeran) described occurrence of foetal growth restriction in 2-year-old male. Please refer to Section 16.3.5.1 for further details. Note: Case [redacted] was presented in

Exposed Population by Age groups	Number of Case Reports Received	MAH Comment on Benefit and/or Risk (any observed differences from overall population)
	• Elasomeran/davesomeran: 9 non-serious cases, • Andusomeran: 160 cases (3 serious, 0 fatal), • SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula: 43 non-serious cases, • SARS-CoV-2 JN.1 mRNA: No cases were reported during this review period, • SPIKEVAX NOS: 4 cases (1 serious fatal case).	both age groups (< 6 months and 6 months to 5 years of age) as the onset date was used for 2 values of PTs foetal growth restriction (Age: 2) and Premature baby (Age: 0). Five cases [redacted] (involved elasomeran), cases [redacted] (involved andusomeran), [redacted] (involved SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula)] reported seizures or febrile convulsions in children aged 2–4 years. In one case, a reported medical history was identified as a confounder ([redacted]). Another case described febrile convulsion potentially triggered by fever by a concurrent mycoplasma infection ([redacted]). Limited information was reported for the other cases. Case[redacted] concerns a 12-month-old patient of unknown gender who died after receiving a dose of SPIKEVAX NOS. Key details, including the vaccination date, onset date of event, cause of death, autopsy findings, medical history, concomitant medications and treatment details, were not reported. The case contained limited information for a meaningful assessment. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children 6-11 years	• Elasomeran: 2 non-serious cases, • Elasomeran/imelasomeran: No cases were reported during this review period, • Elasomeran/davesomeran: 14 cases (1 serious, 0 fatal), • Andusomeran: 122 cases (8 serious, 0 fatal), • SARS-Co-V-2 KP.2 mRNA	The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

Exposed Population by Age groups	Number of Case Reports Received	MAH Comment on Benefit and/or Risk (any observed differences from overall population)
	(COVID-19 Vaccine, mRNA) 2024-2025 Formula: 49 cases (1 serious, 0 fatal). • SARS-CoV-2 JN.1 mRNA: No cases were reported during this review period, • SPIKEVAX NOS: 5 non-serious cases.	
Adolescents (12 to 17 years)	• Elasomeran: 16 cases (4 serious, 0 fatal), • Elasomeran/imelasomeran: No cases were reported during this review period, • Elasomeran/davesomeran: 5 non-serious cases, • Andusomeran: 125 cases (14 serious cases, 0 fatal), • SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula: 51 cases (1 serious, 0 fatal), • SARS-CoV-2 JN.1 mRNA: 1 non-serious case, • SPIKEVAX NOS: 2 serious cases (1 fatal).	5 cases concerning myocarditis /pericarditis/ myopericarditis were reported in this age group: 1 case [redacted] involved elasomeran. 3 cases [redacted] involved andusomeran. 1 case [redacted] involved SPIKEVAX NOS. Please refer to Section 16.3.1.2 for further details. Case [redacted] reported occurrence of anaphylactic reaction in a 15-year-old male, after receiving elasomeran. Please refer to Section 16.3.1.1 for further details. One fatal case ([redacted]) was reported for a 14-year-old male patient who died after receiving a dose of SPIKEVAX NOS. Key details, including vaccination date, onset of event, cause of death, autopsy findings, medical history, concomitant or treatment details were not reported. The case had limited information for a meaningful assessment. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

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.

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.

There was a total of 45 cases with a reported fatal outcome. Most of these cases, irrespective of the variant formulation used, were assessed by the MAH as unlikely related to the Company product due to concurrent polymorbidities that provided alternative aetiologies. Case evaluations and narratives are presented in PSUR appendix 12.2.

4 cases were deemed WHO-possible by the MAH. While a temporal association is noted, significant comorbidities (hypertension, hyperlipidaemia, anxiety, coronary artery disease, aortic

regurgitation, stent, congestive heart failure, frailty) were likely contributory and confound the assessment.

Overall, adverse events (AEs) reported in elderly patients during the review period reflected reactogenicity or those AEs known to occur following vaccination with marketed Moderna vaccines targeting SARS-CoV-2. The reported events did not show any clustering or trends of safety concerns.

No new safety concerns were identified by the MAH in these reports.

Paediatric population

During the reporting period, the MAH received 636 cases (48 serious, 617 medically confirmed, and 3 fatal) with 1,573 events (100 serious) reported for children under 18 years of age who received marketed Moderna vaccines targeting SARS-CoV-2.

The most frequently reported events in children, by Preferred Term (PT) were "No adverse event" (458; 29.1%), "Expired product administered" (180; 11.4%), "Wrong product administered (137; 8.7%)", "Poor quality product administered" (91; 5.8%) and "Overdose" (85; 5.4%).

One fatal case ([redacted] reported in a child <6 months old who experienced the fatal event of foetal hydrops was assessed by MAH as WHO-unlikely related, due to lack of biological plausibility and underlying maternal syphilis as a potential alternative aetiology. This case was also potentially confounded by maternal exposure to the co-suspect products MMR and DT vaccines; and the possibility of rhesus incompatibility and/or exposure to maternal viral infection (Parovirus B19 Herpes virus-CMV).

The remaining two fatal cases were reported in a 12-month old of unknown gender and 14-year old male, however, key details such as vaccination date, onset of event, cause of death, autopsy findings, medical history, concomitant or treatment details were not reported, precluding a meaningful assessment.

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.

1.3.3.2.3. Other clinical topics

1.3.3.2.3.1. Overdose

Source of New Information	• Moderna GSDB • Literature Sources-See PSUR Appendix 13.4 • Retrieved: 0 • 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 of overdose-related terms where an AE was included, most of the reported events included reactogenicity events such as pyrexia, injection site erythema, pain, and headache.

Methods	The MAH queried the GSDB for valid case reports received from HCP, health authority (HA), consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The search criteria applied for identification of overdose cases included the following MedDRA terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.
Results	*Overdose Cases Involving use of Elasomeran* During the review period, the MAH received 12 cases (5 serious) of overdose with 12 events (1 serious), and no cases with a fatal outcome. A total of 10 (10) cases (83.3%) were medically confirmed. The reported events were "Overdose" (12; 100.0%). Of the 12 cases, 6 cases involved paediatric patients (6 months to 3 years of age) who received an overdose of vaccine for one of the doses. All these cases came from the same medical practice, and vaccination occurred between October and November of 2022. None of the reports had any other associated AE. One of the serious cases [redacted] – WWID: [redacted]) is a literature report of a 25-yearold male who 4 days after receiving second dose of mRNA-1273 experienced chest pain and myocarditis was suspected. No additional details (such as diagnostic tests, medical history, concomitant medications etc) were provided. According to the reporter the patient received double dose of mRNA-1273. No other information is available. *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 2 medically confirmed cases (2 events) of overdose with no serious cases and no cases with a fatal outcome. The reported events were "Accidental Overdose" (2 events; 100.0%). Both events are from the same practice, in which expired product was administered as well as administering the entire amount of the multi-dose vial (a full syringe (2.5 ml)). No AEs were reported due to the accidental overdose and expired product administered. *Overdose Cases Involving use of Andusomeran* In 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. The paediatric SDV contained notably more than 0.25 ml of vaccine, which led to provider confusion or administration errors, including overdose. During the current review period, the MAH received 191 cases (191 events) with no serious cases, and no cases with a fatal outcome. A total of 188 cases (98.4%) were medically confirmed. The reported events were "Overdose" (156; 81.7%) and "Accidental overdose" (35; 18.3%). Of the 191 cases, 72 cases involved paediatric patients (6 months to 11 years of

	age) who received an overdose of vaccine due to the overfilling of the SDV. Majority of the paediatric overdose cases showed no AEs, and reactogenicity events such as headache, pyrexia, and vaccination site pain were reported. There were 112 cases that did not provided age information. *Overdose Cases Involving use of SARS-CoV-2 JN.1 mRNA* No cases involving SARS-CoV-2 JN.1 mRNA were received during the reporting period. *Overdose Cases Involving use of* SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula During the review period, the MAH received 47 cases (47 events) with no serious cases, and no cases with a fatal outcome. All 47 cases (100.0%) were medically confirmed. The reported events were "Overdose" (40; 85.1%) and "Accidental overdose" (7; 14.9%). There were 43 cases which involved < 11 years old who received 0.5 ml of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula rather than the indicated 0.25 ml dose for the age group. The majority of the cases (41; 95.3%) had no AEs reported. *Overdose Cases Involving use SPIKEVAX (NOS)* During the review period, the MAH received 4 medically confirmed, non-serious cases (4 non-serious events). No cases with a fatal outcome were reported. The reported events were "Accidental overdose" (3; 75.0%) and "Overdose" (1 event; 25.0%).
Discussion	The MAH received 12 cases (5 serious cases) of overdose for the elasomeran original, no cases of overdose reported involving elasomeran/imelasomeran, 2 cases (no serious cases) of overdose involving elasomeran/davesomeran, 191 cases of overdose involving andusomeran, no cases of overdose reported involving SARS-CoV-2 JN.1 mRNA of overdose involving unspecified SPIKEVAX (NOS). 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 by any vaccine, with most of the events reported being reactogenicity events along with product administration and product quality issues. All of the overdose reports were due to human errors made during administration. The reports concerning medication error, where the entire volume of 0.5 ml of vaccine was administered to children 6 months through 11 years of age rather than 0.25ml dose for the age group, resulted in mostly reactogenicity events in the vaccinees. Please refer to Section 5.2.2.2 (of the PSUR) for further details. Based on the analysis of all the safety data available as well as review of the literature for the reporting period, the MAH considers cases of overdose do not impact the benefits and possible vaccine-associated risks.
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

	elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 JN.1 mRNA and SARS-Co-V- 2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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 12.4 for more detailed information.

1.3.3.2.3.2. Off-label use

Source of New Information	• Moderna GSDB • Literature Sources-See PSUR Appendix 13.4 • Retrieved: 0 • 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 authorisation. Examples include the intentional use of a product in situations other than the ones described in the authorised 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 offlabel use are the terms of marketing authorisation 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 utilising the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) standardised 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 31 cases (32 events) of Off-label use with 19 serious cases (12 serious events), and no cases with a fatal outcome. There were 27 medically confirmed cases involving elasomeran. These cases were reported mostly in females (13 cases, 41.9%) and in males (10 cases, 32.3%). The mean age was 57.4 years (SD: 14.9) and median age was 61.5 years (range: 28.0 to 80.0 years). The country with the most frequent cases of Off-label use was Germany (17; 54.8%) followed by Canada (5; 16.1%). The events reported were "Off-label use" (29; 90.6%), "Intentional product use issue" (2; 6.3%) and

	"Intentional product misuse" (1; 3.1%). Review of cases did not identify any safety issues of concerns. *Off-label Cases Involving use of Elasomeran/Imelasomeran* During this review period, there was only 1 serious medically confirmed case (1 serious event) of Off-label use reported involving Elasomeran/Imelasomeran. This case involved a 49-year-old female from [redacted]. The event reported was "Off-label use" (1; 100.0%). This case was identified as part of a retrospective clean-up activity where certain reports downloaded from EVWeb were missed to be booked-in. *Off-label Cases Involving use of Elasomeran/Davesomeran* During the review period, there were no cases of Off-label use reported involving Elasomeran/Davesomeran. *Off-label Cases Involving use of Andusomeran* During the review period, the MAH received 137 medically confirmed cases (137 events) of Off-label use and no cases with a fatal outcome involving andusomeran. All 137 cases were non-serious. All the cases were missing gender and age information (137; 100.0%). All the cases were received from Israel (137; 100.0%). The events reported were "Offlabel use" (137; 100.0%). No associated AEs were reported. *Off-label Cases Involving use of SARS-CoV-2 JN.1 mRNA* During the review period, there were no cases of Off-label use reported involving SARSCoV-2 JN.1 mRNA. *Off-label Cases Involving use of* SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula During the review period, there were no cases of Off-label use reported with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. *Off-label Cases Involving Use of SPIKEVAX (NOS)* During this review period, there was 1 medically confirmed case of Off-label use (1 event) in a female with an unknown age reported involving SPIKEVAX (NOS). The event reported was Off-label use (1; 100.0%).
Discussion	Consistent with the prior reporting period, "Off-label use" was the most frequently reported PT during the current reporting period. Off-label use observed during the review period did not change the safety profile of marketed Moderna vaccines targeting SARSCoV-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 marketed Moderna vaccines targeting SARS-CoV-2 did not raise any safety issue of concern. The information provided does not support evidence of causality between off-label use and marketed 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 12.5 for more detailed information.

Rapporteur assessment comment:

Overdose

During the reporting period, 12 cases with overdose were identified for elasomeran, 0 cases for elasomeran/imelasomeran, 2 cases for elasomeran/davesomeran, 191 cases for andusomeran, 0 cases for SARS-CoV-2 JN.1 mRNA, 47 cases for SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula and 4 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.

Off-label use

During the reporting period, 31 cases of Off-label use were identified for elasomeran, 1 case for elasomeran/imelasomeran, 0 cases for elasomeran/davesomeran, 137 case for andusomeran, 0 cases for SARS-CoV-2 JN.1 mRNA, 0 cases for SARS-CoV-2 KP.2 mRNA and 1 case for unspecified Spikevax (NOS). No cases were reported with fatal outcome.

Consistent with the prior reporting period, "Off-label use" was the most frequently reported PT during the current reporting period. 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 marketed Moderna vaccines targeting SARS-CoV-2 did not raise any safety issue of concern.

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 27.1 was used for the coding of AEs/adverse drug reactions (ADRs) presented in this report. The line listings and summary tabulations are 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 2024) summary tabulation of Serious Adverse Events (SAEs) from Company-sponsored CTs is provided in Appendix 3 [of the PSUR]. Inclusion requirement parameters for the incorporation of data from Company-sponsored CTs are that the SAE occurred following active treatment, the SAE originated from a clinical study with mRNA-1273, mRNA-

1273.214, mRNA-1273.222, mRNA-1273.815, mRNA-1273.231, mRNA-1273.167, and mRNA-1273.712, 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 2024) and interval (18 Dec 2023 to 17 Dec 2024) summary tabulation of ADRs (serious and non-serious) is provided in Appendix 4 [of the PSUR]. The ADRs presented in this tabulation were derived from spontaneous sources (healthcare professionals [HCPs], consumers, scientific literature, and regulatory authorities [RAs]) as well as serious ADRs from non-interventional studies and non-interventional solicited sources.

1.3.4.1. RESPONSE TO EMA ON ISSUES TO BE ADDRESSED IN THE NEXT PSUR RELATED TO PROCEDURE EMEA/H/C/PSUSA/00010897/202312

Item 1

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.

MAH's Response:

The MAH would like to clarify why the summary tabulations in Appendices 3f and 4f for andusomeran (Spikevax XBB.1.5) did not contain any data in the PBRER #6 (18-Jun-2023 to 17-Dec-2023). This was due to a data classification issue related to how the safety database stored and retrieved case listings.

Specifically, the safety database contained two separate family names: 1. "mRNA-1273.815", which was updated to reflect the marketed andusomeran strain, and 2. "Modified mRNA-1273.815", which was a distinct entry but did not have any associated cases.

As a result, when generating the safety data outputs, cases associated with "Modified mRNA-1273.815" did not contribute to the summary tabulations, leading to the null outputs in Appendices 3f and 4f of PBRER #6.

Corrective Actions for Future PBRERs

To ensure completeness and accuracy of the appended summary tabulations in future reports, the following measures have been implemented:

- A review of case classification and family name assignment in the safety database has been conducted to prevent similar discrepancies.
- Data extraction procedures have been refined to ensure all relevant cases are correctly mapped to the appropriate family name. Additional validation checks have been introduced during the PBRER preparation process to confirm that all active ingredients with reported cases are reflected in the summary tabulations.

These actions will ensure that all relevant data, including cases related to andusomeran, are appropriately included in future PBRERs as requested by PRAC.

Rapporteur assessment comment:

In the previous PSUSA procedure it was noted that presentation of data in summary tabulation of ADRs in appendices 3 and 4 was incomplete.

The MAH has clarified that the summary of tabulations regarding andusomeran did not contain any data due to a data classification issue. Corrective actions taken by the MAH included a review of case classification and family name assignment in the safety database, as well as refinement of data extraction procedures with additional validation checks to confirm all active ingredients with reported cases are reflected in the summary tabulations.

No new important safety information is identified in the reporting period. However, the Rapporteur notes that annexes 3G, 3H, 3I, 4E and 4F in the current PSUR do not contain any data. **Based on the prior issues with data classification, the MAH is requested, within this procedure, to clarify whether or not the issue of missing data in the summary of tabulations has been corrected. If relevant, the updated annexes should be submitted within this PSUSA procedure.**

For future PSURs the MAH is requested to indicate any relevant annex as not applicable, if no data has been found in order to avoid further misunderstandings and to ensure transparency.

Review of Missed ICSRs and Misattributed Cases During the Reporting Period

In the executive summary of the PSUR, the MAH reports the following: "*during the reporting period, the MAH discovered an issue related to a number of individual case safety reports (ICSRs) downloaded from EudraVigilance (EV) database for Spikevax, which remained in the intake tool and were not processed in the Global Safety Database (GSDB). A review was completed to assess the potential impact of the 5,543 missed cases, on the safety profile of Spikevax. Of the 5,543 cases, 2,057 cases were serious, and 99 cases were reported with a fatal outcome. A retrospective ad hoc signal detection review was conducted on the missed ICSRs, focusing on potential impacts on previously closed signals throughout the lifecycle of Spikevax. This review also addressed safety concerns, adverse events of special interest, standard topics, and the identification of any new potential signals. The findings confirmed that these cases did not reveal any new safety information beyond the existing knowledge of Spikevax's safety profile. It is important to note that because these cases were included in EVDAS, they were already considered in the MAHs ongoing signal detection activities, since January 2021, and that any disproportionately reported among the cases in EVDAS would have been promptly reviewed through proactive routine signal detection activities. The benefit-risk profile of Spikevax remains unaffected by this review of the missed cases.*

Also of note, during the review period, the MAH noticed that after SARS-CoV-2 JN.1 mRNA approval, the MAH continued to receive andusomeran cases from a Regulatory Authority (RA). Upon further investigation the RA reporting site had not been updated to include the JN.1 product as an option for selection for reporters. The RA informed that their sites had been updated approximately 1 month after SARS-CoV-2 JN.1 mRNA approval to include JN.1 as a selection. In total 428 cases were mistakenly reported by the RA as related to andusomeran instead of SARS-CoV-2 JN.1 mRNA. In 367 of these cases, MAH added the event of "Discontinued product administered" for purposes of identification.

Conclusion: 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."

Within this procedure, the MAH is requested to specify which corrective actions have been taken to ensure individual case safety reports (ICSRs) downloaded from EudraVigilance (EV) are properly processed in the Global Safety Database (GSDB). Furthermore, the MAH should confirm if all relevant cumulative tables have been updated.

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: 11 Ongoing: 8	Completed: 8 Ongoing: 13 Planned: 3	Investigator-sponsored studies Completed: 9 Ongoing: 2 License partner studies Completed: 4 Ongoing: 5	Elasomeran 805 cases (4,074 events) Elasomeran/imelasomeran 60 cases (182 events) Elasomeran/davsesomeran 151 cases (207 events) Andusomeran 3,607 cases (8,918 events) SARS-CoV-2 JN.1 mRNA 1,199 cases (2,427 events) SARS-Co-V-2 KP.2 mRNA 380 cases (1,106 events) SPIKEVAX (NOS) 64 cases (196 events)	None	4 articles identified	None

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

Completed clinical trials

During the reporting period, 11 ModernaTx, Inc sponsored CTs were completed and presented below:

mRNA-1073-P101: A Phase I/II, randomised, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age.

mRNA-1083-P301: A Phase III, Randomised, Observer-blind, Active control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA 1083 (SARS-CoV-2 and Influenza) Vaccine in Healthy Adult Participants, ≥50 Years of Age.

mRNA-1230-P101: A Phase I, randomised, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of multi-component vaccines mRNA-1045 (Influenza and RSV) or mRNA-1230 (Influenza, RSV, and SARS-CoV-2) compared with mRNA-1010 (Influenza), mRNA-1345 (RSV), and mRNA-1273.214 (SARS-CoV-2) vaccines in healthy adults 50-75 years of age.

mRNA-1273-P203: A Phase II/III, Randomised, Observer-Blind, Placebo-Controlled, Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to <18 years of age.

mRNA-1273-P204: A Phase II/III, Three-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomised, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA 1273 SARS-CoV 2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age.

mRNA-1273-P205: A Phase II/III Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants.

mRNA-1273-P304: A Phase IIIb, Open-Label, Safety and Immunogenicity Study of SARSCoV2 mRNA-1273 Vaccine in Adult Solid Organ Transplant (SOT) Recipients and Healthy Controls.

mRNA-1273-P305: A Phase II/III, Randomised, Observer-blind, Active-controlled, Multicentre Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine.

mRNA-1273-P401: A Randomised, Observer-Blind, Active-Controlled, Clinical Trial to Assess the Immunogenicity of an Investigational mRNA-1273.815 COVID-19 Vaccine in Previously Vaccinated Adults.

mRNA-1283-P101: A Phase I, Randomised, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1283 and mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18-55 Years.

mRNA-1283-P201: A Phase IIa, randomised, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2.

There were no significant safety findings from the 11 CTs that completed during the reporting interval.

Rapporteur assessment comment:

During the reporting period, 11 ModernaTx, Inc sponsored clinical trials were completed. According

to the MAH, no significant safety findings were reported.

This information is acknowledged.

Ongoing clinical trials

During the reporting period, there were 4 ongoing ModernaTx, Inc. sponsored CTs with mRNA-1273 (mRNA-1273-P206, mRNA-1273-P306, mRNA-1273-P403, and mRNA-1273-P404), and there were 4 ongoing CTs that included a mRNA-1273 treatment arm as active control (mRNA-1283-P301, mRNA-1083-P101, mRNA-1345-P302, and mRNA-CRID-001). Cumulative exposure by study is presented in Table 18 below.

There were no significant safety findings that arose from ongoing CTs during the reporting period.

Table 18: Summary of Estimated Cumulative Subject Exposure to mRNA-1273 and its variants by Study[a]

Study ID	Total subjects exposed
mRNA-1083-P101	148[a, b]
mRNA-1273-P206	68
mRNA-1273-P306	1,777[a]
mRNA-1283-P301	7,106[a, b]
mRNA-1345-P302	1,710[a]
mRNA-1273-P403	100[a]
mRNA-1273-P404	997[a]
mRNA-CRID-001	60[a]

[a]=Data from ongoing trials till 17 Dec 2024.
[b]=Estimated numbers per randomisation scheme as the study is currently blinded.

Refer to Appendix 6 [in 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 arose from the 8 ongoing CTs during the reporting period.

This information is acknowledged.

Long-term Follow-up

The Phase 3 study mRNA-1273-P301 included a total of 24 months follow-up; no long-term safety concerns were identified for the 2 dose mRNA-1273 100 mcg primary series based on the final analysis that included 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 completed 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 completed 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 ongoing paediatric Phase 3 Study mRNA-1273-P306, participants 6 months through 5 years have a median follow-up

of 187 (1,386) days from Dose 1 and 168.5 (9,355) days from Dose 2. 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 marketed Moderna vaccines Targeting SARS-CoV-2 there were 2 CTs (mRNA-1073-P101, and mRNA-1230-P101) for combination therapies in which marketed Moderna vaccines Targeting SARS-CoV-2 were part of the fixed combinations. There are separate Development Safety Update Reports (DSURs) for each of these fixed combination therapies. No new safety information was identified from the fixed combination therapy CTs which were completed during this reporting period.

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.

According to the MAH, no new safety information was identified from the fixed combination therapy CTs which were completed during this reporting period.

This information is acknowledged.

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-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 Post-Market Surveillance (PMS) programme was to identify hypotheses for the safety evaluation of this product by confirming the occurrence status of non-acute hospitalisation associated serious events observed after vaccination in persons with underlying diseases considered to be at high-risk of exacerbation of COVID-19 in Japan. There were no major differences in the overall incidence of SAEs associated with hospitalisation in the non-acute phase compared with SAEs associated with all-cause hospitalisation in the year prior to vaccination. In addition, there were no major differences in events observed and their incidences, and no particular trend was observed in the time to onset. Based on the above, the survey did not suggest any new safety concerns of this vaccine.
mRNA-1273-P918	Japan	General use-result 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 programme was 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 immunisation (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 immunisation, 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. No safety or efficacy problems were observed in this programme, and it was judged unnecessary to take any particular measures at this point in time.
mRNA-1273-P919	United States	An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to SPIKEVAX During Pregnancy	mRNA-1273-P919 was an observational post-marketing safety study evaluating the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to SPIKEVAX during pregnancy. A final study report was completed in Mar 2024 and amended in Aug 2024

			Study Design: This claims-based retrospective cohort study compared adverse neonatal, pregnancy, or birth outcomes among pregnant women exposed to SPIKEVAX with 3 reference populations. Exposure windows were defined based on etiologically relevant timing for each specific study outcome (e.g., the first trimester for major congenital malformations [MCM]). Generalised linear regression models and inverse probability of exposure (propensity score [7]) weighting were employed to adjust for confounding factors when comparing event rates in exposed vs reference populations. **Results:** The study population included 277,287 women who met study entry criteria. Of these, 22,622 women were exposed to SPIKEVAX at any time during pregnancy, 8,282 were distantly exposed to SPIKEVAX, and 246,383 were unexposed to any COVID-19 vaccine during pregnancy. Additionally, 23,584 unvaccinated women were diagnosed with COVID-19 during pregnancy. Primary analyses found no evidence of increased risk for any infant outcomes. Among livebirths, the proportion of infants with MCMs was similar among women exposed to SPIKEVAX and distantly exposed women (adjusted RR [8]: 0.96; 95% confidence interval [CI]: 0.75-1.22), unexposed women (aRR: 1.10; 95% CI: 0.91 - 1.36), and less than that among women who had COVID-19 during pregnancy (aRR: 0.74; 95% CI: 0.55-0.99). Similarly, other infant outcomes were not associated with and increased risk after SPIKEVAX exposure during pregnancy. Among the pregnancy complications assessed, no increased risk was observed for post-partum haemorrhage and eclampsia. However, a marginal increase in the risk of pre-eclampsia was noted for both pre-specified exposure windows from last menstrual period (LMP) to 20 gestational weeks (aRR: 1.11; 95% CI 1.00-1.24), and from greater than LMP + 20 weeks to the end of pregnancy (aRR: 1.18; 95% CI 1.03-1.35) compared to women distantly exposed to SPIKEVAX. Gestational hypertension presented a slightly increased risk for the risk window extending from greater than LMP+ 20 weeks to end of pregnancy (aRR: 1.25; 95% CI 1.12-1.39) compared to women distantly exposed to SPIKEVAX. Additionally, a small increased risk for gestational diabetes (GD) was observed for the pre-specified primary exposure window from LMP to 28 gestational weeks (aRR: 1.10; 95% CI 1.00-1.20) when compared to women who were distantly exposed to SPIKEVAX. These results were largely consistent when compared to women unexposed to any

Study ID	Country	Study Title	Study results
			COVID-19 vaccine during pregnancy and across most sensitivity analyses. Among the birth outcomes assessed following exposure to SPIKEVAX during pregnancy, aRRs were <1 when compared to pregnant women who were distantly exposed to SPIKEVAX or unexposed to any vaccines targeting SARS-CoV-2 during pregnancy. **Discussion** Consistent with the known safety profile of SPIKEVAX, this study showed no increased risks for infant outcomes (including MCM, neonatal encephalopathy, SGA, hospitalisation due to infections (including COVID-19) in the first year of life), stillbirth, or eclampsia. Lower rates among vaccinated women were observed for respiratory distress in the newborn, preterm birth, spontaneous abortions, and post-partum haemorrhage. Small increases were observed in rates of pre-eclampsia, gestational hypertension, and GD. Safety of Moderna COVID-19 will be further investigated in ongoing studies mRNA-1273-P905 and mRNA-1273-P951.
mRNA-1273-P920	United States	Post-marketing safety of elasomeran/ davesomeran and andusomeran vaccines in the United States	mRNA-1273-P920 was an observational post-marketing study that evaluated the safety of the elasomeran/davesomeran and andusomeran vaccines as used in routine clinical practice. A final study report was completed in Sep 2024. **Study Design** This retrospective observational cohort study used administrative healthcare data from HealthVerity (01 Sep 2022 through 15 Jan 2024) to compare the observed rates of AESI among patients who received at least one dose of elasomeran/davesomeran or andusomeran to 2 concurrent comparator groups (influenza vaccine and medically-attended COVID-19, analysed separately). When a potential increase in the rate of an AESI following elasomeran/davesomeran or andusomeran was identified, self-controlled risk interval (SCRI) analyses for signal refinement were planned. **Results** In analyses comparing elasomeran/davesomeran or andusomeran vs influenza vaccinated persons, 1,146,808 vaccinations of elasomeran/davesomeran or andusomeran and 13,082,338 episodes of influenza vaccination among adults (≥18 years of age) met inclusion criteria (without excluding any prevalent AESI as required for each AESI-specific analysis). Among children (<18 years of

Study ID	Country	Study Title	Study results
			age), 47,186 episodes of elasomeran/davesomeran or andusomeran and 5,827,873 influenza vaccinations were included. In analyses where elasomeran/davesomeran or andusomeran recipients and individuals diagnosed with COVID-19 were described, 3,059,540 vaccinations of elasomeran/davesomeran or andusomeran and 2,573,696 medically-attended COVID-19 disease episodes among adults met inclusion criteria (without excluding any prevalent AESI). Among children, 140,154 vaccinations of elasomeran/davesomeran or andusomeran and 521,570 medically-attended COVID-19 disease episodes were eligible. *Myocarditis* In primary analyses comparing elasomeran/davesomeran or andusomeran (without co-administration with influenza vaccine) vs influenza vaccinated adults, there were 6 myocarditis cases observed on days 1 to 7 following elasomeran/davesomeran or andusomeran (weighted IR 32.49, 95% CI: 24.92 - 42.38 per 100,000 PY) and 33 cases following influenza vaccination (weighted IR 15.74, 95% CI: 11.27 – 21.56). The proportional hazards assumption was not met in this model, and Restricted Mean Survival Time (RMST) did not show an increased risk (RMST = 0.999999, 95% CI: 0.999997 - 1.000001). Analyses restricted to 01 Sep 2023 – 15 Jan 2024 showed a weighted HR of 5.51 (95% CI: 1.14 - 26.61), however there were only 2 and 8 cases of myocarditis identified following elasomeran/davesomeran or andusomeran and influenza vaccination, respectively, and should thus be interpreted with caution. Case counts were not sufficient to support subgroups examining young adults in the primary analyses. In secondary analyses including individuals receiving concomitant influenza vaccine with elasomeran/davesomeran or andusomeran, an increased risk was observed individuals ages 25-39 years (weighted HR = 4.40, 95% CI: 1.29 – 15.02). Self-controlled risk interval analyses were largely consistent with the primary analysis. No cases were observed in children following elasomeran/davesomeran or andusomeran in primary analyses, and one case was observed in secondary analyses. In analyses describing elasomeran/davesomeran or andusomeran and medically-attended COVID-19 episodes among adults, 13 and 106 myocarditis cases were observed, respectively, in the 1-7 days following vaccination (weighted IR 30.11, 95% CI: 20.75 - 43.80) and COVID-19 diagnosis (weighted IR of 251.70, 95% CI: 221.20 – 285.88). Across all subgroups of interest, the weighted IRs of myocarditis were substantially lower following

Study ID	Country	Study Title	Study results
			elasomeran/davesomeran or andusomeran compared to medically-attended COVID-19, which persisted with sensitivity analyses that restricted to 1-21- and 1-28-day risk windows. *Pericarditis* Pericarditis was observed in 2 cases observed on days 1 to 7 following elasomeran/davesomeran andusomeran (weighted IR 12.04, 95% CI: 7.36 – 18.60 per 100,000 PY) and 80 cases on days 1 to 7 following influenza vaccination (weighted IR 37.35, 95% CI: 30.19 – 46.02) in the primary analysis. Among adults, the estimated HR from the weighted Cox model indicated no increased risk of pericarditis in the 1-7 days following elasomeran/davesomeran or andusomeran compared to influenza vaccination overall (weighted HR= 0.35, 95% CI: 0.08 – 1.55) or in subgroups of interest. Sensitivity analyses extending the risk window to 1-21 and 1-28 days led to similar conclusions. Results from SCRI analyses were generally consistent with the primary analysis across risk windows. No increased risk of pericarditis was observed; however, a numerical elevation was present in females aged 40-54 in the 1–28-day risk window. An increased risk of pericarditis was suggested in the 1-28 days following vaccination in a secondary analysis comparing elasomeran/davesomeran or andusomeran administrations with or without influenza vaccinations to influenza vaccination alone, wherein an ERR of 3.58 (95% CI: 1.12 – 11.45) was observed in SCRI analyses. This was again based on small numbers (10 and 4 cases in the 1-28- and 1-42-day risk and control windows, respectively). Among children, there were no cases of pericarditis observed in the 1-28 days following elasomeran/davesomeran or andusomeran administration. In analyses describing elasomeran/davesomeran or andusomeran and medically-attended COVID-19 episodes among adults, the weighted IR in the 1-7 days following elasomeran/davesomeran or andusomeran administration was 30.15 (95% CI: 19.87 – 42.54) per 100,000 PY compared to a weighted IR of 196.94 (95% CI: 170.13 – 227.41) per 100,000 PY following medically-attended COVID-19. Similar to myocarditis, rates of pericarditis were consistently lower following elasomeran/davesomeran or andusomeran than medically-attended COVID-19 across subgroups of interest and in sensitivity analyses using 1-21- and 1-28-day risk windows. ***Other AESI*** Across all other AESI, observed incidence was similar following elasomeran/davesomeran or andusomeran compared to influenza.

Study ID	Country	Study Title	Study results
			Event rates were often elevated following a diagnosis of medically-attended COVID-19. Variation in increased rates of other AESI was observed across age and sex strata for both comparator 1 and 2 analyses among adults and children, however in many instances low event counts following elasomeran/davesomeran or andusomeran administration led to imprecise effect estimates that indicated no differential risk with either influenza or medically-attended COVID-19 episodes. No AESI met the threshold for conduct of SCRI analyses, and as such no SCRI analyses were performed for outcomes other than myocarditis and pericarditis. **Discussion** This post-authorisation safety surveillance study, which analysed 41 AESI (including myocarditis and pericarditis) among adults and children following vaccination with elasomeran/davesomeran or andusomeran, confirmed the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2 consistent with published literature. No clear, new safety findings emerged in primary analyses, and elevated incidence rates of several AESI following medically-attended COVID-19 supports a favourable benefit-risk profile.
mRNA-1273-P935	Australia	Vaccine effectiveness against COVID-19 variants in Victoria, Australia	**Summary:** **Aims:** To assess the relative vaccine effectiveness (VE) of 3 vs. 2 doses and 4 vs. 3 doses of monovalent COVID-19 vaccines in preventing hospitalisations and deaths in Victoria during Omicron variant-dominant periods. **Design:** Retrospective analysis of linked national and state-wide administrative health data (Dec 2021–Feb 2023) using a modified Cox model for time-varying VE stratified by age and vaccination status. Outcomes included hospitalisations and deaths. The study included individuals aged 5 years and older who had received at least 2 vaccine doses. **Vaccines included/excluded:** The study focused on monovalent vaccines for the analyses. The following vaccines were included: Comirnaty (Pfizer/BioNTech), Spikevax (Moderna), Vaxzevria (AstraZeneca), Covishield (AstraZeneca/Serum Institute of India), Nuvaxovid (Novavax), Covaxin (Bharat Biotech), Sputnik V (Gamaleya Research Institute), Janssen COVID-19 Vaccine (Johnson & Johnson), Sinopharm BBIBP-CorV, and Sinovac Coronavac. Bivalent vaccines were excluded from the analysis (e.g.,

Study ID	Country	Study Title	Study results
			Moderna Biv BA.1, Moderna Biv BA.4-5, Pfizer Comirnaty Biv BA.1, Pfizer Comirnaty Biv BA.4-5). **Results:** • Older Adults (≥65 years): VE against hospitalisation and death was highest after booster doses. For example, VE against death was 80.9% after 3 doses (BA.1/BA.2 period) and 64.7% after 4 doses (BA.4/BA.5 period). • Younger Adults (<65 years): VE was lower and less precise due to fewer hospitalisations and deaths in these groups. **Discussion** Booster doses significantly reduced severe COVID-19 outcomes, particularly in older adults.
mRNA-1273-P942	United States	Evaluating the effectiveness of mRNA-1273.815 against COVID-19 in the United States	This non-interventional, retrospective cohort study using administrative claims data was conducted to evaluate the effectiveness of mRNA-1273.815 in preventing COVID-19 associated hospitalisation and medically-attended COVID-19. **Study Design** This study compared individuals vaccinated with mRNA-1273.815 versus matched individuals ("referent") who had not received mRNA-1273.815 at the time of the corresponding matched individual's vaccination date. Data accrual occurred from 01 Sep 2022 to 21 Feb 2024 (latest available data), and individuals were eligible for cohort entry between 12 Sep 2023 (approval date for monovalent XBB.1.5) to 20 Feb 2024 (one day prior to end of last available data at time of analysis). Individuals were matched on age, sex, geographic region within the US, and race. The eligible follow-up period was from 20 Sep 2023 through 21 Feb 2024. Individuals were censored on occurrence of the outcome (for each outcome separately), receipt of a dose of any 2023-2024 COVID-19 vaccine (mRNA-1278.815 or other), death, end of follow-up, or disenrollment. Inverse probability of treatment weighting (IPTW) was used to adjust for potential confounding. Hazard ratios (HRs) were used to estimate VE in the weighted study population. The estimated VE and 95% CIs were reported as (1-HR) * 100%. **Results** The final study population included 903,349 vaccinated and 903,349 matched referent patients. The median follow-up was 111 days in the vaccinated group and 99 days in the referent group for the primary outcome. For the primary outcome of COVID-19 associated hospitalisation (coded in the primary position), the weighted

Study ID	Country	Study Title	Study results
			incidence rate per 1,000 person-years was 4.10 in the vaccinated group, and 9.34 in the referent group. The estimated VE was 56% (95% CI: 52%, 60%). A similar VE was observed across all subpopulations, ranging from 52% in immunocompromised patients, to 62% in patients aged 50-64 years. For the secondary outcome of medically-attended COVID-19, the estimated VE was 24% (95% CI: 22%, 25%). **Discussion** In this large-scale, real-world study involving over 900,000 vaccinated patients, the mRNA-1273.815 vaccine demonstrated protection against COVID-19-related hospitalisations and medically-attended COVID-19 relative to those not having received mRNA-1273.815. The current study included a substantial proportion of participants who had previously received COVID-19 vaccine doses, highlighting the incremental protection provided by the additional dose regardless of prior vaccination history.
mRNA-1273-P943	United States	Evaluating the effectiveness of mRNA-1273.815 against COVID-19 hospitalisation among adults aged ≥ 18 years in the United States	In this real-world study, we estimated the VE of mRNA-1273.815 (XBB.1.5-containing mRNA COVID-19 vaccine) administered between 12 Sep 2023 and 31 Dec 2023 at preventing COVID-19 illness requiring hospitalisation, as well as medically-attended COVID-19, in adults ≥ 18 years. **Study Design** This observational, matched cohort study used aggregated medical and pharmacy claims data from HealthVerity. Adults vaccinated with mRNA-1273.815 between 12 Sep 2023, and 31 Dec 2023, were followed through 26 Jan 2024. Vaccinated individuals were matched 1:1 with individuals unvaccinated with any 2023-2024 COVID-19 vaccine on demographic and clinical characteristics. The primary outcome was COVID-19 hospitalisation, and the secondary outcome was medically-attended COVID-19. IPTW and Cox-proportional hazards regression were utilised to estimate VE. **Results** The study included 1,272,161 vaccinated individuals matched 1:1 with unvaccinated, with a maximum follow-up of 128 days (median 84 days). The VE against COVID-19 hospitalisation was 51% (95% CI: 48%-54%). Subgroup analyses showed a VE of 56% (95% CI: 51%-61%) among adults 65 and older and 46% (95% CI: 39%-52%) in immunocompromised adults. For medically-attended COVID-19, the VE was 25% (95% CI: 24%-27%). Time-varying analyses

Study ID	Country	Study Title	Study results
			showed that while VE declined over time, the effect remained significant. **Discussion** During the 2023-2024 respiratory season, which included the emergence of JN.1, the mRNA-1273.815 vaccine significantly protected against COVID-19-related hospitalisations and medically-attended COVID-19 across diverse adult populations. These results support the continued use of updated COVID-19 vaccines to mitigate severe outcomes and maintain public health safety. The consistent effectiveness across subpopulations underscores the vaccine's role in protecting high-risk groups and the general adult population. The durability of effectiveness over time further emphasises the vaccine's importance in ongoing COVID-19 management.
mRNA-1273-P946	United States	Effectiveness of the 2023–2024 Omicron XBB.1.5-containing mRNA COVID-19 Vaccine (mRNA-1273.815) in Preventing COVID-19–related Hospitalisations and Medical Encounters Among Adults in the United States	This study aimed to evaluate the VE of mRNA-1273.815, a 2023–2024 Omicron XBB.1.5-containing mRNA COVID-19 vaccine, at preventing COVID-19–related hospitalisations and any medically-attended COVID-19 in adults. **Design** In a linked electronic health record–claims dataset, we identified US adults (≥18 years) who received the mRNA-1273.815 vaccine (exposed cohort) between 12 Sep and 15 Dec 2023, matched 1:1 to individuals who did not receive a 2023–2024 updated COVID-19 vaccine (unexposed cohort). Cohorts were balanced using IPTW on demographics, vaccination and infection history, and underlying medical conditions. Study cohorts were followed until 31 Dec 2023 for COVID-19–related hospitalisations and medically-attended COVID-19. Cox regression was used to estimate HRs and VE. Subgroup analyses were performed for adults ≥50 years, adults ≥65 years, and individuals with underlying medical conditions. **Results** Overall, 859 335 matched pairs of mRNA-1273.815 recipients and unexposed adults were identified. The mean (standard deviation) age was 63 (16) years. More than 60% of individuals in both cohorts had an underlying medical condition. Among the overall adult population, VE was 60.2% (95% CI, 53.4–66.0) against COVID-19–related hospitalisation and 33.1% (30.2–35.9) against medically-attended COVID-19 over a median follow-up of 63 (interquartile range: 44–78) days. VE estimates by age and underlying medical conditions were similar.

Study ID	Country	Study Title	Study results
			Discussion These results demonstrate the significant protection provided by mRNA-1273.815 against COVID-19–related hospitalisations and any medically-attended COVID-19 in adults, regardless of vaccination history, and support CDC and Prevention recommendations to stay up to date with COVID-19 vaccination to prevent COVID-19–related outcomes, including hospitalisations.

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

Study ID	Country	Study Title	Status
mRNA-1273-P901	United States	Real-world study of the effectiveness of the Moderna COVID-19 Vaccine	For this observational cohort study carried using data from Kaiser Permanente Southern California, the most recent interim study analyses. The final study report is expected in Apr 2025.
mRNA-1273-P904	Denmark, Norway, Spain, United Kingdom	Post-Authorisation Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU	For this observational cohort study carried using large administrative databases in Denmark, Norway, Spain, and the UK, interim analyses described in the Mar 2023 interim study update. The final study report is expected in Mar 2025.
mRNA-1273-P905	Denmark, Norway, Spain, United Kingdom	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in 4 European countries	For this observational cohort study carried using large administrative databases in Denmark, Norway, Spain, and the UK, with feasibility counts were described in the Mar 2023 interim study update. The final study report is expected in Mar 2025.
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 SARS-CoV-2	The overarching goal of this study is to characterise the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and elasomeran bivalent vaccination. Analyses are ongoing, and the final study report is expected in Jun 2025.
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 characterise presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (elasomeran). An interim report was completed 31 Oct 2024. Cases of myocarditis identified

Study ID	Country	Study Title	Status
			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, however no relevant safety information was identified at this time. The final study report is expected in Oct 2028.
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 (XBB.1.5)	The study was amended to remove the optional long-term follow-up for Part A on 08 Jan 2024, and amended to remove the optional long-term follow-up for Part B on 07 May 2024. The study includes 2 parts: Part A: 2022-2023 mRNA COVID-19 Bivalent Vaccine (Original and Omicron BA.4/BA.5) A six-month observational prospective study, to investigate antibody levels with respect to time since receiving a bivalent COVID-19 booster dose. The original protocol was dated 04 Jan 2023. At this time, no safety findings have been identified. The protocol was amended on 25 Jul 2023 to add Part B: 2023 mRNA COVID-19 Updated Vaccine (XBB.1.5). A six-month observational prospective study, to investigate antibody levels with respect to time since receiving an updated monovalent COVID-19 vaccine (XBB.1.5).
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. Enrolment for this study is ongoing. No safety findings have been identified that differ from the known safety profile.
mRNA-1273-P929	Japan	Special Use Results Survey: Assess the safety of Moderna vaccines targeting SARS-CoV-2 in the Japanese paediatric population	The overarching aim of the study is to characterise the safety of Moderna vaccines targeting SARS-CoV-2 in the paediatric population in Japan. No safety findings have been identified to date.
mRNA-1273-P934	United States	Effectiveness Comparison Between the 2 mRNA Monovalent COVID-19	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.

Study ID	Country	Study Title	Status
		Vaccine Boosters in Medicare Fee-For-Service	**Study Design** This retrospective cohort study used Medicare Fee-For-Service (FFS) claims data from Oct 2020 through Aug 2022. Individuals who received a BD of mRNA-1273 (2.4 million) or BNT162b2 (1.6 million) after ≥1 dose of mRNA-based primary vaccine series were followed from 14 days after index until receipt of an additional BD, outcome occurrence, end of continuous enrolment, or end of study period. IPTW was applied to adjust for baseline confounding. Comparative VE against COVID-19 hospitalisation (principal or secondary diagnosis) and differences in total expenditures during hospitalisation and up to 90 days post-discharge were estimated. **Results** After IPTW, individuals who received mRNA-1273 as a booster had a reduced risk of hospitalisation (HR 0.789; 95% CI: 0.766, 0.813) compared to BNT162b2. Differences in total expenditures during hospitalisation and up to 60 days post-discharge between mRNA-1273 versus BNT162b2 recipients were -$723 (USD) or -1.8% (p=0.08), showing savings compared with BNT162b2. In sensitivity analysis, differences in total expenditures during stay up to 30 days post-discharge were -$678 (-2.4%, p=0.02); up to 90 days post-discharge were $10 (0.0%, p=0.99); and for hospitalisations with COVID-19 as principal diagnosis (up to 60 days post-discharge) were -$2,224 (-6.3%, p<0.001), respectively. **Discussion** mRNA-1273 administered as a first booster was more effective than BNT162b2 in preventing COVID-19 hospitalisations and associated with lower medium-term Medicare expenditures for those hospitalised.
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 completed the primary series of mRNA-based COVID-19 vaccines. A study report is expected to be complete in 2025 Q1.

Study ID	Country	Study Title	Status
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 2025 Q1.
mRNA-1273-P941	United States	mRNA1273 Bivalent BA4/5 US Nursing Home comparative effectiveness study	The aim of this study is to assess effectiveness of mRNA-1273.222 booster vaccination among nursing home residents. A study report is expected to be complete in 2025 Q1.
mRNA-1273-P949	United States	Observational Study to Assess Maternal and Infant Outcomes Following Exposure to Updated Moderna Vaccines Targeting SARS-CoV-2 During Pregnancy	Retrospective cohort study assessing whether receipt of updated Spikevax formulations (mRNA-1273.222 or mRNA-1273.815) during pregnancy is associated with an increased rate of pregnancy complications, adverse pregnancy outcomes, or adverse infant outcomes. Analyses are currently ongoing.

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 SPIKEVAX (elasomeran) in the Kingdom of Saudi Arabia (KSA)	The overarching aim of this study is to characterise 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 characterise 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-P951	United States	Post-marketing safety of the Moderna COVID-19 vaccine following the 2024/2025 strain change in the United States	Retrospective cohort study assessing whether the risk of myocarditis, pericarditis and other safety topics of interest for active surveillance among persons vaccinated with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is higher than the expected risk in a similar population in absence of this vaccine. A SAP is currently under review.

Rapporteur assessment comment:

8 Non-Interventional Studies were completed during the reporting period, 13 are ongoing, and 3 are planned as of DLP of the PBRER.

Exposure to Spikevax during pregnancy

mRNA-1273-P919 (completed NIS) was an observational post-marketing safety study evaluating the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to SPIKEVAX during pregnancy.

The study showed no increased risks for infant outcomes (including congenital malformations, neonatal encephalopathy, SGA, hospitalisation due to infections (including COVID-19) in the first year of life), stillbirth, or eclampsia. However, small increases were observed in rates of pre-

eclampsia, gestational hypertension, and gestational diabetes. Safety of Moderna COVID-19 will be further investigated in ongoing studies mRNA-1273-P905 and mRNA-1273-P951.

Please refer to section 2.2.4 and 2.3.1.3.1 of this assessment report for more information on use in pregnancy.

For the remaining studies, no new safety or efficacy problems were identified.

The provided information is acknowledged.

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: Fukushima Community Vaccine Study.

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

Summary: For this study enrolment is complete, the first patient first visit was on 31 Aug 2023, and study ended 31 Mar 2024. The total number of subjects enrolled was 1,353. The study assessed a range of systemic and localised AEs following the second, third, and fourth doses of COVID-19 vaccines. Fever, fatigue, and local pain were among the most frequently reported AEs. The study reported a consistent pattern where younger individuals, females, and those with a history of allergies were more likely to experience AEs from both Moderna and Pfizer vaccines. The analysis does not specify separate adverse event details or immune responses (IgG and T-spot values) for Pfizer and Moderna within each group but combines them under overall group results.

Additionally, this study aimed to understand the longitudinal AEs patterns after a fourth dose of the COVID-19 vaccine of 1,175 participants (of which 903 participants received Moderna vaccines) using a latent class analysis. The CSR was published on 18 Mar 2024. While this study explored various factors associated with the occurrence of adverse events, it did not evaluate Adverse Events of Special Interest (AESI). No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: A survey of COVID-19 vaccine acceptance across 23 countries in 2023.

Title: A survey of COVID-19 vaccine acceptance across 23 countries in 2023.

Summary: For this survey enrolment is complete, the first patient first visit was on 30 Sep 2023, and study ended 01 May 2024. The total number of subjects surveyed were 23,000. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: Predictors of Hospitalisation.

Title: Predictors of Hospitalisation and Severe Disease due to Breakthrough COVID-19 Infection in Fully Vaccinated Individuals.

Summary: For this study enrolment is complete, the first patient first visit was on 01 Jun 2023, and study ended 15 Dec 2023. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER. Data from 20,584 emergency department visits between 15 Dec 2020 and 19 Dec 2021 were analysed.

Short Title: Vaccine uptake.

Title: Enhancing COVID-19 immunisation uptake amongst culturally and linguistically diverse populations.

Summary: For this study enrolment is complete, the first patient first visit was on 01 Nov 2023, and the final report date was 11 Nov 2024. The total number of subjects enrolled was 24 (qualitative interviews). No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

Short Title: VI

Title: Update of HS-CoVulnerability Index (VI) d score to assess eligibility and prioritisation for anti-COVID first ever vaccination or booster.

Summary: The first patient first visit was on 01 Feb 2023 and study ended on 01 Aug 2024. A total of 2,192 patients were included in secondary analysis. No AEs were reported. 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 on 26 Oct 2022 and study ended 31 Aug 2024. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

Short Title: ARNCOMBI

Title: Multicentre, Randomised, Open-label Trial Comparing the Immunological Efficacy of a Vaccine Regimen Combining 2 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 on 22 Nov 2022 and study ended 30 Aug 2024. The total number of subjects enrolled was 414. No AEs were reported. No significant safety findings were 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 on 01 Aug 2022 and study ended 01 Aug 2024. The total number of subjects enrolled was 917. No AEs were reported. No significant safety findings were 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 on 01 Dec 2022 and study ended 01 Nov 2024. The total number of subjects enrolled was 320. 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: PARACOV Study in Japan.

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

Summary: The study enrolment commenced on 06 Nov 2023 and completed 31 Mar 2024. The total number of subjects enrolled were 109. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER. The expected study end date in 31 May 2025.

Short Title: BE-Direct

Title: Determining the Immune Response in Ethnic minority healthcare workers to COVID-19 infection and Vaccination –Autumn 2022 COV-19 boosters (a sub-study of UK-REACH).

Summary: Planned enrolment for this study is not reported, first patient first visit was on 12 Sep 2023 and expected study end date is 31 Oct 2025. The total number of subjects enrolled was 384. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

License partner studies

Completed 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, randomised study to access the safety and immunogenicity of a SARS-CoV-2 variant vaccine (mRNA-1273.351) in naïve and previously vaccinated adults.

Country: US

Dosing details: In this study, dosing was conducted in 2 different arms and further 2nd arm was divided into 8 arms according to the doses as follows:

1. ARM 1A: 50 µg 1273.351,
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 CSR has been finalised for cohort 1 on 12 Jan 2024 and for cohort 2 on 13 Feb 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.

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 BD 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. 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 has been completed. The CSR was completed for cohort 1 on 21 Oct 2022 and for the addendum on 18 Oct 2023.

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 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 Merck, Sharp and Dohme (MSD):

Study or Protocol Number: V110-911-00:

A Phase 3, Randomised, 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 BD 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 received 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 received placebo (blinded) in the left arm 30 days later at Visit 3 (Day 30). Participants enrolled in the non-concomitant groups received placebo (blinded) in the left arm and mRNA-1273 (openlabel) in the right arm on Day 1, and then received 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. The CSR was finalised on 01 Feb 2024 and the CSR synopsis was submitted to FDA with Investigational New Drug (IND) annual report on Aug-2024.

Study conclusions:

Immunogenicity for V110:

• Serotype-specific OPA GMTs at 30 days postvaccination with V110 were generally comparable when V110 was administered concomitantly or nonconcomitantly with mRNA-1273.

• SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V110 compared with mRNA-1273 administered with placebo.

Immunogenicity for V114:

• Serotype-specific OPA GMTs at 30 days postvaccination with V114 were generally comparable when V114 was administered concomitantly or nonconcomitantly with mRNA-1273.

• SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V114 compared with mRNA-1273 administered with placebo.

Concomitant administration of either V110 or V114 with mRNA-1273 is generally well-tolerated, with a safety profile comparable to V110 or V114 alone.

Ongoing trials

Sponsored by DMID of National Institute of Allergy and Infectious Diseases (NIAID):

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 (154); mRNA-1273-50 µg (143), 1273-211-100 µg (93), 1273.222-50 µg (23).

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 cohort 2 CSR is estimated early 2025.

Protocol or Study Number: mRNA-1273-P511/22-0004:

Phase 2 Clinical Trial to Optimise 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 Haematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumours 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 2024, 19 subjects were exposed to mRNA-1273. Start date for this study was 30 Apr 2021 and estimated study completion date is 31 Dec 2025. No significant safety findings in this ongoing CT have been identified during the reporting period.

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 2 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 12,342 subjects. Actual recruitment end date was 12 Nov 2022 and last subject visit was on 09 May 2023. One hundred and 15 AEs have been reported, of which 18 were Grade 1 related AEs and 4 were Grade 2 related AEs. Seventeen SAEs were reported, all of which were assessed as not related to the study product. Seven AEs of special interest have been reported, 4 of which were related to study product (Grade 1 and 2). Three unrelated events met seriousness criteria. 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 met criteria for severe disease. 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 MSD:

Study or Protocol Number: V503-076-00:

A Phase 3, Multicentre, 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 1601 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 2nd quarter of 2025. No new safety concerns, and no regulatory actions taken for safety reasons during the reporting period. There is no information that would affect the safety profile of the product with no AESIs identified in trial participants through the reporting period. There is no new efficacy, effectiveness, or immunogenicity information.

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 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.

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 19: 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. In the UK, the SARS-CoV-2 JN.1 mRNA (mRNA-1273.167; JN.1) variant formulation was approved on 02 Sep 2024. However, it was noted that after the JN.1 approval, Moderna continued to receive spontaneous cases from the UK (MHRA) which were coded to the SPIKEVAX 2023-24 (XBB.1.5) variant formulation. Upon further investigation, it became evident that the MHRA Yellow card reporting site was not updated to include the JN.1 product as an option for selection for reporters. The issue was raised with the MHRA and subsequently their website was updated to include JN.1 at the top of their drop-down list for selection. Internally, the Moderna case processing added the event of "discontinued product administered" to identify these cases.
Methods	The ModernaTx, Inc. GSDB was searched using the standard MedDRA query (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	**Medication Errors Involving Use of Elasomeran** During this review period, the MAH received 805 cases (4,074 events) of Medication errors with 373 serious cases (1,286 serious events), and 11 cases with a fatal outcome. There were 601 medically confirmed cases involving elasomeran. The most frequently reported PTs were "No adverse event" (347; 8.5%), followed by "Expired product administered" (332; 8.1%) and Interchange of vaccine products (236; 5.8%). During the review period, there were 407 cases (2,672 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (127; 4.8%), followed by "Drug ineffective" (89; 3.3%) and "Fatigue" (68; 2.5%). **Medication Errors Involving Use of Elasomeran/Imelasomeran**

	During the review period, the MAH received 60 cases (182 events) of Medication errors with 19 serious cases (48 serious events), and 1 case with a fatal outcome. There were 59 medically confirmed cases involving elasomeran/imelasomeran. The most frequently reported PTs were Expired product administered", "No adverse event" and "Product expiration date issue" (38 events; 20.9% each). During the review period, there were 58 cases (83 events) of medication error reported with an associated AE. The most frequent AE reported were "Product expiration date issue" (38; 45.8%) and "Myocardial injury" (12; 14.5%). The 12 cases were described in an abstract with limited information. All were women with mild symptoms with good outcome. There was insufficient information presented to make any conclusions from the report. **Medication Errors Involving Use of Elasomeran/Davesomeran** During the review period, the MAH received 151 cases (207 events) of Medication errors with 9 serious cases (24 serious events), and no cases with a fatal outcome. There were 143 medically confirmed cases involving elasomeran/davesomeran. The most frequently reported PTs were "Medication error" (115; 55.6%) followed by "Expired product administered" (25; 12.1%) and "No adverse event" (17, 8.2%). During the review period, there were 19 cases (30 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID- 19" and "Drug ineffective" (7 events; 23.3% each), followed by "Irritability" (6; 20.0%). **Medication Errors Involving Use of Andusomeran** During the review period, the MAH received 3,607 cases (8,918 events) of Medication errors with 284 serious cases (697 serious events), and 3 cases with a fatal outcome. There were 3,237 medically confirmed cases involving andusomeran. The most frequently reported PTs were "No adverse event" (3,002; 33.7%) followed by "Expired product administered" (2,478; 27.8%), and "Discontinued product administered" (392; 4.4%). During the review period, there were 609 cases (1,672 events) of medication error reported with an associated AE. The most frequent AE reported were "Pain in extremity" (141; 8.4%) followed by "Headache" (95; 5.7%), and "Pyrexia" (85; 5.1%). **Medication Errors Involving Use of SARS-CoV-2 JN.1 mRNA** During the review period, the MAH received 1,199 cases (2,427 events) of Medication errors with 3 serious cases (8 serious events), and 1 case with a fatal outcome. There were 1,186 medically confirmed cases involving SARS-CoV-2 JN.1 mRNA. The most frequently reported PTs were "No adverse event" (1,190; 49.0%) followed by "Expired product administered" (1,162; 47.9%). During the review period, there were 9 cases (13 events) of medication error reported with an associated AE. The AE reported were Arthralgia, Back pain, Cerebral infarction, Headache, Increased tendency to bruise, Inflammation, Pain, Pain in extremity, Product expiration date issue, Pyrexia, Rash Macular, Seizure, and Swelling (1 event each; 7.7%). **Medication Errors Involving Use of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula**

	During the review period, the MAH received 380 cases (1,106 events) of Medication errors with 2 serious cases (3 serious events), and no cases with a fatal outcome. There were 372 medically confirmed cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The most frequently reported PTs were "No adverse event" (369; 33.4%) followed by "Wrong product administered" (213; 19.3%), and "Underdose" (121; 10.9%). During the review period, there were 12 cases (40 events) of medication error reported with an associated AE. The most frequently reported AE was "Malaise" (3; 7.5%). **Medication Errors Involving Use of Unspecified SPIKEVAX COVID-19 Vaccine-SPIKEVAX (NOS)** During the review period, the MAH received 64 cases (196 events) of Medication errors with 14 serious cases (45 serious events), and no cases with a fatal outcome. There were 52 medically confirmed cases involving SPIKEVAX (NOS). The most frequently reported PTs were "No adverse event" (37; 18.9%) followed by "Interchange of vaccine products" (18; 9.2%) and COVID-19 immunisation (14; 7.1%). During the review period, there were 27 cases (65 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (8; 12.3%) and "Drug ineffective" (5; 7.7%).
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 beyond the primary series or any interchange of other COVID-19 vaccine products. There appeared to be no difference for the nature of reported medication errors and importantly associated AEs among marketed Moderna vaccines targeting SARS-CoV-2 in general. AEs associated with reported medication errors were usually known to the safety profile, and no events were associated with significant harm to the patient due to the medication error. A few cases involving medication errors described fatal events; however, based on a detailed review of the case narratives, no evidence was found to suggest that the medication errors directly contributed to the fatal outcomes. As stated in the background, during the review period, the MAH noticed that after SARS-CoV-2 JN.1 mRNA approval, the MAH continued to receive andusomeran formula cases from the MHRA. Upon further investigation it appeared that the MHRA Yellow card reporting site had not been updated to include the JN.1 product as an option for selection for reporters. The MHRA informed that their sites had been updated approximately 1 month after JN.1 approval to include JN.1 at the top of their drop-down list for selection. In total, 428 cases from the UK were mistakenly reported by the MHRA as related to andusomeran instead of SARS-CoV-2 JN.1 mRNA. In 367 of these cases, MAH added the event of "Discontinued product administered" for purposes of identification.
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.

The information provided is acknowledged.

1.3.5.3.3. Medical device incidents

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

1.3.5.4. Non-clinical data

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

1.3.5.5. Literature

A global literature search and analysis were performed utilising Embase, Medline and PubMed databases for the reporting period 18 Dec 2023 to 17 Dec 2024. The literature search was performed for the publications related to Spikevax 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 (Prefilled Syringe), Spikevax 2024-2025 Formula, SARS-CoV-2 JN.1 mRNA, Spikevax KP.2, SARSCoV-2 JN.1 mRNA, mRNA COVID-19 vaccine and other elaborated key terms. 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 Dec 2023 to 17 Dec 2024. Please find the journal list under Appendix 13.3.

During the reporting period, there were a total of 33,726 abstracts retrieved and upon removal of duplicates, 17,071 abstracts reviewed from the global searches. There were 20,558 local journal searches performed, and 124 abstracts were reviewed. From all the searches performed, there

were no articles that had new significant safety information but there were 4 articles identified with relevant safety information and these are summarised below:

Article Summary: This article describes a comparative retrospective observational cohort study, leveraging deidentified data of N3C (a large dataset managed by the National Institutes of Health (NIH) with over 20 million individuals) from 11 Dec 2020 (COVID-19 vaccine introduction) to 01 Aug 2023 [8]. The authors identified 2 cohorts defined as the vaccination group and the infection group based on patients' index events, either COVID-19 vaccination or infection. The primary follow-up period was 30 days after index event, with secondary analyses conducted using follow-up periods of 60 and 90 days.

For the vaccination group, the inclusion criteria included: (1) patients receiving the first dose of COVID-19 vaccines between 11 Dec 2020, and 01 Aug 2023. Only the first dose was considered for patients who received multiple doses. (2) patients having never been diagnosed with COVID-19 infection or tested positive for COVID-19 before the index date or during the follow-up period.

For the infection group, the inclusion criteria included: (1) patients who were first diagnosed with COVID-19 infection or testing positive for COVID-19 between 11 Dec 2020, and 01 Aug 2023; (2) patients who had never received COVID-19 vaccines before the first infection or during the follow-up period. Patients were censored at death or the end of the follow-up period. Patients who were (1) ≤18 years old, (2) diagnosed with end-stage kidney disease, or (3) with diagnostic AKI codes within the 30 days before the index date were excluded.

There were 20,905,766 subjects reviewed and after inclusion and exclusion criteria were applied, the vaccinated cohort had 2,953,215 subjects while the infected group had 3,616,802. The absolute risk of AKI was 0.66% in the vaccination group versus 4.88% in the infection group. There were significant differences between the baseline characteristics between the 2 cohorts, including age, race, gender, previous AKI, HBP, DM, heart failure, CVD, and obesity. After adjusting for various confounders, COVID-19 infection was associated with a significantly higher risk of AKI than COVID-19 vaccination (aHR = 10.31, $P < 0.001$). The authors conclude that the study demonstrated that COVID-19 vaccination is associated with a significant lower AKI risk compared to COVID-19 infection.

There were limitations to the study, such that the findings need to be interpreted with caution. Inherent weaknesses of Electronic Health Record (EHR) data posed challenges, such as potential inaccuracies, missing or incomplete records about COVID-19 vaccination and infection in N3C, and variations in data quality. Secondly, despite the extensive data available in N3C, it represents only a portion of the country rather than its entirety, limiting the generalizability of the authors findings. Third, the study design was retrospective and observational, introducing potential biases due to unmeasured confounders and lacking the ability to establish causal relationships between outcomes and exposures. However, the N3C dataset provides the largest ever EHR dataset related to COVID-19 and a unique opportunity to investigate the vaccine AEs and compare them with the occurrences of the diseases or symptoms following infections. It is critical that the COVID-19 vaccination campaigns significantly limited the impact of the COVID-19 pandemic. The comparison AKI rates provide a unique perspective examining the risk of a health outcome following vaccination or natural infection.

Company comment: In spite of its limitations, the article provides compelling data demonstrating that COVID-19 vaccination has a much lower risk of a temporal association with AKI than COVID-19 infection. However, it does not provide direct data on elasomeran.

Article Summary: This article describes a population-based retrospective cohort study and sibling matched analysis in Ontario, Canada's most populous province with about 15.1 million residents and 140,000 live births each year [9]. The authors primary objective was examining the

association between maternal mRNA covid-19 vaccination during the first trimester of pregnancy and the prevalence of major congenital anomalies in offspring. The primary cohort included singleton live births after >20 weeks' gestation with an expected birth date between 16 Oct 2021 and 01 May 2023. The authors examined 174,296 singleton live births: 34,181 (20%) born to mothers who received one or 2 doses of an mRNA covid-19 vaccine in the first trimester and 34,951 (20%) born to mothers who did not receive a vaccine before or during pregnancy. The sibling matched analysis included 13,312 infants exposed to a Covid-19 vaccine in the first trimester and 15,089 matched older siblings with no reported in-utero exposure to a Covid-19 vaccine. The primary outcome was major congenital anomalies, overall and grouped by specific organ systems, diagnosed within 28 days of birth.

The authors found that the major congenital anomalies were present in 832 (24.3 per 1000 live births) infants exposed to an mRNA COVID-19 vaccine in the first trimester compared with 927 (26.5 per 1000 live births) infants not exposed to a vaccine, resulting in an adjusted prevalence ratio (vaccinated/not vaccinated) of 0.89 (95% CI 0.79 to 1.01). Major congenital anomalies were present in 283 (21.3 per 1000 livebirths) and 343 (22.7 per 1000 live births) infants exposed to an mRNA covid-19 vaccine in the first trimester and their older siblings not exposed to a vaccine, respectively (adjusted prevalence ratio 0.91, 95% CI 0.77 to 1.07). Results were similar across a range of subgroup and sensitivity analyses.

The authors concluded that mRNA Covid-19 vaccination during the first trimester of pregnancy was not associated with an increase in major congenital anomalies in offspring, overall or grouped by organ system, when compared to non-vaccinated mothers, as well as compared to matched older siblings. The strengths of the article were the large cohort size: however, there were limitations that included the inability to rule out residual confounders such as smoking or excessive alcohol intake. In addition, outcomes were assessed at 28 days rather than a longer period. Finally, the authors only looked at live births and did not include stillbirths or spontaneous abortions.

Company comment: This study supports the safety of mRNA COVID-19 vaccination during early pregnancy, demonstrating no increased risk of major congenital anomalies. Findings align with previous research on the topic and provide reassurance for public health recommendations encouraging vaccination during pregnancy.

For additional information, see topic of pregnancy in Appendix 12.10.

Article Summary: For detailed summary of the article [10], please see the topic of Myocarditis and Pericarditis in Section 16.3.1.2.

Company Comment: please see the topic of Myocarditis and Pericarditis in Section 16.3.1.2.

Article Summary: This article describes a retrospective study with a primary objective to analyse the clinical features and evolution of patients who develop Chronic Urticaria [11]. The authors asked a group of 16 allergists to identify eligible patients with chronic urticaria (CU) after receiving a dose of COVID-19 mRNA vaccine. Subjects were asked for consent, and when given, were sent a link to online questionnaire in 2022. All patients received a link to a second online questionnaire in 2023. Additional objectives included defining the contribution of COVID-19 infection to the onset of CU, and to compare the sensitisation rate against the vaccine in CU patient with a control population. To that end, blood tests were performed in subset of 50 patients, and their results were compared with individuals without a history of urticaria (N=135).

The authors found that among the 111 identified CU patients, they were able to contact 110, and 88 responded to our first survey. Of these 88 patients, 66% were middle-aged female (median age 41, IQR 35-48, Fig. 1b). In 89% of cases, CU started after the booster shot and not after primary vaccination. As of Jun 2022, CU remained active in 81% of these cases. The authors found that most-vaccination CU occurs after a median interval of 10 days and significantly more after the

Spikevax booster, affecting middle-aged individuals (median age 41, and 66% females). In 2023, CU was still active in 53% of the cases. Inducible forms of CU, primarily dermographism, are reported in 54% (2022) and 61% (2023) of the cases.

Basophil Activation Test (BAT) positivity was not specific to CU, anti-nucleocapsid positivity, or atopy but is significantly associated with higher anti-spike neutralising activities and younger age. Importantly, 4 CU patients received a BD, and all tolerate the additional dose of mRNA vaccine with no disease exacerbation/recurrence.

The authors concluded that the Spikevax booster induces anti-vaccine Immunoglobulin E (IgE) independently of CU, the latter being not directly associated with COVID-19 infection nor atopy. The tolerance to a new booster in 4/4 patients suggests that the mRNA vaccines potentially indirectly trigger CU in predisposed individuals. Limitations of this study include a retrospective design in which subjects were identified by a non-random collection of allergists from their practices. Further bias could be introduced as only 88 of the 111 potential subjects participated in the first survey. The small sample size and nature of subject identification limit generalizability of the finding.

Company Comment: The study postulates a potential link between mRNA COVID-19 vaccination and CU in predisposed individuals but does not establish direct causality. The lack of a control group of non-vaccinated individual for the primary analysis limits the applicability of the finding. And the authors note the majority of the selected subject were exposed to Spikevax, it failed to provide a general background exposure to different background rates to contextualise this finding.

1.3.5.5.1. RESPONSE TO EMA ON ISSUES TO BE ADDRESSED IN THE NEXT PSUR RELATED TO PROCEDURE EMEA/H/C/PSUSA/00010897/202312

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.

MAH's Response:

The article (Marchand et al.), identified by the assessors, was reviewed by the MAH and determined as an article with no new and significant safety information. The Rapporteur reviewed the MAH's assessment and confirmed that no further action is warranted. As this article was retrieved through the MAH's routine literature search activities and was assessed accordingly, the current literature search strategy is considered adequate, and no modifications are proposed at this time.

The MAH confirms that its existing practice includes presenting all relevant literature publications with new and significant safety findings in the PSURs, along with a scientific assessment and critical analysis of the authors' conclusions. This practice will continue in future PSURs, including literature articles where the MAH disagrees with the authors' conclusions.

Rapporteur assessment comment:

During the reporting interval, the MAH reviewed 17,071 abstracts retrieved from global searches (Embase, Medline, PubMed), and 124 abstracts retrieved from local journal searches (not indexed in Medline or Embase). The search strategy is presented in PSUR appendix 13.

The MAH included four articles with relevant safety information in section 11 of the PSUR. However, according to the MAH, no new significant safety information was identified in the literature reviewed during the reporting interval.

The rapporteur agrees that no new significant safety information is identified in three of the four presented articles, regarding acute kidney injury, major congenital anomalies, and chronic urticaria. However, as also noted in PSUR table 16-12, the publication regarding vaccine-associated myocarditis, by Jain SS et al. (2024) contributes new and significant safety information.

Acute Kidney Injury (AKI)

Pan et al. (2024): A large-scale cohort study found that the risk of AKI within 30 days was significantly lower after COVID-19 vaccination (0.66%) compared to COVID-19 infection (4.88%), with an adjusted Hazard Ratio of 10.31, P<0.001). Although direct data on elasomeran is not provided, the incidence of AKI among recipients of the mRNA vaccines (BNT162b2 [Pfizer] and mRNA-1273 [Moderna]) was 0.6%, compared to 0.9% among recipients of the viral vector vaccine (Ad26.COV2.S [Johnson & Johnson]).

Major congenital anomalies

Jorgensen et al. (2024): A population-based retrospective cohort study and sibling matched analysis found that first trimester vaccination was not associated with an increase in major congenital anomalies overall or grouped by organ system.

The study found that 24.3 per 1,000 live births whose mothers were vaccinated with an mRNA COVID-19 vaccine in the first trimester had major congenital anomalies, compared to 26.5 per 1,000 among unvaccinated pregnancies (adjusted prevalence ratio 0.89, 95% CI: 0.79–1.01). In the sibling comparison, 21.3 per 1,000 vaccinated babies had anomalies versus 22.7 per 1,000 of their older unvaccinated siblings (adjusted prevalence ratio 0.91, 95% CI: 0.77–1.07).

Chronic urticaria (CU)

Schwab et al. (2024): A retrospective observational study evaluated patients with CU after COVID-19 mRNA vaccination. The study found that 53% had persistent symptoms at one year. There was no direct correlation between CU onset and PEG sensitization, atopy, or concurrent Omicron infection. Four patients were re-exposed to mRNA vaccines without symptom exacerbation, suggesting the vaccine may act as a trigger in predisposed individuals, rather than a direct cause. The study is limited by the lack of a control group of non-vaccinated individuals for the primary analysis. The authors recommend future research should focus on characterizing the nature of the auto-antibody response and comparing it to CU cases that are temporally unrelated to mRNA vaccines.

Vaccine-associated myocarditis

Please refer to section 2.3.1.1.2 of this assessment report for more information. However, it should be noted that no regulatory actions are considered necessary at this point in time.

The MAH response to EMA on item 2 requested in procedure EMEA/H/C/PSUSA/00010897/202312 is endorsed.

1.3.5.6. Other periodic reports

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

2. Signal and risk evaluation

2.1. Summary of safety concerns

Summary of safety concerns valid at the beginning of the reporting period (as per RMP v8.1 approved on 23-10-2023)	
Important identified risks	• Myocarditis • Pericarditis
Important potential risks	• None
Missing information	• Use in pregnancy and while breastfeeding • Long-term safety

Summary of safety concerns valid at the end of the reporting period (as per RMP v9.1 approved on 10-09-2024)	
Important identified risks	• Myocarditis • Pericarditis
Important potential risks	• None
Missing information	• Use in pregnancy and while breastfeeding • Long-term safety

Rapporteur assessment comment:

The provided summary tables of safety concerns are acknowledged. However, the MAH should note that it is sufficient to list only the safety concerns that were applicable at the end of the reporting period.

Endorsed.

2.2. Signal evaluation

- Tabular overview of signals: new, ongoing or closed during the reporting interval 18-12-2023 to 17-12-2024.

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Cerebral venous thrombosis (CVT)	17-09-2024 (request received from the Therapeutics Goods Administration (TGA) Health authority Australia	Closed	Not known	HA request from TGA	Following a signal evaluation in Singapore the MAH was mandated to include CVT to their product information in Singapore	External safety database, epidemiological studies, global safety database	Refuted No update to the Australian product information Routine pharmacovigilance activities are continued
Renal failure	25-12-2023 (request received from the Saudi FDA)	Closed	Not known	HA request from the Saudi FDA	The Saudi FDA requested the following: "to submit a comprehensive signal evaluation report within 60 days regarding the potential risk of Renal Failure with the use of SPIKEVAX® (mRNA-1273; elasomeran) The evaluation should include, but not be limited to, background rate, results from clinical trials database, epidemiology, preclinical findings, PASS, global pharmacovigilance database medical literature, estimated	A cumulative review of renal failure was performed and submitted for assessment at the Saudi FDA.	Refuted No update to the Saudi Arabic product information Routine pharmacovigilance activities are continued

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					reporting rate, integrated benefit-risk analysis, conclusion and recommendation.		
Erectile dysfunction	13-02-2024 (request from the Rwandan FDA)	Closed	Not known	HA request from the Rwanda FDA	The Rwanda FDA requested "more evidence and further investigation" on the signal.	Clinical trial data, post-marketing data, literature search	Refuted No update to the Rwanda product information Routine pharmacovigilance activities are continued
Pre-eclampsia, gestational hypertension and GD	21-08-2024 (signal raised based on data retrieved from the PASS mRNA-1273-P919	Closed	Not known	Signal raised based on retrieved data from the PAS study mRNA-1273-P919	A statistically significant increase in the risk of pre-eclampsia, gestational hypertension and gestational diabetes was found in the PAS study.	Clinical trial data, non-clinical data, post-marketing data, literature search	Refuted No update to the product information Routine pharmacovigilance activities are continued
Ischaemic stroke	27-06-2024 (request from the CDC following the ACIP meeting in June 2024)	Closed	Not known	HA request from the CDC / FDA	The CDC noted a statistically significant signal for ischaemic stroke and presented it on the ACIP meeting. The signal was only significant for patients aged 65 or older	Clinical trial data, post-marketing data, literature search	Refuted No update to the US product information Routine pharmacovigilance activities are continued
Dermatitis allergic	07-11-2024 (request received from the Saudi FDA)	Closed	Not known	HA request from the SFDA	The SFDA identified the signal through a literature search	Literature search, observed vs. expected analysis, post-marketing data	Refuted No update to the Saudi Arabic product information Routine

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
							pharmacovigilance activities are continued
Hypotension	07-11-2024 (request received from the Saudi FDA)	Closed	Not known	HA request from the SFDA	The SFDA identified the signal through a literature search	Literature search, clinical trial data, observed vs. expected analysis, post-marketing data	Refuted No update to the Saudi Arabic product information Routine pharmacovigilance activities are continued

Rapporteur assessment comment:

The MAH closed and refuted 7 signals during the reporting interval. This is endorsed. However, the MAH is reminded of their obligation to conduct their own signal detection and to present the validated signals in this section of the PSUR, rather than limiting the presented signals to health authority requests from the reporting period. Furthermore, the MAH is reminded not to present already assessed topics as signals in future PSURs.

Within this procedure, for five of the presented signals (cerebral venous thrombosis, erectile dysfunction, ischaemic stroke, dermatitis allergic, and hypotension), the MAH is requested to discuss the impact of the cumulative reviews on the current information in the EU SmPC.

2.2.1. Cerebral venous thrombosis (CVT)

Source

The MAH considered Cerebral venous thrombosis (CVT) as validated signal, based on the request from the Therapeutics Goods Administration (TGA) Health authority Australia.

On 17 Sep2024, The TGA requested Moderna to provide a signal analysis for all Spikevax vaccines and the risk of CVT.

Exact request is stated below:

As a guide, information to include (but is not limited to) in this safety analysis are as follows:

- An observed versus expected analysis, using risk windows out to 7, 14 and 21 days. Justification for the background rates chosen should be provided.
- An analysis of any global Company held data, case reports and literature regarding the risk of CVT and Spikevax.

As well as the results and analysis of these searches, please include:

    - The literature search strategy.
    - The MedDRA search terms used for the search of global case reports and rationale for selection of these.
    - The case series inclusion and exclusion criteria, with justification for these.

- Details of any other regulatory actions undertaken by Moderna relevant to this issue.
- A risk-benefit analysis for the approved indications of Spikevax.
- An analysis if an update to include the risk of CVT to the Australian PI for Spikevax is warranted.

Background

On 12 Apr 2024, Singapore Health authority (HSA) notified Moderna that based on their Nationwide safety surveillance study on COVID-19 mRNA vaccines, they found an elevated risk for CVT with Spikevax Vaccination and proposed to update the local PI and PIL for Spikevax XBB.1.5.

On 26 Apr 2024, MAH responded to HSA stating that:

- Multiple evaluations were conducted for the safety topic "Cerebral venous thrombosis (CVT)", including Cerebral venous sinus thrombosis (CVST) in the context of requests from health authorities and as part of ongoing monitoring of adverse events of special interest (AESI) within signal detection activities.
- Review of the data did not indicate any safety issue of concern with CVST/CVT.
- In addition, the accumulating post-authorisation safety data over the last 3 years provide insufficient evidence of a potential causal association between CVST and the administration of Spikevax.
- MAH considers that an update to Spikevax's RSI is not warranted at this point of time.
- The MAH continues to monitor the reported events of CVST using routine surveillance activities.

On 03 May 2024, SG HSA provided a response back and mandated to include CVT in Singapore PI for Spikevax XBB.1.5. under post-marketing experience indicating that these events have occurred without ascribing causality and for HCP to be aware.

After this second request MAH agreed to SG HSA proposal to include CVT to the Singapore product label.

Moderna indicated all the health authorities including TGA (on 29 May 2024) about the Singapore HSA decision to include CVT in the local product information (PI) for Spikevax XBB.1.5 (andusomeran).

Methodology

A cumulative search of the GSDB was performed as of 17 Sep 2024 with the following PTs using the MedDRA v27.1:

- Cavernous sinus thrombosis, CVST, Cerebral venous thrombosis, Sigmoid sinus thrombosis, Superior sagittal sinus thrombosis, Transverse sinus thrombosis.

The above specified MedDRA terms were chosen to provide a detailed and thorough approach to identify cases of CVT by including both general and anatomically specific forms of the condition. Use of these PTs will help to capture all possible variations of CVT cases in different parts of the brain's venous drainage system.

The cases retrieved form the GSDB were classified using The Brighton Collaboration case definition for Thrombosis and Thromboembolism (V1, Sep 2022) Categories:

- Level of Certainty 1 –Definitive case,
- Level of Certainty 2 – Probable case,
- Level of Certainty 3 – Possible case,
- Level 4 – Insufficient information available to confirm a possible, probable or definitive case of venous thrombosis/ thromboembolism,
- Level 5 – Sufficient information to determine that it is NOT a case of venous thrombosis/ thromboembolism.

The WHO causality assessment was applied for the assessment of the cases. The CVST risk factors identified from UpToDate were used for the assessment of the cases.

Results

The cumulative search of the GSDB (Cumulative through 17 Sep 2024) retrieved 296 cases. 321 events were reported across the 296 cases. Several of the cases described more than one of the PTs:

- 277 cases reported only one PT,
- 13 cases reported 2 PTs,
- 6 cases reported 3 PTs.

The majority (n=264, 82.2%) described a preferred term that did not specify a specific anatomical location other than cerebral (CVST and CVT.

Review of 296 cases with 321 events:

All 296 cases were carefully reviewed by a clinician. Each case was classified using the Brighton case definition for Thrombosis and Thromboembolism (V1, Sep.2022), detailed in Methodology. All

cases were categorised carefully as Level 1 to Level 5 and WHO causality assessment was applied for all cases.

- 120 cases were determined to be Level 1. In all of these Level 1 cases, this was due to the presence of imagining (venogram, MRI, CT) that led to the diagnosis. However, large number of these cases provided generally limited information other than the imaging study.
- No cases were determined to be level 2.
- 58 cases were determined to be level 3. Generally, these cases contained limited information. However, if the reports did describe symptoms generally associated with CVT in addition to the reported term, they were placed in this level.
- 115 cases were Level 4. These cases contained very limited information regarding the event of CVT and described no symptoms or diagnostics suggestive of CVT other than the reported term.
- 3 cases met Level 5 definition. On review, the verbatim reported term was purely speculative or described a different medical issue.

The 296 cases were identified as at least a Level 4 of CVT were reviewed to determine if any pattern indicating a potential safety signal was discernible. Age and gender were generally consistent with epidemiology of CVT. A review of the dose number and time to onset after vaccination did not show a clear pattern across these reports.

Review of the clinical course, presenting symptoms, and diagnostic findings also failed to identify any concerning pattern. The presenting symptoms were not consistent across cases, and reflected a range of underlying cerebral venous structures that would be expected in the general population experiencing CVT. Diagnostic findings (MRI, CT and venogram) did not show a consistent pattern in terms of the location or evolution of the CVT.

WHO-UMC causality assessment of the 296 cases:

- No cases described elements that would suggest either Probably/Likely or Certain causal association.
- One hundred forty-three (143) of the cases were deemed Unassessable. These cases did not include key clinical data elements to allow a causal assessment. These reports were all missing at least 3 critical data elements, including past medical history, concomitant medications, details of the clinical course of the events, information on the time to onset vis a vis vaccination, treatment details, diagnostic results, or age/gender.
- One hundred thirty-one (131) of the cases were deemed as Unlikely. These reports contained strong confounding factors that provide a plausible explanation for the event. These included factors such as a history of a coagulopathy (included Factor V Leiden disease), a concurrent cancer diagnosis, or use of medications strongly associated with CVT, especially oral contraceptives.
- Twenty-two (22) cases were determined to have a Possible causal association with vaccination.
    - Six (6) of these were only Level 3 in terms of Brighton classification. These cases generally provided limited information; the causal relationship was generally only based on a plausible temporal relationship. But these cases failed to provide a confirm diagnosis or enough detail to truly assess causality.
    - 16 cases met the Level 1 case definition and are further described below.

Sixteen Level 1 Reports with Possible Causal Association

Sixteen cases described case with evidence of being a true event of CVT and were deemed to have a Possible association with vaccination. These reports either contained at some risk factor(s) for CVT, or an ongoing disease entity that could explain the events. Many also failed to provide critical data elements that would allow a full causal analysis for the complex event of CVT.

Generally, these 16 cases were not meaningfully different from the overall cases in terms of age or dose number. They did tend to have a shorter time to onset, but this is reflective of their being cases with at least a potential association. They also reflected a higher proportion of male patients, but this is most likely a difference to the small numbers of cases in the subset. Review of these 16 Level 1/Possibly Related reports did not identify any sentinel case of concern for a potential association with vaccination. All reports described potential confounder for the events or provided limited information limiting a full medical assessment of causality. Review across the reports, including clinical course, presenting symptoms, and diagnostic findings failed to identify any concerning pattern. The presenting symptoms were not consistent across reports, and reflected a range of underlying cerebral venous structures that would be expected in the general population experiencing CVT. Diagnostic findings (MRI, CT and venogram) and clinical examination (when provided) did not show a consistent pattern in terms of the location or evolution of the CVT.

Review of fatal reports

Of the 296 cases, only 10 cases reported a fatal outcome. Among these 10 cases, 6 were female and 4 were male. Seven cases were reported in the Elderly age group ≥65 years and 3 cases were reported in the adult age group (42-64Y). Time to onset ranged from 0-138 days.

Based on the Brighton collaboration case definition: 2 cases met Level 1 definition, 3 cases met the Level 3 definition, and 5 cases met Level 4 definition.

According to the WHO causality assessment, 6 cases were assessed as Unlikely; and 4 cases assessed as Unassessable.

Summary:

In summary, the review of the 296 cases showed that the age and gender reported in these cases were consistent with the background rates in general population. Time to onset did not identify any pattern. Case assessment showed that 48.3% (143/296) were unassessable; 44.3% (131/296) were unlikely; and only 7.4% (22/296) were assessed as possible based on plausible temporal association and these possible cases contained potential risk factors and/or had limited information. No Sentinel cases were identified. The review did not identify any significant safety issue of concern or any pattern/trend.

Discussion

Cerebral venous sinus thrombosis is a rare form of venous thrombosis disorder affecting the cerebral veins and Dural sinuses. The annual incidence of CVT ranges from 1.16-2.202 per 100,00 in the general population, with an increased risk in patients with COVID-19 infection (42.8 per million ref:[12]).

In COVID-19 patients, especially those in intensive care units, CVT and other thrombotic events occur between 3–30 days after infection onset [13]. Venous thromboembolic (VTE) complications have been consistently reported to be increased in SARS-CoV-2 infection, most probably as the results of a thrombophilic state secondary to inflammation and immune thrombosis [13].

Several cases of Unusual thrombotic events including CVT, have been reported with the recombinant adenoviral vector vaccines. The primary mechanism by which adenoviral vector vaccines such as ChAdOx1 (AstraZeneca) and Ad26 (Johnson & Johnson) cause thrombotic events

is through Vaccine Induced Thrombotic Thrombocytopenia (VITT). VITT is caused by antibodies that recognise platelet factor 4 (PF4), leading to platelet activation and subsequent thromboembolism. However, no similar immunopathogenic mechanism has been described for mRNA vaccines. A cumulative review of clinical trial data did not identify any cases for the safety topic of interest and the cumulative review of the post-marketing data did not identify any sentinel case. Majority of the post-marketing data cases were assessed as either Unassessable (48.3%) or Unlikely (44.3%), and only 7.4% were assessed as possible based on temporal association. These possible cases described potential confounder(s) for the events or provided limited information precluding adequate medical assessment. In addition, the clinical review did not identify any safety concern/pattern/trend.

Review of the external safety databases EVDAS and VAERS did not provide any significant disproportionality for the product event combination.

Review of the published literature identified articles that showed the mechanism by which COVID infection causes CVT. There were many articles that showed an established mechanism (VITT) by which ChADOX1 CoV-19 Vaccine (AstraZeneca) and Ad 26. CoV2 (Jansen) would cause CVT. The literature review did not identify articles that would suggest an established mechanism by which mRNA vaccine could cause CVT.

The Observed to expected analysis and the PASS studies (P920 and P903) did not identify any elevated risk for CVT with all Spikevax marketed products.

In summary, CVT is a recognised complication of COVID-19 infection and a known ADR for adenoviral vector vaccines. However, there are no well-established mechanism of action by which the mRNA vaccine could cause CVT. The review of the available data from the different sources (Clinical trial, postmarketing, literature, external safety databases, O/E analysis and PASS study) does not support a clear causal association between mRNA vaccines and the development of CVT. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to be favourable.

Conclusion

The comprehensive evaluation of available data from CTs, pharmacovigilance databases, external databases, epidemiological studies, and published literature does not substantiate a relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the occurrence of CVST.

The current CCDS (version 19.0) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified. The cumulative safety data evaluated do not provide a sufficient basis for new recommendations or product labelling changes and/or RMP, including relevant risk minimisation measures regarding CVT. The validated signal of CVT is refuted and closed at this point of time.

The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive. The MAH will continue to monitor through routine pharmacovigilance activities and as an AESI through additional pharmacovigilance activities (PASS study mRNA-1273-P951).

Rapporteur assessment comment:

The signal was initiated by the TGA and was based on an update to the product information regarding cerebral venous thrombosis in Singapore.

The MAH performed a cumulative review and it was submitted to the TGA. The cumulative review did not result in any updates to the Australian product information for Spikevax.

The data lock point for the cumulative review is 17-09-2024 and the MAH has identified 296 cases with 321 adverse events.

Using the WHO-UMC causality scale the MAH assessed the cases and the results were:

0 cases were assessed to be "probable/likely/certain".

131 cases were assessed to be "unlikely".

143 cases were un-assessable.

22 cases were assessed to be "possible".

Ten fatal cases (included in the 296 cases) were also identified. However, six of these cases were assessed as unlikely and four were un-assessable.

The provided signal evaluation is acknowledged. However, the provided signal assessment report (included in annex 5 in the PSUR) does not discuss the cumulative review's impact on the current information regarding cerebral venous thrombosis in the EU-SmPC, as it is focused on the HA request from TGA. The MAH should therefore include a brief discussion of this during the current PSUSA procedure.

2.2.2. Renal failure

Source

On 25 Dec 2023, Moderna received a request from the SFDA via the local affiliate (Tabuk Pharmaceuticals), for the following information:

- We would like from you to Submit a comprehensive signal evaluation report within 60 days regarding the potential risk of Renal Failure with the use of SPIKEVAX (mRNA-1273; elasomeran).
- The evaluation should include, but not be limited to, background rate, results from CTs database, epidemiology, preclinical findings, PASS, global pharmacovigilance database medical literature, estimated reporting rate, integrated benefit-risk analysis, conclusion and recommendation.

Background

The MAH considered renal failure as a validated signal following receipt of a request from the SFDA requesting the MAH for Spikevax (Moderna Biotech Spain S.L.) to perform a cumulative review of all cases of renal failure.

Acute Kidney Injury (AKI) has generally become the PT replacing Acute Renal Failure (ARF). It can be defined as an abrupt decrease in kidney function leading to azotaemia, may or may not involve decrease in urine output. The loss of kidney function may also involve structural damage/injury to the renal interstitial tissue, glomerular apparatus, vasculature. Aetiology can be multi-factorial and with early identification and adequate treatment of the underlying cause, it is generally reversable. If untreated, it can lead to accumulation of fluid overload and electrolyte disturbances (hyperkalaemia, hyperphosphatemia, hypocalcaemia), and may also have a cascading impact on the functioning of other organ systems.

Methodology

The MAH's clinical database and the GSDB were queried for valid case reports of Renal failure received from HCP, HA, consumers, and literature, worldwide, for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran using the MedDRA SMQ

Narrow 'ARF' which includes the following PTs: " AKI; Acute phosphate nephropathy; Anuria; Azotaemia; Continuous haemodiafiltration; Dialysis; Foetal renal impairment; Haemodialysis; Haemofiltration; Neonatal anuria; Nephropathy toxic; Oliguria; Peritoneal dialysis; Prerenal failure; Renal failure; Renal failure neonatal; Renal impairment; Renal impairment neonatal; Subacute kidney injury".

Two different MedDRA versions were used. For the CTs MedDRA version 23.0 was used and for querying the GSDB, cumulative as of 17 December 2023, the MedDRA version 26.1 was used.

Identified cases were classified into one of 5 categories, following the Company case definition that was developed using the above KDIGO guideline as a basis, as follows:

Definite case: per KDIGO criteria contains all relevant diagnostic information available.

Probable case: event reported as AKI/ARF with full supportive renal diagnostic information provided [however KDIGO criteria specifically was not met].

Possible case: event reported as AKI/ARF/or SMQ term with only partial supportive renal diagnostic information provided.

Unassessable: event reported as AKI/ARF/or SMQ term with no supportive renal diagnostic information provided.

Not a case – Not a case for Spikevax; containing alternative diagnosis.

This search retrieved a total of 1185 cases (1260 events) of which 1153 were considered serious cases (1224 serious events).

A list of key terms was developed for relevant (i) concomitant medication(s) which have well known association with ARF/AKI (or related terms) based on the approved labels; and (ii) Medical history/concurrent co-morbidities which likely constitute clear risk factors in the development of ARF/AKI (or related events).

The medical history and concomitant medication fields for all identified cases were searched to determine if they had a match for the above terms.

- All cases that had both a medical history match and a concomitant medication match to the above lists were assumed to be likely confounded for review. However, all of these cases were medically reviewed to confirm they had confounding factors that could present a more plausible explanation the events of AKI.
- Cases reporting only medical history matches to the above list were medically reviewed carefully to confirm that the reported medical history could present a more plausible explanation for the reported events of AKI.
    - Critically, all cases confounded by a history of significant kidney disease were carefully reviewed to confirm there was no pattern of exacerbation of disease after vaccination with Spikevax.
- Cases reporting only concomitant medication matches to the above list were medically reviewed carefully to confirm that the reported concomitant medication(s) could present a more plausible explanation for the reported events of AKI.
- If these medical reviews determined that a case was not truly confounded, they were moved to the next step of screening.

All remaining cases (not medically confirmed to be confounded) were classified to determine if they provided medical history and concomitant medications information to determine if any cases had

insufficient information to medically assess any relationship to vaccination or another source of AKI.

- If the case was missing both of these elements, the other available information (e.g., narrative) was medically reviewed to confirm the case did not contain sufficient medical information to allow an assessment.
- If the case was missing only one of these elements, the available information was medically reviewed to confirm whether the case had sufficient evidence to make a meaningful medical assessment.
- Only those reports with sufficient information to provide a medical assessment were further reviewed.

All remaining cases (not truly confounded or without sufficient information) were screened to determine if they medically confirmed, and if not, did they contain sufficient medical information to allow a thorough clinical assessment.

- Any of the remaining cases that was not medically confirmed were highlighted. These cases were medically reviewed to confirm whether they had sufficient clinically valid information to allow a full medical assessment. If not, they were not further reviewed.
    - Though most of these reports did not contain sufficient clinical detail to allow assessment, they were still reviewed to determine if they had any meaningful pattern suggesting an association with Spikevax vaccination.

Remaining cases (not confounded, with sufficient information, medically confirmed) were further reviewed.

A final screen of these reports was performed, focused on the time to onset between vaccination and the event of AKI. Given the potential mechanisms for a potential for a vaccination to be associated with AKI, any case with a TTO of greater than 30 days was deemed unlikely to be associated with vaccination. These cases were medically reviewed to confirm the sequence of clinical events and to determine if any pattern of potential association could be determined. The applicable cases that met the Company case definition criteria of 'definite', 'probable' or 'possible' were subsequently assessed for causality using the WHO-UMC standardised causality assessment criteria.

Results

Non-clinical data

The available non-clinical safety data for mRNA-1273 did not demonstrate the potential to induce AKI (or related events).

Clinical Studies

mRNA-1273-P301 Study: There were 24 participants (15 in the placebo group and 8 in the mRNA-1273 treatment group) in the P301 study, in whom AKI (or a related event term) were reported. There was not an imbalanced noted in study P301 for any of the study arm participants.

mRNA-1273-P205-Part H Study: No participants in P205-Part H reported the events from the MedDRA SMQ Narrow "ARF".

mRNA-1273-P205-Part J Study: No participants in P205-Part J reported the events from the MedDRA SMQ Narrow "ARF".

The MAH GSDB was queried cumulative as of 17 Dec 2023, for valid case reports of ARF received from HCP, HA, consumers, and literature, worldwide, for elasomeran, elasomeran/imelasomeran,

elasomeran/davesomeran and andusomeran using the MedDRA narrow SMQ of AKI v.26.0. This search retrieved a total of 1185 cases (1260 events) of which 1153 were considered serious cases (1224 serious events). A total of 985 cases were medically confirmed, and there were 204 cases that reported a fatal outcome. There were no important differences between males (637; 53.8%) and females (537; 45.3%), with 11 cases (0.9%) not reporting sex information. The mean age of these reports was 65.9 years with a median of 69.0 (min:0.2/max:102.0).

All cases in which medical review did not determine they belonged into one of the above 4 categories were determined to need additional medical review and assessment. A description of the reports in each of these categories, especially those receiving the most thorough medical review, is provided below. In summary, after screening and medical review of the 1185 case reports, they were classified as follow:

- 428 reports were deemed to have confounding factors that provided a more plausible explanation for the reported events of AK.
    - These case reports predominantly involved elderly patient population with 238 males (mean/median age 72 years; range 13 to 92 years), and 186 females (mean/median age 69; range 15 to 99 years) and 4 (4) did not have information on gender, often in poor/critical health status or received care in hospital setting and largely involved progression/complications of underlying or concurrent significant medical conditions. A number of these patients notedly received polypharmacy including medications having known associations with AKI (or related events). These included: various Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), furosemide, lisinopril, lithium, losartan, methotrexate, tacrolimus, enalapril ramipril, cyclosporine, acyclovir, omeprazole, acetaminophen; aspirin, etc.
    - Majority of these reports were reported via RA (348 cases), followed by spontaneous (48 cases) and Literature-Non-Study (32 cases).
    - The more commonly reported relevant medical history and/or concurrent medical conditions which preceded and likely contributed towards the reported AKI (or related events) in these case reports included, but not limited to: chronic kidney disease, hypertension, hyperlipidaemia/ dyslipidaemia, diabetes mellitus, COVID-19 infection, benign prostatic hyperplasia, pneumonia, pulmonary hypertension, dialysis, respiratory failure/arrest, hypotension, hypovolemia, dehydration, cardiac failure/congestive, atrial flutter, myocardial infarction, sepsis/septic shock, end-stage renal disease, renal transplant, AKI, cardiomyopathy, renal failure, urinary tract infection, left ventricular failure/ejection fraction decreased, mechanical ventilation, nephrolithiasis, IgA nephropathy, urinary retention, diabetic nephropathy, gastrointestinal haemorrhage, dilated cardiomyopathy, hepatic cirrhosis, haemodialysis, hyperkalaemia, renal disorder, pulmonary embolism, respiratory failure, aortic stenosis, cardiac disorder, lung/ heart transplant, hydronephrosis, chemotherapy, cancer (breast, prostrate, etc.), malignant neoplasm, nephropathy, lactic acidosis, malnutrition/ feeding disorder, peripheral arterial occlusive disease, single functional kidney, vascular graft, acute respiratory distress syndrome, anaemia of chronic disease, bacteraemia, bradycardia, cerebrovascular accident, chronic lymphocytic leukaemia, lymphoma, hepatocellular carcinoma, proteinuria, renal cell carcinoma, renal impairment, hypothyroidism, myasthenia gravis, and major surgeries (cardiac bypass, cancer surgery, etc.).
    - No other specific patterns were identified following a review of these case reports.

- 461 reports were deemed upon screening and medical review to contain insufficient information to allow a meaningful medical assessment of any relationship to Spikevax vaccination.
    - These cases were reported in 253 males (mean/median age 69 years; range 20 to 98 years), 202 females (mean/median age 72; range 1 to 98 years) and 6 were unknown gender. Majority of these reports were reported via RA (411 cases), followed by Spontaneous (40 cases) and Literature-Non-Study (10 Cases).
- Vital information was deemed missing from these reports for a detailed causality assessment, including, but not limited to:
    - missing relevant medical history and/or concomitant medication details.
    - relevant details around the clinical course of the reported AKI event, including supportive renal diagnostic data were missing or unremarkable (no corresponding elevated blood creatinine and/or eGFR decrease or the laboratory data were inconclusive).
    - the precise information on time to onset (latency) of the reported renal event could not be ascertained with respect to Spikevax administration; In other cases, the timing of administration of Spikevax was not known/reported in relation to the reported AKI event.
    - consumer cases with insufficient details; non-medically confirmed information.
    - reports involving a related SMQ term e.g., anuria; lacking further details establishing an AKI.
- In a number of these cases, where the information was available, significant comorbidities were often noted that may have been potentially contributory towards the reported renal event e.g., pulmonary embolism, heart failure, liver failure, CLL, sepsis, etc.
- No other specific patterns were identified following a review of these cases.
- 86 non-medically confirmed reports after review were determined to not contain medically valid information to allow for a thorough medical review for any potential association with vaccination.
    - These cases were reported in 44 males (mean/median age 61 years; range 15 to 88 years), 42 females (mean/median age 59 Years; range 27 to 87 years). Majority of these reports were reported from regulatory authorities (51) and spontaneous (35) source.
    - These cases were lacking information to observe any pattern suggesting an association given the lack of medically confirmed information.
- 30 reports had a time to onset of greater than 30 days and upon medical review were determined to not demonstrate a potential relationship with vaccination.
    - These cases were reported in 17 males (mean/median age 69 years; range 18 to 91 years), 12 females (mean/median age 64; range 21 to 80 years) and One (1) patient did not report gender. Majority of these reports were reported via RA (26) and Spontaneous (4).
    - The median time to onset for the reported renal event in these cases was 67 days (range 32 to 259) following Spikevax administration.

- In the majority of these cases, where the information was available, the reported renal event occurred in the setting of other severe comorbidities which provided a more likely explanation for the renal event e.g. a concurrent severe infection (including Covid-19), pneumonia, sepsis, septic shock, bacteraemia, chronic kidney disease, lupus, vasculitis, tubulointerstitial nephritis, acute respiratory failure, multiple organ dysfunction, cardiac failure, right ventricular failure, cardiac valve insufficiency, myocardial infarction, cardiac arrest, cardiogenic shock, atrial/ventricular fibrillation, hepatic failure, haemorrhage, End-Stage renal disease, renal aplasia, reduced fluid intake, etc. Also, these involved patients, mostly elderly, with significant medical history: heart failure, coronary artery disease, BPH, hypertension, diabetes (poorly controlled in some cases), hyperlipidaemia, atopic dermatitis, cancers, SLE, COPD, lupus, etc.
- Given the long time to onset and reports involving significant comorbidities, often severe in nature and/or the underlying medical history of the patients which were likely contributory, no other specific patterns were identified following a review of these cases.

- After this review, 180 Reports could not be confirmed as fitting in any of these categories and were deemed to require a more thorough medical review.

Discussion

Acute Kidney Injury (AKI) has generally become the PT replacing ARF. It can be defined as an abrupt decrease in kidney function, including both structural damage/injury and loss of function/impairment. In generally signifies a sudden, and often reversable reduction in kidney function, usually noted by a reduced glomerular filtration rate. The medical concept of AKI has been complex, and over the years multiple AKI definitions (up to 35) were developed, but this has also led to some variance when the AKI data and case reports have been described in medical literature. For the purpose of this safety review, a more recent and widely accepted definition from KDIGO were utilised to evaluate the AKI case reports, as these provide a framework for diagnosis, staging, and management of AKI case reports based on changes in serum creatinine levels, urine output, or the need for renal replacement therapy.

A total of 1185 case reports (1260 events) of ARF retrieved from the MAH GSDB using narrow SMQ of AKI for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran were evaluated in detail using a stepwise approach. The majority of case reports for AKI (or related event including for flare-ups/recurrence), where the information was available, involved elderly patients often in poor/critical health status or received care in hospital setting and often a result of progression/complications of underlying or concurrent significant medical conditions (alternative aetiologies). Also, number of these patients notedly received polypharmacy including medications having known associations with AKI (or related events). No other clear trends or patterns were observed (time to onset, dose number, etc.) that would suggest an association of AKI (or a related event) with Spikevax administration.

A review of the available published literature articles have highlighted the enormous benefits of mass vaccination for COVID-19 and postulated potential mechanisms of COVID-19 vaccination may potentially lead to AKI, including the effect of a COVID-19 infection leading to renal insult, however, there have been no high-quality studies which may provide sufficient evidence yet for a plausible direct mechanism towards a causal association between AKI/ARF and SPIKEVAX vaccination.

A review of the available clinical trial data from a phase 3 study for mRNA-1273 (N=30,346), there was not an imbalanced noted in study P301 for any of the study arm participants as the incidence

of the event of ARF (or related term) in the mRNA-1273 arm (<0.1%; 8 events) compared to the comparator (placebo) arm (<0.1%; 15 events) and none of the events in the mRNA-1273 arm were considered to be related to the mRNA-1273 by the investigators. Also, there has been no relevant non-clinical safety findings demonstrating a renal injury potential for mRNA-1273.

Further, the available data from the 2 PASS studies involving Spikevax suggest instances of ARF post-vaccination were rare and not statistically linked to the vaccine. Data from these 2 studies has showed no evidence of increased risk of AKI following elasomeran vaccination. These findings are also in line with the observed to expected (O/E) analysis which has shown the observed reporting rate for AKI was 1.98 per 100,000 person-years (based on the 1185 case reports cumulatively). Overall incidence described by [14] (data from Netherlands) was 185.51 per 100,000 person-years, corresponding to an estimated 111,306 cases expected. The rate ratio was (95% CI: 0.01, 0.01). Further, no disproportionality was observed for the PTs from the MeDDRA SMQ of 'Renal Failure' in the EVDAS and VAERS databases.

Overall, a review of available safety data from various sources has not yielded any new significant safety findings or demonstrated a potential for AKI/ARF with Spikevax use.

Conclusion

Overall, based on the analysis of all safety data available as of 17 Dec 2023 including the data from all sources as discussed above, the MAH considers that there is insufficient information to establish a causal relationship between the administration of Spikevax and ARF (or related events).

The current CCDS (version 18.0) is considered to adequately reflect the safety profile of Spikevax.

No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor ARF 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 minimisation measures with regard to ARF. The signal of ARF is refuted and closed.

Rapporteur assessment comment:

The signal was initiated by the SFDA, who requested a comprehensive signal report. The signal was subsequently refuted and no updates were made to the Saudi product information. The MAH has included cases from the global company safety database, non-clinical data, clinical trials and literature in their signal report to the SFDA and in the current PSUR.

In total, 1185 cases (1260 adverse events) were identified in the global safety database. 1153 cases were considered serious and 985 cases were medically confirmed. A total of 204 cases were fatal. The 1185 cases were classified by the MAH as follows:

- 478 cases were considered confounded
- 461 cases were considered un-assessable.
- 86 cases were not medically confirmed
- 30 cases had a time-to-onset greater than 30 days
- 180 cases did not match any of the above categories

The MAH concludes that the majority of the identified cases occurred in the elderly and vulnerable patient population and considered this to be a confounding issue.

The provided signal evaluation is acknowledged.

2.2.3. Erectile dysfunction (ED)

Source

The MAH considered Erectile Dysfunction as a validated signal for the marketed Moderna COVID19 vaccines (mRNA-1273-related vaccines), upon receipt of a request from the Rwanda HA to gather "more evidence and further investigation" on the safety signal.

Background

The MAH considered "Erectile dysfunction" as a validated signal with COVID-19 vaccine Moderna (mRNA vaccine) following a request from Rwanda FDA to gather "more evidence and further investigation" on the safety signal.

Erectile dysfunction (ED), previously known as impotence, is defined as consistent or recurrent inability to achieve or maintain a rigid penile erection for satisfactory sexual intercourse. ED can be (i) Primary, when the man has never been able to attain or sustain erections; and (ii) Secondary, which is acquired later in life in a man who was previously able to attain erections. Secondary ED is more common than Primary. Erectile dysfunction is more common in men 40 years and older, and the prevalence increases with age and co-existing co-morbidities. ED is considered an important social problem, which significantly impacts the quality of life of a patient and his partner. Patient's suffering from ED often delays or avoid seeking treatment. ED can be the initial manifestation of underlying vascular disease that increases the risk of cardiovascular/cerebrovascular events, so addressing ED is important to improve the patient's quality of life and to identify and treat underlying aetiologies.

Methodology

The MAH GSDB was queried cumulative as of 17 Feb 2024, for valid case reports of ED received from HCP, HA, consumers and literature, worldwide for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran using the MedDRA high level term (HLT) Erection and ejaculation conditions and disorders v.26.1.

Results

A total of 252 reports were identified in the database. Eighteen (18) of the reports described a female patient. All these reports were from regulatory sources and could not be further queried. These 18 reports were reviewed separately, and none described a true case of ED. No pattern suggesting a safety issue was seen in these cases.

Out of the 252 cases, 234 reports remained for analysis. There were 253 events meeting the search criteria associated with the 234 reports, as 15 reports contained 2 or more events.

One hundred and fifty-five cases (155) were considered serious, and 156 of the events of interest were considered serious. The vast majority of the serious events were serious due to medical significance of the reported term only; 15 events were considered serious due to disability, and 5 events were considered serious due to hospitalisation, with one report describing both.

Time to onset could be determined in 158 of the 234 reports. The average TTO was 9.5 days, with a median of 2.0 days, ranging from 0 to 262 days. No consistent pattern in terms of TTO was noted.

Age was reported in 214 of the 234 reports. The average age of the patients' reporting age was 46.4 years, ranging from 18-78 years. 139 reports were from non-medically confirmed reports, while just 85 were from medically confirmed sources. 204 reports were from regulatory sources, and only 30 reports were spontaneous reports. 174 reports were from Europe, 54 from the United States, and 6 from the rest of the world.

All 234 reports were medically reviewed and a WHO-UMC based causality assessment was conducted.

- 184 reports were medically unassessable due to lack of key information such as a combination of missing medical history, concomitant medications, age, time to onset, or a clinical course of events and treatment.
- 48 reports were deemed unlikely related to Spikevax vaccination. These cases were confounded due to reported medical history, concomitant medications, or had a clear alternative aetiology for the events of interest. These included medical conditions and medications commonly associated with ED, and/or another medical condition and a course of events which likely contributed to the event(s) of interest.
- There were 2 reports assessed as possibly related to vaccination, but generally provided limited information.

[redacted] (WW Identifier: [redacted]): This is a regulatory report (EMA) regarding a male patient of unknown age, with no reported medical history or concomitant medications reported events erection failure, rash, anxiety (worry due to erection failure), 2 days after the 3rd dose of mRNA-1273 vaccination. Outcome of ED was reported as not resolved.

- MAH Comment: The case lacked information pertaining to age of the patient, medical history, sexual history, concomitant medications, event details, diagnostic/laboratory tests, physical/psychological examination etc. limiting causality assessment.

[redacted] (WW Identifier: [redacted]): This is a report from a regulatory source ([redacted]), regarding a 41-year-old male patient with medical history of Tourette's disorder experienced the events ED (had difficulty achieving and maintaining an erection) and libido decreased, 3 days after the first dose of mRNA-1273 vaccine. The events were reported as recovered 3 weeks after the first dose. Following the second dose administration, the patient reported the same events (erection difficulties and drop in libido) on an unknown date. Treatment details were not provided. The symptoms had not resolved at the time of last update.

- MAH Comment: Though the case described a positive re-challenge, there was lack of information pertaining to treatment medications for Tourette's disorder, sexual history including information about previous history of adequate erections, laboratory tests/diagnostic tests, physical / psychosocial examination etc., limiting adequate medical assessment.

Discussion

ED is the inability to develop and maintain an erection for satisfactory sexual intercourse or activity. The Diagnostic and Statistical Manual of Mental disorder-5 specifies a duration of at least 6 months in its definition of ED. ED is increasingly prevalent with age: approximately 40% of men are affected at age 40 and nearly 70% of men are affected at age 70. Aetiologies of erectile dysfunction is classified by psychogenic and organic causes. Diagnosis of an ED requires a careful medical history, sexual history, medication history, psychological history, physical examination, and diagnostic/laboratory to rule out and/or for the treatment of underlying aetiologies.

ED is not labelled as an Adverse drug reaction in current CCDS/IB. ED is not labelled as an ADR in other COVID vaccines label.

Results from Clinical trial data showed the incidence of the event was very low and roughly equal in both the placebo and mRNA-1273 group. No specific pattern or trend was noted.

Results from the GSDB: Cumulatively through 17Feb2024, 252 cases reporting PTs within the HLT Erection and ejaculation conditions and disorders were retrieved from the GSDB. Of the 252 cases, 18 reported female gender and review of these cases did not identify any safety concerns. Review of the remaining 234 cases showed that the average age in these cases was 46.4 years old which is consistent with epidemiological data. The majority of cases (87%) were from RA. WHO-UMC causality assessment was applied for all 234 reports. Of these 234 reports, 184 were assessed as un-assessable, 48 were assessed as unlikely, and 2 cases were assessed as possible which contained limited information pertaining to medical history, sexual history, concomitant medications, laboratory/diagnostic tests, psychological examination/physical examination, etc. thereby precluding a meaningful medical assessment.

The observed to expected analysis did not identify an elevated risk of ED following marketed Moderna vaccines targeting SARS-CoV-2.

Results from the external safety database VAERS, showed that the PTs within the HLT Erection and ejaculation conditions and disorders did not meet the disproportionality threshold. Results from the external safety database EVDAS showed the PTs within the HLT Erection and ejaculation conditions and disorders did not meet the disproportionality threshold except for one PT Ejaculation delayed for the product andusomeran, and it should be noted that disproportionality was not meaningful due to low counts (1case count) reported for this product event combination.

The literature review identified articles indicating COVID infection could affect the endothelial cells impacting endothelial function and cardiovascular health in males and thereby leading to ED. The literature review did not identify articles that proposes a plausible biological mechanism of action of mRNA vaccine leading to ED and/or articles that would suggest/imply a causal association between mRNA vaccination and ED.

Overall, the review of the data from all the available data sources (MAH safety database, external safety databases, O/E analysis, and literature review) showed that there is insufficient evidence to suggest a reasonably possible causal association between use of mRNA vaccination and ED.

Conclusion

Overall, based on the analysis of all safety data available as of 17 Feb 2024 including the data from all sources as discussed above, the MAH considers that there is insufficient information to establish a causal relationship between the administration of SPIKEVAX and ED. The current CCDS (version 17.0) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor ED 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 minimisation measures with regard to ED. The validated signal of ED is refuted and closed.

Rapporteur assessment comment:

The signal was started by the MAH upon a request from the Rwanda Health Authority to gather more evidence on the safety signal "erectile dysfunction".

The MAH identified 252 cases in their global company safety database. 18 of the 252 cases were excluded as these were females. The remaining 234 cases included a total of 253 adverse events. 155 cases were classified as serious.

The 252 cases were classified by the MAH as follows:

- 184 cases were considered un-assessable

- 48 cases were considered unlikely

- 2 cases were considered possible (the two cases are briefly described below)

The case [redacted]" was identified in the EVDAS and was reported after the third dose of the mRNA vaccine mRNA-1273. The male patient reported erection dysfunction, rash and anxiety but the report did not include information regarding age, medical history nor concomitant medication. The event remained un-resolved.

The case [redacted]" was identified in the VAERS. The 41-year old male patient with a history of Tourette's disorder experienced erection dysfunction 3 days after the first dose of the mRNA vaccine mRNA-1273. The patient recovered 3 weeks after the first dose. Following the second dose of the mRNA vaccine mRNA-1273, the patient reported the same event. The date of the second onset of erectile dysfunction is unknown as well as information regarding recovering.

The MAH concludes that the two cases are inconclusive and that an update to the product information is not warranted based on these two cases, as there is still some missing information in the cases.

The provided signal evaluation is acknowledged. However, the provided signal assessment report (included in annex 5 in the PSUR) does not discuss the cumulative review's impact on the current information regarding erectile dysfunction in the EU-SmPC, as it is focused on the HA request from Rwanda. The MAH should therefore include a brief discussion of this during the current PSUSA procedure.

2.2.4. Pre-eclampsia, gestational hypertension and GD (P919)

Source

The MAH considered gestational hypertension, pre-eclampsia, and GD as a validated signal, based on the results from the post-authorisation safety study mRNA-1273-P919, which are as follows:

- A small but statistically significant increase in the risk of pre-eclampsia, gestational hypertension, and GD was observed following exposure to SPIKEVAX during pregnancy when compared to distantly vaccinated and unexposed populations.
- The relative risk was more pronounced when exposure to SPIKEVAX occurred during the second trimester of pregnancy.
- Pre-eclampsia, gestational hypertension, and GD did not show any statistical increase when compared to individuals with COVID-19 diagnosis during pregnancy.

Background

The MAH considered gestational hypertension, pre-eclampsia, and GD as validated signals, based on the results from the post-authorisation pregnancy safety study mRNA1273-P919.

Hypertensive disorders in pregnancy are the common medical complications of pregnancy, affecting approximately 10% of pregnancies globally. Hypertensive disorders in pregnancy accounts for at least 14% of maternal mortality and 10-25% of perinatal deaths and affects the mother and new-born to varying degrees.

Hypertensive disorders in Pregnancy may be chronic (predating pregnancy or diagnosed before 20 weeks of pregnancy) or de novo (either gestational hypertension or pre-eclampsia).

Methodology

The MAH GSDB was queried cumulative as of 17 Feb 2024, for valid case reports of gestational hypertension/pre-eclampsia and GD received from HCP, HA, consumers and literature, worldwide for SPIKEVAX(Original), both bivalent vaccines [SPIKEVAX Bivalent .214 (Original/BA.1) and SPIKEVAX Bivalent.222 (Original/BA.4/5)] and SPIKEVAX 2023-2024 Formula.

- For the topic of Gestational hypertension and Pre-eclampsia, the MedDRA HLT of Hypertension associated disorders of pregnancy was used. This HLT included the following PTs: Eclampsia; Gestational hypertension; Haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; Mirror syndrome; Preeclampsia and Superimposed pre-eclampsia.
- For the topic of GD, the MedDRA SMQ (Narrow)- Hyperglycaemia/new onset diabetes mellitus was used. It was applied to all pregnancy reports identified in the GSDB. This SMQ included the following PTs: Acquired generalised lipodystrophy; Alpha hydroxybutyric acid increased; Blood 1,5anhydroglucitol decreased; Blood glucose increased; Diabetes complicating pregnancy; Diabetes mellitus; Diabetes mellitus inadequate control; Diabetes with hyperosmolarity; Diabetic arteritis; Diabetic coma; Diabetic coronary microangiopathy; Diabetic hepatopathy; Diabetic hyperglycaemic coma; Diabetic hyperosmolar coma; Diabetic ketoacidosis; Diabetic ketoacidotic hyperglycaemic coma; Diabetic ketosis; Diabetic metabolic decompensation; Diabetic wound; Euglycaemic diabetic ketoacidosis; Fructosamine increased; Fulminant type 1 diabetes mellitus; GD; Glucose tolerance impaired; Glucose tolerance impaired in pregnancy; Glucose urine present; Glycated albumin increased; Glycated serum protein increased; Glycosuria; Glycosuria during pregnancy; Glycosylated haemoglobin abnormal; Glycosylated haemoglobin increased; Hepatogenous diabetes; Hyperglycaemia; Hyperglycaemic crisis; Hyperglycaemic hyperosmolar nonketotic syndrome; Hyperglycaemic seizure; Hyperglycaemic unconsciousness; Impaired fasting glucose; Insulin resistance; Insulin resistant diabetes; Insulin-requiring type 2 diabetes mellitus; Ketoacidosis; Ketonuria; Ketosis; Ketosis-prone diabetes mellitus; Latent autoimmune diabetes in adults; Maternally inherited diabetes and deafness; Monogenic diabetes; Neonatal diabetes mellitus; Neonatal hyperglycaemia; New onset diabetes after transplantation; Pancreatogenous diabetes; Pseudodiabetes; Steroid diabetes; Type 1 diabetes mellitus; Type 2 diabetes mellitus; Type 3 diabetes mellitus; and Urine ketone body present.
- Additionally, all reports of pregnancies (cumulatively) in the global safety data base (GSDB) were identified through 17 Feb 2024. There were 5469 reports of pregnancy with 18,173 associated events. All the PTs associated with these reports were manually reviewed by a safety physician. Any preferred terms suggestive of a potential report of Gestational Hypertension, Pre-eclampsia, or GD were identified. Pregnancy reports with any of the following PTs were reviewed as potential cases by a physician, and included for the current review if they met the criteria for the events of interest.
- Hypertension (17), Seizure (12), Blood pressure increased (8), Thrombocytopenia (7), Epilepsy (5), AKI (3), Blood glucose (3), Immune thrombocytopenia (3), Acute hepatic failure (2), Cluster headache (2), Pulmonary oedema (2), Blood pressure fluctuation (1), Chronic kidney disease (1), Epileptic encephalopathy (1), Hepatic failure (1), Hypertensive crisis (1), Protein urine (1), Protein urine present (1), Urine albumin/creatinine ratio (1).

Once all potential reports of Gestational hypertension, Pre-eclampsia, Eclampsia, HELLP and GD were identified based on the above-described methodology, cases were classified following the case definitions presented in the Brighton Collaboration website from the article by Appendix 13.4 for gestational hypertension and preeclampsia (with and without severe features); and for GD using the case definition included in the article by Appendix 13.4.

The Company causality assessment is provided utilising the WHO-UMC standardised case causality assessment.

Results

Cumulatively as of 17 Feb 2024, a total of 81 cases (excluding 2 cases of Eclampsia & HELLP [1 each]) were identified by the search strategy across the 3 topics of interest.

Of the 32 Reports that were associated with Gestational Hypertension:

- 2 reports clearly did not meet the case definition as the events occurred during the first trimester. (Both reports had otherwise very limited information).
- 26 reports did not provide enough information to allow an assessment. They did not provide diagnostic information to document blood pressure measurement meeting the definition, and other than the reported terms, did not provide information to contribute to analysis of this topic.
- These reports were reviewed in detail, and no pattern with regards to age, TTO, vaccine timing, etc. of interest was noted.
- There are 4 (4) reports did meet the definition for gestational hypertension but did not provide enough information to assign a diagnostic level (proteinuria information was not available). Of the 4 reports, 1 case had WHO-UMC Causality of "Possible" and 3 cases were assessed "Un-assessable", but generally provided limited information.

Of the 26 Reports that were associated with the term Pre-eclampsia (1 also described eclampsia):

- 1 report clearly did not meet the case definition as the events occurred during the first trimester (otherwise very limited information was provided).
- 23 reports did not provide enough information to allow an assessment. They did not provide diagnostic information to document blood pressure measurement or evidence of proteinuria to meet the case definition, and other than the reported terms, did not provide information to contribute to analysis of this topic.
- In addition, one case of eclampsia and one case HELLP were identified. Neither met the case definition.
- The 2 (2) reports met the definition for pre-eclampsia of which one provided enough information to be considered Diagnostic Level 1 per the definition and another one (1) report provided enough information to be considered Diagnostic Level 2 per the definition.

Of the 23 Reports that were associated with the term GD:

- 2 cases were not a true pregnancy case (did not report an exposure during pregnancy).
- 4 cases were categorised as Level 5, as they did not meet the case definition for GD.
- 12 cases reported the diagnosis of GD and were categorised as level 4.
- 5 cases were classified as Level 3, of which 3 were assessed as unlikely, 1 was assessed as possible, and 1 was un-assessable.

Discussion

The Moderna post-authorisation safety studies, particularly mRNA-1273-P919 and mRNA-1273-P903 studies, provided valuable insights into the potential association between SPIKEVAX™ vaccination and pregnancy outcomes. The results from mRNA-1273-P919 study, showed a small but statistically significant increase in the adjusted relative risk for preeclampsia, gestational

hypertension, and GD when compared to distantly vaccinated and unexposed populations, particularly when exposure occurred during the second trimester. However, the outcomes did not show any evidence of increased risk for these outcomes when compared to COVID-19 infection during pregnancy. Results from mRNA-1273P903 study showed similar observation as mRNA1273-P919 study. The crude risk ratio was increased for GD and pre-eclampsia in mRNA-273-P919. The results from the study mRNA-1273-P919 triggered the signal evaluation of these 3 topics gestational hypertension, pre-eclampsia, and GD.

Review of RSI showed that Gestational hypertension, pre-eclampsia, and GD are not labelled as ADR in the current Moderna mRNA-1273 CCDS. Gestational hypertension, pre-eclampsia and GD are not labelled as an ADR in other COVID-19 vaccines label.

There were 175 reports of pregnancy identified in mRNA-1273-P301. Of these 175 reports, there were 13 cases of the events of interest: gestational hypertension (3), pre-eclampsia (7), and GD (3). None of the 13 reports were considered related by the investigator. The observed long time to onset between vaccination and the events (152 – 582 days) make an association with vaccination unlikely. Additionally, many cases included other risk factors that confound potential association with vaccination. Medical review of these cases did not reveal any significant safety concerns related to pregnancy and the use of marketed Moderna vaccines targeting SARS-CoV-2.

Review of the 60 reports for gestational hypertensive disorder, and 23 cases for GD from the GSDB revealed that there were only few reports that met the case definition for gestational hypertension (4); pre-eclampsia (2), and GD (5). Review of cases did not identify any sentinel case and/or any significant safety concern and/or any reasonably possible association between use of marketed Moderna vaccines targeting SARS-CoV-2 administration and the events gestational hypertension, pre-eclampsia, and GD.

Literature review identified articles that demonstrated a potential association between COVID-19 infection itself and the events gestational hypertension, pre-eclampsia, and GD, though the finding were not consistent in all studies. Review of the literature articles did not identify any articles that may provide sufficient evidence of an association between gestational hypertension, preeclampsia, and GD and marketed Moderna vaccines targeting SARS-CoV-2 vaccination. Identified articles demonstrated that COVID mRNA vaccination does not affect the syncytiotrophoblasts and placental development. Several articles showed there was no consistent or significant increased risk of GD, gestational hypertension and pre-eclampsia following receipt of COVID-19 vaccination.

The results from the external safety databases (EVDAS, VAERS) showed that the events gestational hypertension, pre-eclampsia and GD, did not meet the disproportionality threshold.

Overall, the review of the data from all the available data sources (MAH safety database, Clinical trial data, external safety databases, epidemiological studies, and literature review) showed that there is insufficient evidence to suggest a possible causal association between use of marketed Moderna vaccines targeting SARS-CoV-2 and the 3 pregnancy-related outcomes at this point of time. The findings are consistent with the known safety profile of the vaccine, and the benefits of vaccination in the prevention of COVID-19 during pregnancy are clear. Continued surveillance and research are essential to monitor the safety of COVID-19 vaccines and to further understand their impact on pregnancy outcomes.

Conclusion

The comprehensive evaluation of available data from CTs, pharmacovigilance databases, external databases, epidemiological studies, and published literature does not substantiate a relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the occurrence of gestational hypertension, pre-eclampsia, or GD. While 2 post-authorisation safety

studies (PASS) indicated a marginal increase in risk, these findings have not been corroborated by other data sources.

The validated signal of gestational hypertension, pre-eclampsia, or GD is considered refuted and closed at this point of time. The MAH will continue to monitor Use during pregnancy (missing information in RMP), and these safety topics (gestational hypertension, preeclampsia, and GD) through routine pharmacovigilance activities.

COVID-19 vaccination during pregnancy significantly reduces the risks of maternal SARS-CoV2 infection, hospitalisation, and ICU admission without increasing the risk of adverse pregnancy outcomes such as miscarriage, GD, or hypertension. These findings are reassuring and suggest that vaccination with the COVID-19 vaccines is safe during pregnancy.

The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive.

Rapporteur assessment comment:

The signal "pre-eclampsia, gestational hypertension and GD (P919)" was initiated by the MAH based on final results from the PAS study mRNA-1293-P909. The study was completed in 2024 and the final study report was assessed during the procedure EMEA/H/C/005791/II/0131. The data collection for the PAS study started on 01-03-2023 and ended on 20-10-2023 and covered the study period of 01-12-2019 to 01-01-2023 (both dates included).

The study population included 271,179 women who met study entry criteria. Of these, 24,796 women were exposed to Spikevax through vaccination at any time during pregnancy, and 246,383 women were unvaccinated with any COVID-19 vaccine. In the group of women who were unvaccinated during pregnancy, two sub-groups were identified: 10,749 women who were distantly exposed to Spikevax (i.e. vaccinated at least 60 days prior to last menstrual period (LMP)), and 23,584 unvaccinated women who were diagnosed with COVID-19 during pregnancy.

Based on data in the final study report, the PRAC rapporteur concluded "*...that observed increased risks of pre-eclampsia, gestational hypertension, and gestational diabetes (all adjusted relative risks were below 1.60) do not warrant any regulatory actions at this point in time. The results of the Spikevax EU pregnancy study and the final study report is awaited according to study milestones 31 Mar 2025, which may further clarify the association between Spikevax vaccination in relation to pregnancy and subsequent risk of various outcomes*". The procedure was finalised in November 2024.

In the current PSUR, the MAH summarises the results obtain from the study mRNA-1273-P909, which were assessed during the procedure EMEA/H/C/005791/II/0131.

In addition, the MAH has performed a cumulative search in their global company safety database with a cut-off-date of 17-02-2024 and identified 81 cases concerning: gestational hypertension (32 cases), pre-eclampsia (26 cases) and GD (23 cases). The MAH concludes that few reports met the case definitions - gestational hypertension (4 cases), pre-eclampsia (2 cases) and GD (5 cases). The presented literature review confirms these conclusions.

The rapporteur maintains the position clarified during the procedure EMEA/H/C/005791/II/0131 i.e. that currently there is observed a slightly increased risk of pre-eclampsia, gestational hypertension and gestational diabetes based on data from the US-pregnancy PAS study. The PRAC rapporteur considers that the final study report from the EU PAS pregnancy study should be awaited before any further conclusions and/or actions can be decided.

2.2.5. Ischaemic stroke

Source

The signal of "ischaemic stroke" was considered validated based on a CDC presentation at ACIP on 27 Jun 2024, showing a Vaccine Safety Datalink (VSD) statistical signal for ischaemic stroke for mRNA COVID-19 vaccines during the 2023-2024 season, requiring further evaluation.

Statistical signal of ischaemic stroke was noted for the following:

- Pfizer-BioNTech vaccine in patients 50-65 years of age, in the 1–21-day window.
- Moderna COVID-19 Vaccine in patients 65 plus years of age, in the 1–42-day window.

Background

The MAH considered ischaemic stroke as a validated signal, based on the presentation by CDC at the ACIP meeting on 27 Jun 2024.

Methodology

The AHA/ASA Expert Consensus paper [15] emerged as the most accepted definition for stroke and Ischaemic Stroke and being referred to in numerous other literature article. It provided a very helpful and important flow chart to guide clinicians in diagnosing specifically an Ischaemic Stroke, with the end goal of accurate diagnosis leading to best treatment choices.

This diagram (and accompanying elements) was especially useful for developing a robust case definition to be applied to the identified by our search strategy to find true cases of Ischaemic Stroke. It was supplemented with additional data from the AHA/ASA consensus document, and other sources, to help define details of what represented positive imaging, or which symptoms would be considered with consistent with ischaemic stroke. As well, this document provided definition for both haemorrhagic stroke and Transient Ischaemic Attack (TIA), and any cases meeting those definition rather than ischaemic stroke were identified if they met those definitions.

With this additional information identified, this flow chart was applied to each report in a systematic way by a clinician. Definitions of how well each case described a potential case of ischaemic stroke given the nature of post marketed data were developed for use in this report.

- A Definite report of Ischaemic Stroke:
- A definite case needed all the key elements. It had to include clinical symptoms consistent with an ischaemic stroke, and there had to be evidence that the symptoms lasted at least 24 hours. And there could not be a more likely disease process that explained the symptoms (e.g., migraines, trauma). As per the guidelines from AHA/ASA, if these conditions were met, imaging could be positive, or it could be not done/not provided/inconclusive. Cases were tracked as definite with positive imaging and definite without positive imaging, but they are treated equally in this report.
- A report could also be considered definite for a silent infarction if there as positive imaging performed, but no specific symptoms provided. However, these would only be considering silent infarctions if the presenting events were deemed to last at least 24 hours.

For presentation all definite cases will be described together.

A Likely report of Ischaemic Stroke:

- A likely report of ischaemic stroke is one in which the imaging is positive, but 1 of the elements of the confirmatory symptoms is not provided. If a report had positive imaging and providing a symptom consistent with ischaemic stroke but failed to provide a

timeframe for the symptoms, it will be defined as a likely case of ischaemic stroke. (note: if the symptoms were reported as less than 24 hours, then the case would be considered a TIA).

- Similarly, if imaging is positive for ischaemic stroke, and no specific symptoms was included, but it was clear the event lasted greater than 24 hours, then the case will also be considered likely.

A Probable report of Ischaemic Stroke:

- A probable case of is stroke is defined for this report as in which imaging is not provided/unknown/inconclusive but a symptom(s) consistent with an ischaemic stroke are demonstrated. However, it is considered only probably because there was no data provided showing that the symptoms lasted more than 24 hours (that is, length of symptoms is unknown).
- If symptoms provided are known to have resolved in less than 24 hours, this case would be considered a TIA.

A Potential report of Ischaemic Stroke:

- A probable case of is stroke is defined for this report as in which imaging is not provided/unknown/inconclusive but a symptom(s) consistent with an ischaemic stroke are demonstrated. However, it is considered only probably because there was no data provided showing that the symptoms lasted more than 24 hours (that is, length of symptoms is unknown).
- If symptoms provided are known to have resolved in less than 24 hours, this case would be considered a TIA.

A Potential report of Ischaemic Stroke:

- A report is considered only to be a potential ischaemic stroke if imaging is not provided/unknown/inconclusive, and no specific symptoms c/w ischaemic stroke is provided. However, a term consistent with ischaemic stroke was provided, and it was noted that the event lasted more than 24 hours.

A Term Only report of Ischaemic Stroke:

- A report is term only for an ischaemic stroke if imaging is not provided/unknown/inconclusive, no specific symptoms consistent with ischaemic stroke are demonstrated, and the timing of the events is unknown (no proof they lasted more than 24 hours). Effectively, the only positive evidence of an ischaemic stroke is that a term consistent with ischaemic stroke was provided by the reporter. Finally, if upon review a case was determined to be a TIA (e.g. symptoms we noted to have resolved in less than 24 hours), or a Haemorrhagic Stroke (e.g., the presenting symptoms and/or imaging were consistent with a haemorrhagic stroke (without evidence it evolved from an ischaemic stroke), they were categorised as such.

Results

Cumulatively as of 09 Jul 2024, review of GSDB search retrieve, a total of 663 cases were identified by the search strategy.

Overview of the Reports

Age and gender were broadly consistent with the epidemiology of Ischaemic Stroke. In terms of gender, there were 360 males (54.3%), 298 females (44.9%), and gender was not provided in 5

reports. In terms of age, the average age of these patients was 64 years. The median age was also 64 years. Age ranged from 20 to 96 years. Age was provided in all but 13 reports. Six hundred and sixty-one (661) reports were serious (99.7%). Most reports, 658 (99.2%) were spontaneous, with only 5 literature-non-study reports. Reports came from a wide variety of countries, with the United States and France providing the largest number of reports.

- United States (n=180), France (n=144), Italy (n=67), Switzerland (n=58), Taiwan (n=36) Germany (n=34), Netherlands (n=30), UK (n=21), Spain (n=12), Slovakia (n=10), Sweden (n=8), Australia (n=7), Austria (n=6), Poland (n=6), Greece (n=5), Portugal (n=5), Brunei (n=4), Thailand (n=4), Belgium (n=3), Argentina (n=2), Canada (n=2), Croatia (n=2), Czech Republic (n=2), Denmark (n=2), Japan (n=2), Lithuania (n=2), Cyprus (n=1), Estonia (n=1), Israel (n=1), Latvia (n=1), Luxembourg (n=1), Norway (n=1), Philippines (n=1), Singapore (n=1), and Romania (n=1)

Overview of Reports by Case Definition and WHO-UMC Causality

All reports were reviewed by a clinician to see if they met case definition for Ischaemic Stroke, using the definitions outlined above. The results were:

15 were determined to be reports with TIA as a more likely diagnosis.

38 were determined to be reports with haemorrhagic stroke as a more likely diagnosis.

265 had only a reported term consistent with ischaemic stroke, but no elements of an ischaemic stroke were provided.

102 reports described a potential case of ischaemic stroke.

61 reports were determined to be probable reports of ischaemic stroke, with only limited details supporting this diagnosis provided.

70 reports described a likely case of ischaemic stroke.

112 reports described definite reports of ischaemic stroke.

Regardless of the whether the reports met the case definition, all reports were reviewed for potential causal association with mRNA-1273 by a clinician. As 345 reports were identified as at least a potential case of Ischaemic Stroke, they were further reviewed to determine if any pattern indicating a potential safety signal was discernible. As with the overall review, age and gender were consistent with epidemiology of ischaemic stroke. A review of the dose number and time to onset after vaccination did not show a clear pattern across these reports and was consistent with an event more closely related to the patient's underlying disease and risk factors rather than causally related to vaccination.

Review of the clinical course, presenting symptoms, and diagnostic findings also failed to identify any concerning pattern. The presenting symptoms were not consistent across reports and reflected a range of underlying vascular structures and causes of ischaemic stroke that would be expected in the general population experiencing stroke. Diagnostic findings (MRI and CT) did not show a consistent pattern in terms of the location or evolution of the ischaemic injury. Clinical examination was similar.

As part of the careful review of these reports at least providing minimum data consistent with the diagnosis of ischaemic stroke, the potential causal association was confirmed and demonstrated a similar pattern to the overall reports. Amongst these 345 reports:

Ninety-nine (99) of the reports were deemed Unassessable. These reports did not include key clinical data elements to allow a causal assessment. These reports were all missing at least 3 critical data elements, including past medical history, concomitant medications, details of the

clinical course of the events, information on the time to onset vis a vis vaccination, treatment details, diagnostic results, or age/gender.

Two hundred and forty (240) of the reports were deemed as Unlikely. These reports contained strong confounding factors that provide a plausible explanation for the event. hese reports contained at least 2 or more risk factors for ischaemic stroke (as outlined in the background of this document), or other concurrent disease processes that are more likely the cause of the report of Ischaemic Stroke.

No reports described elements that would suggest either Probably/Likely or Certain causal association.

Six (6) reports described a Possible causal relationship to mRNA-1273.

Additional Analysis: Concomitant/Co-Suspect Influenza Vaccination

No pattern was noted concerning the concomitant use of influenza vaccine across the 663 reports. Only 8 (1.2%) of the reports described concomitant influenza vaccination (n=2) or influenza vaccine as a co-suspect (n=6). No reports described the influenza vaccination as "high-dose" or adjuvanted. Notably, reports of concurrent use occurred in older patients, range 71-94, average age 82. One patient did not have a reported age.

In terms of case definition, 4 of these reports contained an Ischaemic Stroke term only. One described a TIA, not meeting the definition of stroke. Only 3 were likely or definite reports of ischaemic stroke. 2 these were strongly confounded. The remaining case is described in the table above, and the concomitant influenza vaccine use is highlighted.

Given the small number of reports with concurrent influenza vaccination, and the limitations of post-marketing data, no conclusion regarding the concomitant use of Spikevax and influenza vaccine can be determined from review of the GSDB.

Discussion

A statistical signal for ischaemic stroke and administration of Spikevax vaccines, including concurrent administration of high-dose influenza vaccines, was presented by the CDC during the ACIP meeting on 27 Jun 2024. The signal was identified in the VSD for the time period of 10 Sep 2023, through 27 Apr 2024, evaluating first COVID-19 vaccine dose received during this period.

Statistical signals were noted for both marketed mRNA COVID-19 vaccine:

For Pfizer vaccine, a statistical signal for ischaemic stroke was noted in the age group of 18-64 years of age, in the 1–21-day window after vaccination. This signal was especially notable in the age group of 50-64 years of age and was not seen in those aged 18-49 upon sub-analysis.

For the Moderna vaccine, a statistical signal for ischaemic stroke was noted in the age group of 65 years plus, in the 1–42-day window after vaccination.

For Moderna, the signal was only statistically significant when the vaccine was given the same day as influenza vaccine. (2.53, 1.10-5.91), although the CI was quite wide.

The CDC noted that there was a lack of consistent finding across age groups or risk interval. The concluded that this season's findings are consistent with CDC Immunisation Safety Office's prior interpretation based on data review in Oct 2023 that stated: "Available data do not provide clear and consistent evidence of a safety problem for ischaemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccine" still, the MAH considered this a validated signal, and undertook a signal evaluation of ischaemic stroke in association with all Spikevax variants, reviewing all available data.

Review of RSI showed that ischaemic stroke is not labelled as ADR in the current Moderna mRNA 1273 CCDS. Ischaemic stroke is not labelled as an ADR in other COVID-19 vaccines label.

In terms of clinical data, cases of ischaemic stroke from the mRNA-1273-301 study were reviewed. Seven (7) reports were identified. One (1) report occurred in a subject after receive placebo, and 6 reports occurred after receiving vaccination. Given the design of this study, in which all subject receiving placebo in part A were offered vaccination in the open-label Part B, this ratio of reports was in line with the exposure time to placebo and vaccine. Notably, none of these cases, other than the placebo case, occurred at least 60 days after vaccination, outside the window noted by the CDC and all occurred in elderly subjects who are at higher risk for ischaemic stroke.

In terms the GSDB, 663 reports of ischaemic stroke were identified. Three hundred forty-five (345) of these reports were identified as at being at least a potential report of ischaemic stroke when case definitions based on the AHA/ASA Consensus Expert report were applied. Careful review of these reports, including review of age, gender, time to onset, dose number, clinical course, presenting symptoms, did not identify a consistent pattern suggesting a causal association with mRNA-1273.

On an individual report basis, 99 of these reports were deemed to have an Unassessable causality as they did not provide sufficient information to review an association. A further 240 reports were deemed to have an Unlikely causality as they described patients with at least 2 risk factors for ischaemic stroke or had another concurrent disease process that provided a plausible explanation for the events.

None of the reports described elements suggesting a Probably/Likely or Certain causal association with mRNA-1273. Only 6 reports were determined to have a Possible causal association. All 6 of these reports contained a relatively limited amount of clinical data, and all 6 described at risk factor for ischaemic stroke.

Review of available epidemiological data focused on the US PASS mRNA-1273-P920. In this study, no increased risk ischaemic stroke following exposure to elasomeran/davesomeran or andusomeran was observed compared to influenza vaccinated cohort and medically-attended COVID-19 cohort within 1-28 days. The secondary analysis concluded no increased risk ischaemic stroke following exposure to Elasomeran/davesomeran or andusomeran with or without coadministration of influenza vaccine was observed compared to influenza vaccinated cohort and medically-attended COVID-19 cohort within 1-28 days. Further, the sensitivity analysis showed no increased risk of ischaemic stroke following exposure to elasomeran/davesomeran or andusomeran with or without coadministration of influenza vaccine was observed compared to influenza vaccinated cohort within 1-21- and 22-42-days.

Review of the literature did not identify any articles that may provide sufficient evidence of a causal association between Ischaemic stroke and SPIKEVAX vaccination. Generally, ischaemic stroke was shown to be causally associated with COVID-19 infection, and several mechanisms of action for such an association were speculated in the literature. However, none of these mechanisms were demonstrated to be pertinent for vaccination, and the literature review failed to support a safety issue of concern.

The results from the external safety databases (EVDAS, VAERS) showed ischaemic stroke did not meet the disproportionality threshold on a consistent basis.

Overall, the review of the data from all the available data sources (MAH safety database, Clinical trial data, external safety databases, epidemiological studies, and literature review) showed that there is insufficient evidence to suggest a potential causal association between use of marketed Moderna vaccines targeting SARS-CoV-2 and ischaemic stroke at this point of time; the Company considers ischaemic stroke as a refuted signal. The findings are consistent with the known safety

profile of the vaccine, and the benefits of vaccination in the prevention of COVID-19 is clear. The MAH will continue to monitor ischaemic stroke as part of its pharmacovigilance activities and will add ischaemic stroke as a close monitoring event.

Conclusion

The comprehensive evaluation of available data from CTs, pharmacovigilance databases, external databases, epidemiological studies, and published literature does not substantiate a relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the occurrence of ischaemic stroke, including co-administration with influenza vaccines. While the CDC presented a statistical signal at the ACIP of an increased risk of ischaemic stroke in those over 65 years of age, especially with concomitant influenza use, these findings have not been corroborated by other data sources.

The MAH concludes that there is insufficient evidence to support a causal association between SPIKEVAX administration (marketed Moderna vaccines targeting SARS-CoV-2) and ischaemic stroke; the Company considers ischaemic stroke as a refuted signal. The MAH will continue to monitor ischaemic stroke as part of its pharmacovigilance activities and will add ischaemic stroke as a close monitoring event.

COVID-19 vaccination has been shown to reduce stroke risk over time, as it reduces COVID-19 infection and its sequalae. These findings are reassuring and suggest that vaccination with the COVID-19 vaccines is safe for older patients. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive.

Rapporteur assessment comment:

The signal was presented by CDC at the ACIP meeting on 27-06-2024, where the CDC presented a statistically significant signal of ischaemic stroke for both mRNA vaccines (Cominarty and Spikevax). For Spikevax, the signal was observed in patients over 65 years of age and in the window 1 – 42 days (post-vaccination). The CDC presentation concluded: " *that there was a lack of consistent finding across age groups or risk interval. The concluded that this season's findings are consistent with CDC Immunisation Safety Office's prior interpretation based on data review in Oct 2023 that stated: "Available data do not provide clear and consistent evidence of a safety problem for ischaemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccines".*

The MAH has subsequently made their own signal assessment of the risk "ischaemic stroke". Their search in the global company safety database resulted in 663 cases of which 345 cases were considered to be true cases of ischaemic stroke. 99 of these 345 cases were un-assessable, 240 cases were assessed as unlikely and six cases were considered possible but all six cases concerned patients with known risks factors for ischaemic stroke.

The MAH concludes that currently there is insufficient evidence to support a causal association between use of Spikevax and ischaemic stroke.

The provided signal evaluation is acknowledged. However, the provided signal assessment report (included in annex 5 in the PSUR) replicates the conclusions made by the CDC. The MAH is therefore reminded not to present already assessed topics as signals in future PSURs. The MAH is also reminded of their obligation to conduct their own signal detection and not to present HA requests and topics raised for discussion at ACIP meeting as signals in future PSURS.

2.2.6. Dermatitis allergic

Source

The MAH considered dermatitis allergic in association with Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) as a validated signal following a request from Saudi-FDA to present hypotension in next Spikevax PSUR. Saudi-FDA identified this signal from medical literature with elasomeran but did not share the source.

Background

Generally, a medical definition of allergic dermatitis was not consistently identified. When searching for this term, it usually returned allergic contact dermatitis.

- Several sources noted the 2 terms as basically interchangeable,
- True allergic contact dermatitis is Type IV, T-cell-mediated allergic reaction, and symptoms should be consistent with that.

Overview of Allergic Contact Dermatitis (ACD)

Allergic contact dermatitis as defined by Mayo Clinic and the American Academy of Allergy, Asthma, and Immunology is a skin reaction caused by exposure to allergens, triggering an immune response. This form of dermatitis is a delayed-type hypersensitivity reaction, typically occurring hours to days after contact with an allergen. Common allergens include metals (e.g., nickel), cosmetics, fragrances, medications, and plants such as poison ivy.

Incidence and Risk Factors

ACD can affect people of all ages, but it is more common in those with a genetic predisposition to allergies or those repeatedly exposed to allergens. Occupations like healthcare, construction, cosmetology, and food service often involve higher risk due to frequent exposure to irritants and allergens.

Methodology

The evaluation of the occurrence of dermatitis allergic in association with the administration of Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) used in the indication of Covid-19 was performed using several data sources. The methods of evaluation and the results obtained from each of the analysed data sources are described below:

Non-Clinical Data

There are no data to assess the effects of vaccine on Dermatitis allergic in (SPIKEVAX IB v. 9.0)

Clinical Trial Data

The Data from the CTs listed in the Table-xx was reviewed to identify cases reporting the MedDRA PTs in section 3.2.1.

The topic of dermatitis allergic was reviewed in the clinical trial setting using the following search criteria using MedDRA PT: Dermatitis allergic. Any report with this MedDRA PT, within 2 weeks of vaccination were retrieved and reviewed.

Results

Review of clinical trial data showed the relevant data on dermatitis allergic from study mRNA-1273P301; mRNA-1273-P203 and mRNA-1273-P204, remaining studied had no reports related to dermatitis allergic. There were 14 reports of which 4 were reported within 2 weeks of the study vaccination.

The cumulative search of the GSDB (Cumulative through 17Sep2024) retrieved 573 cases (2 cases were invalid). There were 576 events reported across the 573 cases (3 cases reported same PT more than once). The majority of cases were reported in the European Economic Area, the UK, and

the United States. As a known factor, Female patients were accounted for the majority of cases (78.0%). There were cases (2.3%) for which gender information was not reported. A significant portion of cases (34.5%) had an unknown dose number. The average time to onset was approximately 2 weeks, but with a large standard deviation, indicating high variability among cases.

The scientific literature search retrieved 476 literature hits of which, most of these (90%) articles discuss the different types of Dermatitis, such as, atopic Dermatitis, Psoriasiform Dermatitis, and Allergic Contact Dermatitis.

Of the 40 articles, most described Dermatitis allergic and covid-19 infection or were associated with Dermatitis allergic and adenoviral vector vaccines.

Review of these literature hits did not identify any articles that could provide sufficient evidence of an association between Dermatitis allergic and SPIKEVAX vaccination.

- No new Individual Case Safety Reports (ICSRs) beyond what was already documented in the Company's safety database were identified.
- There were few articles which speculated mechanism etc., but none of these articles confirmed a well-established mechanism associated with Dermatitis allergic and mRNA vaccination.

However, there are multiple articles describing the association of Dermatitis allergic with COVID-19 infection were selected 3 articles describing the Dermatitis allergic with COVID-19 infection.

- Battis N, Ekstein SF, Cosky E (Eugene P, Neeley AB. Patient Reported Association Between COVID-19 Infection or Vaccination and Onset of Allergic Contact Dermatitis. Dermatitis® 2024.
- Daneshbod Y, Ahmed I, Kerstetter J. Psoriasiform Dermatitis Associated With the Moderna COVID-19 Messenger RNA Vaccine. Cutis. 2022;110(5):E1–4.
- Sidlow JS, Reichel TR, Reichel M, Lowenstein EJ. Localised and generalised urticarial allergic dermatitis secondary to SARS-CoV-2 vaccination in a series of 6 patients. Jaad Case Reports. 2021;14:13–6.

In summary, review of the literature did not identify any articles that may provide sufficient evidence of a causal association between Dermatitis allergic and SPIKEVAX vaccination.

Discussion

- No disproportionate reporting of Dermatitis allergic was observed in EVDAS or VAERS,
- No pattern was identified regarding Dermatitis allergic during CTs,
- Literature output review was inconsistent for Dermatitis allergic association with vaccination,
- Post marketed data review showed that majority of cases were spontaneous type reports (of 571 cases only 4 were literature non-study reports) lacking important information (e.g medical history and/ or concomitant medications); there were 209 cases (36.6.%) unassessable; 145 (25.4%) cases reported confounding factors. Reported local events (rash, pruritus, erythema, swelling, etc.) are listed in current CCDS,
- Review of labelling of other COVID-19 Vaccines revealed that Dermatitis allergic is not listed in other manufacturer's labels (Pfizer/BNT162b2, Janssen and Novavax).

Conclusion

Symptoms of dermatitis allergic are adequately reflected in current CCDS. Besides, the higher severity events of Hypersensitivity and Anaphylaxis are listed as well. The current CCDS (version 19.0) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified.

The cumulative safety data evaluated does not provide a sufficient basis for new recommendations or product labelling changes and/or RMP, including relevant risk minimisation measures with regard to Dermatitis allergic. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive. The MAH will continue to monitor through routine pharmacovigilance activities.

Rapporteur assessment comment:

The MAH has indicated that the Saudi FDA requested a presentation of "dermatitis allergic" in the next PSUR. However, the current text in the PSUR reads as follows: *"The MAH considered dermatitis allergic in association with Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) as a validated signal following a request from Saudi-FDA to present hypotension in next Spikevax PSUR. Saudi-FDA identified this signal from medical literature with elasomeran but did not share the source".* **To avoid any misunderstandings the MAH is requested to clarify in this PSUSA procedure, whether the SFDA requested the topic of "dermatitis allergic" to be presented, as the same text is presented in section 2.2.7 for the signal "hypotension" or if the signal of dermatitis allergic was triggered by another source.**

The MAH has modified their search of cases in their global company safety database and in the literature to include the term "allergic contact dermatitis" as the term "dermatitis allergic" could not be defined medically. This is agreed.

No data was identified from non-clinical sources. There were 14 cases reported from clinical trial data and the global company safety database identified 573 cases (cumulatively). The MAH has furthermore indicated that no disproportionality was observed in analyses performed on the data from EVDAS and from VAERS.

The 573 cases included three duplicates. Of the remaining 571 cases, 209 cases were deemed un-assessable and 145 cases were considered confounded by the MAH. The remaining cases confirmed the listed PTs of e.g. rash, pruritus, erythema and swelling.

The MAH concludes that the currently listed PTs are sufficient and that no further actions are necessary at this point in time. This is agreed.

2.2.7. Hypotension

Source

The MAH considered hypotension in association with Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) as a validated signal following a request from Saudi-FDA to present hypotension in next Spikevax PSUR. Saudi-FDA identified this signal from medical literature with elasomeran but did not share the source.

Background

Hypotension is a decrease in systemic blood pressure below accepted lower bound values, which is any blood pressure below 90/60: that is if the systolic blood pressure if below 90 mm Hg, or the diastolic is below 60 mmHg, it is considered hypotension. While much more rarely used, hypotension can also be considered when the mean arterial pressure (2/3 diastolic + 1/3 systolic) is below 65 mm Hg. While hypotension can be accompanied by symptoms, they are not necessary

for diagnosis. In fact, the condition is often underdiagnosed because it is often not symptomatic. Hypotension may be subclassified as orthostatic in nature if there is a documented drop of 20 mm Hg systolic, or 10 mm Hg when the patient changes from lying to standing.

Methodology

The evaluation of the occurrence of Hypotension in association with the administration of Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) used in the indication of Covid-19 was performed using several data sources.

Results

Non-Clinical Data

There are no data to assess the effects of vaccine on hypotension in (SPIKEVAX IB v. 9.0).

Clinical Trial Data

The topic of hypotension was reviewed in the clinical trial setting using the following search criteria using MedDRA PTs: Hypotension, Orthostatic hypotension, Diastolic hypotension. Review of clinical trial data showed the relevant data from study mRNA-1273-P301 and mRNA-1273P304, remaining studied had no reports related to hypotension.

Clinical Trial Study mRNA-1273 P301

In part A of this trial (the first portion which was blinded, with a 1:1 vaccine to placebo ratio), a total of 27 events of hypotension in 25 separate subjects was identified.

Clinical Trial Study mRNA-1273-P304

This trial did not have a placebo control, so all reports identified received mRNA-1273. Notably, these patients, who were all immunocompromised, had significant medical history and a number of potential confounders. A total of 4 reports were identified. Three had underlying liver disease/transplant, and 1 had underlying kidney disease/transplant leading to their immunocompromised status. They ranged in age from 49-67 year.

No cases were identified in the paediatric trials (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P306).

Overall, review of the data seen in clinical did not demonstrate any signal of concern for an association between mRNA-1273 immunisation and hypotension.

Company GSDB

Cumulatively, a total of 2,515 hypotension cases (2,515 events) of which 906 (36.0 %) were reported as serious cases were retrieved from the Company GSDB in association with SPIKEVAX. Out of the total 2515 cases, 99 cases reported a fatal outcome. Most reports came from the US and Europe. Almost two-thirds of the reports were non-serious. The age range of the reports was wide, with mild peaks at 25-39 years, and 50-64 years. No specific pattern in terms of dose number was noted, and number of reports declined with the number of doses, as would be expected given the use of the vaccine. Time to onset had an average of 10.8 days, but a median of just 1 day. This is consistent with many of reports describing vasovagal reactions to vaccination, as is seen with all vaccines. Most reports were either deemed to not be true reports of hypotension (n=231) or did not provide enough information to assign a definition (n=1487). Another 433 reports failed to provide a blood pressure measurement but did provide symptoms consistent with hypotension that were not due to another aetiology and were at least Potential reports of hypotension. Three hundred sixty-six (366) did meet the Definite case definition, providing a blood pressure below 90/60. Amongst these reports meeting the case definition, no pattern representing

a safety concern for Spikevax was noted. Only 27 of these Definite reports were deemed to be possibly related to Spikevax. Most of these 27 reports did have potential confounders for the event of hypotension, and generally they provided very limited information that would allow a full review of a potential causal association. These 27 reports were mild in nature, often not requiring medical intervention beyond fluid intake. More than half were consistent with vasovagal symptoms commonly seen with all vaccines.

Review of the GSDB identified no sentinel cases and did not demonstrate a consistent pattern that could represent a safety signal for Spikevax and a potential association with hypotension.

Discussion

Hypotension is often associated with other diseases, including COVID-19 itself. Vasovagal symptoms, due vasovagal hypotension, have been associated with all vaccines, and is related to vaccine process, not the vaccine itself.

Review of multiple data sources failed to identify an association between Spikevax itself and events of hypotension:

- Observed vs. expected analysis did not demonstrate an elevated reporting rate for hypotension.
- Review of EVDAS and VAERS did not provide any significant disproportionality.
- Review of the clinical trial data did not demonstrate any signal of a safety concern.
- Review of the literature failed to identify an association between Spikevax immunization and hypotension, nor an established mechanism for such an association.
- Review of the Post-Marketing database did not identify any signal of concern.

Conclusion

Based on the review of all data presented in this report, the cumulative evidence shows an insufficient data to support a causal association between validated signal of hypotension and Spikevax vaccination; the Company considered Hypotension as a refuted signal.

The current CCDS (version V19) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified. The cumulative safety data evaluated do not provide a sufficient basis for new recommendations or product labelling changes and/or RMP, including relevant risk minimisation measures with regard to hypotension.

The validated signal of hypotension is considered as refuted signal and closed at this point of time.

The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive. The MAH will continue to monitor hypotension through routine pharmacovigilance activities.

Rapporteur assessment comment:

The signal "hypotension" was triggered by the Saudi FDA with a request to present "hypotension" in the next PSUR. The SFDA identified the signal from medical literature.

A search in the available non-clinical and clinical trial data did not reveal any signal of concern according to the MAH.

2515 cases of hypotension were identified in the global company database and 906 cases of these were classified as serious cases. 99 cases of the 2515 cases were fatal. The average time-to-onset was 10,8 days and the median was calculated to be 1 day. 231 cases were considered not "true reports" of hypotension and 1487 cases did not contain sufficient information to assign a diagnosis.

433 cases did not provide a blood pressure measurement but the symptoms were described and were consistent with hypotension.

The MAH concludes that there is insufficient evidence to support a causal association between use of Spikevax and hypotension and refutes the signal. This is agreed.

Endorsed.

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 clinically relevant new safety information for this topic. The characterisation of this important risk as described in Section 16.4, remains valid.

A thorough evaluation of information receiving during this PBRER #7 reporting interval relating to the use of marketed Moderna vaccines targeting SARS-Cov-2 and known important identified risk of anaphylaxis has not identified any additional clinically relevant new safety information.

Table 20: Anaphylaxis

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
Source of new information	• Moderna GSDB • Literature Sources o Search Criteria Applied: [PSUR] Appendix 13.4 o Retrieved: 132 o New and Significant Safety Information: There was no new and significant safety information identified. Refer to [PSUR] Section 11 for additional information.
Background	Anaphylaxis is a listed event for SPIKEVAX. The MAH's CCDS contains specific guidance that the vaccine is contraindicated in individuals with known severe allergic reactions to any component of the vaccine or to a previous dose of the vaccine, including, any subsequent doses should not be given to those who have experienced anaphylaxis to the first dose of SPIKEVAX. Further, it specifies that appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Guidance is also included for close observation for 15 mins for all persons receiving the vaccine and for 30-minutes for people with a history of allergic reaction/anaphylaxis to another vaccine.

	Anaphylaxis is considered an important identified risk only for the PBRER. Anaphylaxis was removed from the RMP as an important identified risk and reclassified it as an identified risk (not important). While anaphylaxis, remains as an identified risk for the product, as with any other biologicals, it does not have a considerable impact on the benefit-risk balance of the vaccine.
Methods of evaluation	The MAH applied the MedDRA SMQ "anaphylactic reaction" (narrow scope) to retrieve all cases in the review period reporting AEs suggestive of anaphylaxis from the GSDB for individuals who received marketed Moderna vaccines targeting SARS-CoV-2. Cases were classified following the Brighton Collaboration case definition for Anaphylaxis [16,17]. The Company causality assessment was provided utilising the WHO-UMC standardised case causality assessment.
Results	Refer to [PSUR] Appendix 12.7 for additional information. Overview of Anaphylaxis Cases involving elasomeran: It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide after June 2023. During the reporting period, the MAH received 36 serious cases (36 serious events) containing the reported PT of anaphylaxis. Of these, 26 cases were medically confirmed. The majority of cases (27 cases, 75.0%) were reported in females, compared to 8 cases (22.2%) in males, with 1 case (2.8%) lacking gender information. The mean age was 44.7 years (SD: 13.6), and median age was 46.0 years (range: 15.0 to 70.0 years). There was one case [redacted] with a reported fatal outcome. This involved a male patient of unknown age, who after receiving the first dose of elasomeran reportedly developed multiple AEs. However, anaphylaxis was not a reported event in this case. The events experienced by this patient were likely complications arising from progression/worsening of the underlying pre-existing comorbidities involving multiple organs (generalised atherosclerosis, condition after a previous heart attack, cardiomyopathy, cirrhosis of the kidneys, lung changes including pleural and pericardial effusions, hyperaemic gastritis) and a concurrent infection which provided a more likely explanation of the reported events in this case (circulatory failure, shock due to pulmonary oedema). *Overview of Anaphylaxis Cases involving elasomeran/imelasomeran:* During the reporting period, no cases were received for elasomeran/imelasomeran. *Overview of Anaphylaxis Cases involving elasomeran/davesomeran:* During the reporting period, the MAH received 4 serious medically confirmed cases (4 serious events) containing the PT of anaphylaxis. The majority of cases (3 cases,75.0%) were reported in females, compared to 1 case (25.0%) in males. The mean age was 64.0 years (SD: 15.5) and median age was 58.0 years (range: 53.0 to 87.0 years).

	There was one case ([redacted] with a reported fatal outcome. Anaphylaxis (PT) was not a reported term in this case, which involved an 87-year-old male patient with known concurrent Interstitial Lung Disease (ILD). The patient also experienced the event of shock, which occurred 8 months after vaccination with elasomeran/davesomeran. *Overview of Anaphylaxis Cases involving andusomeran:* During the reporting period, the MAH received 13 serious cases (13 serious events) containing the PT of anaphylaxis. There were 10 medically confirmed cases involving andusomeran. The majority of cases (8 cases, 61.5%) were reported in females, compared to 5 cases (38.5%) in males. The mean age was 72.2 years (SD: 20.1) and median age was 77.0 years (range: 29.0 to 95.0 years). One case was missing age information. There were 2 cases [redacted] with a reported fatal outcome. In both cases, anaphylaxis (PT) was not a reported term. Additionally, a delayed latency/ time to onset (TTO) of >1 day noted, which is atypical in the context of vaccine induced anaphylaxis. Alternative aetiologies provided a more likely explanation of the reported event(s) in both cases. *Overview of Anaphylaxis Cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA)* *2024-2025 Formula* During the reporting period, the MAH received 3 serious cases (3 serious events) containing the PT of anaphylaxis. There were 2 medically confirmed cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The majority of cases (8 cases, 61.5%) were reported in females, compared to 1 case (33.3%) in males. The mean age was 44.0 years (SD: 26.9) and median age was 44.0 years (range: 25.0 to 63.0 years). One case was missing information on age. There were no cases with a fatal outcome. Overview of Anaphylaxis Cases Involving SARS-CoV-2 JN.1 mRNA: During the reporting period, the MAH received 4 serious medically confirmed cases (4 serious events) containing the PT of anaphylaxis. The majority of cases (3 cases, 75.0%) were reported in females, while 1 case (25.0%) was missing gender information. The mean age was 66.0 years (SD: 17.8) and median age was 60.0 years (range: 52.0 to 86.0 years). There were no cases with a fatal outcome. Overview of Anaphylaxis Cases Involving SPIKEVAX NOS: During the reporting period, the MAH received one serious medically confirmed case cases (one serious event; non-fatal) containing the reported PT of anaphylaxis. The reported case involved a female (1 cases, 100.0%).
Discussion	A total of 61 cases were reported during this period, containing the reported term of anaphylaxis across

	various Moderna SARS-CoV-2 vaccines, including 4 cases with fatal outcomes. These cases were assessed using the Brighton Collaboration Criteria (BCC) and the WHO causality criteria, as follows: • Level 1: 1 case (WHO causality: Unlikely), • Level 2: 3 cases (WHO causality: 1 possible, 2 probable), • Level 3: 2 cases (WHO causality: 1 probable, 1 possible), • Level 4: 32 cases (WHO causality: 1 possible, 31 unassessable), • Level 5: 23 cases (cases not meeting the BCC case definition of anaphylaxis). Analysis of reported cases of anaphylaxis, including the events following the administration of marketed Moderna vaccines targeting SARS-CoV-2 are consistent with the known safety profile of the vaccines. Overall, a causal association between the marketed Moderna vaccines targeting SARSCoV-2 and the event of anaphylaxis is considered of at least a reasonable possibility.
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 anaphylaxis, 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 for anaphylaxis using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has presented a review for the latest one-year period about anaphylaxis in relation to use of Moderna's mRNA-vaccines targeting SARS-CoV-2. The vaccines are contraindicated in individuals with known severe allergic reactions to one or more components of these vaccines. Furthermore, vaccinated individuals should be observed for at least 15 minutes following vaccination, and appropriate treatment of unforeseen acute allergic reactions should always be available when vaccines are administered.

The MAH has presented data from the latest review period, 18 December 2023 through 17 December 2024, from the MAH's global safety database and the literature.

Results

Literature:

The MAH has performed a literature search and retrieved 132 articles, which did not contribute any new and significant safety information.

Global Safety Database:

Within the latest period, the MAH received 61 cases (61 events) reporting anaphylaxis. All cases were assessed according to the Brighton Collaboration Criteria for anaphylaxis and causality assessed according to WHO-UMC. Of the 61 cases, six (6) cases fulfilled the criteria for being a definitive, probable or possible case according to the BCC; according to WHO-UMC the vaccine-associated causality for these six (6) cases was concluded as being 3 probable, 2 possible and 1 unlikely. The other 55 cases were according to the BCC not sufficiently defined to meet the case criteria.

Cases by vaccine:

During the review period, the MAH received 36 serious cases (36 serious events) reporting anaphylaxis following exposure to Elasomeran. For Elasomeran/Davesomeran, the MAH received 4 serious cases (4 serious events), and for Andusomeran 13 serious cases (13 serious events) were reported. The MAH received also three (3) serious cases (3 serious events) following KP.2 and four (4) serious cases (4 serious events) following JN.1. One (1) serious case (1 serious event) was reported for not otherwise specified vaccines from Moderna against SARS-Cov-2. No cases were reported for anaphylaxis after Elasomeran/Imelasomeran.

Fatal cases:

In the review period, one (1) case related to Elasomeran was reported as fatal, nevertheless, the complications and fatal outcome in this patient were more likely due to underlying severe diseases. Likewise, one (1) case related to Elasomeran/Davesomeran reported a fatal outcome, however, the TTO in this case was eighth (8) months and it was therefore not a relevant case. For Andusomeran, two (2) cases had a fatal outcome, but causal association to Andusomeran was unlikely in these two cases since anaphylaxis was not a reported PT, TTO was more than a day, and other aetiological explanations were more likely. None of the eight (8) cases related to SARS-CoV-2 KP.2 mRNA (COVID-19 vaccine, mRNA) and SARS-CoV-2 JN.1 mRNA and SPIKEVAX NOS were fatal.

Conclusion:

Within the latest one-year review period, the MAH received in total 61 cases (61 events) regarding anaphylaxis, all serious. Four (4) reported a fatal outcome, but none of them indicated a causal association to the SARS-CoV-2 vaccine. Anaphylaxis is treated as a safety concern in the PBRER only; it is a known but very rare side effect, and guidelines for administration include relevant precautions including that vaccines are contraindicated in individuals with known severe allergic reactions to any of the vaccine components, and that all vaccinated individuals should be observed for at least 15 minutes following vaccination and longer if allergic reactions are observed, just as treatment of unforeseen acute allergic reaction should always be available where vaccines are administered.

The information collected in this review period did not give rise any new safety concerns. The MAH will continue to monitor anaphylaxis using routine surveillance.

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 characterisation of these important risks as described in the current RMP and in [PSUR] Section 16.4, remains valid.

Table 21: Myocarditis and Pericarditis

Important Identified Risk	**Myocarditis and pericarditis**
Source of new information	• Moderna GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 195 o New and Significant Safety Information: 1 o During the reporting period, the EMA requested to include MAH's reflection and discussion on the article "Myocardial injury safety signal for mRNA COVID-19 vaccines (Myocarditis After COVID Vaccination (MACiV) study findings)" [10] in the upcoming PBRER.
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 7 days after Dose 2.
Methods	Cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [16,17], and the CDC working case definition [18] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilising the WHO-UMC standardised case causality assessment (WHO 2013).
Results	*Myocarditis and Pericarditis Cases Involving Elasomeran* During the review period, the MAH received 185 serious cases (195 events) of myocarditis and pericarditis following receipt of elasomeran. Majority of cases were from health authorities. There were 114 medically confirmed cases, and 2 cases reported a fatal outcome (one case is a possible duplicate) for the events of myocarditis or pericarditis. A total of 103 (55.7%) cases involved males and 79 cases (42.7%) involved females; 3 cases (1.6%) were missing gender information. The mean age of the patients was 42.7 (SD:15.3), with a median 42.0 years (range 17.0 to 84.0 years); 16 cases were missing age data (See Appendix 12.8). A total of 64 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 Brighton Collaboration case definition for myocarditis and pericarditis, 26 cases met Level 1 definition, 25 cases met Level 2 definition, 8

	cases met Level 3 definition, 122 cases met Level 4 definition, and 4 cases met Level 5 definition. According to the CDC working definition, 14 cases were classified as "Confirmed"; 41 cases were classified as "Probable"; 126 cases were classified as "Unassessable"; and 4 cases were considered "Not a case" of myocarditis or pericarditis (Appendix 12.8). According to the WHO causality assessment, 39 cases considered "Possible"; 105 cases considered "Unassessable", 37 cases considered "Unlikely" related to the vaccine, and 4 cases were not assessed as they were not considered a case of myocarditis or pericarditis. There were 2 cases which reported a fatal outcome for the events of myocarditis and/or myopericarditis and/or Pericarditis and these are summarised below: [redacted] A 33-year-old female patient with medical history of asthma and family history of cardiomegaly, experienced Pericarditis constrictive, Pleural effusion, Re-expansion pulmonary oedema, Pericardial fibrosis, Cardiac valve disease, Oedema peripheral, Ascites, Congestive hepatopathy, Pneumothorax, Pulmonary oedema, Vasculitis, Cardiac failure, Pectus excavatum, Ventricular extrasystoles, Hepatosplenomegaly, Anaemia and Weight decreased. The event of pectus excavatum occurred about 8 months after 2nd dose of mRNA-1273 and Ventricular extrasystoles 10 months and all the other events occurred about one year and a half after the same dose. The patient received third dose with Tozinameran. It was reported that the patient initially presented with symptoms of increased work of breathing, wheeze on exertion and cough about 5 months after 2nd dose with mRNA-1273 vaccine; treatment for suspected asthma exacerbation was initiated, which later evolved into concerns of heart failure following persistent symptoms and abnormal chest radiograph findings. Despite various investigations and consultations, including CT and MRI imaging, a definitive diagnosis remained elusive, and a cardiac MRI was consistent with constrictive physiology. A possible diagnosis of transient viral cardiomyopathy was proposed. Later the patient experienced recurrent pleural effusions and persistent symptoms, prompting ongoing medical intervention and multidisciplinary collaboration. 1. 5 litres of pleural fluid was drained from her right-side lung. The fluid was found to be exudative in nature with fluid protein measured at 35 g/L. Reactive mesothelial cells were also found in subsequent cytology, but there were no malignant cells seen. There were no infective organisms. The pleural effusion was thought to be reactive in nature. Despite efforts to manage the condition, the patient's clinical status progressively deteriorated, ultimately leading to a fatal outcome. The reported cause of death was Pleural fluid exudate, Constrictive pericarditis and Re-expansion pulmonary oedema. An autopsy was performed which determined cause of death was Hepatic congestion, Lung oedema, Ascites, Pericardial fibrosis, heart valve disorder, Vasculitis, Peripheral oedema and Collapse of lung.

	As per the BCC the case met Level 1 definition (autopsy report showed pericarditis). According to WHO causality, the assessment is Unlikely considering there is a long onset latency, and the patient's medical history and family history (cardiomegaly), third dose with Tozinameran, and suspected viral cardiomyopathy were considered as potential confounding factors. [redacted] This case appears to be a potential duplicate of the above-mentioned case [redacted] *Myocarditis and Pericarditis Cases Involving Elasomeran/Imelasomeran* During the review period, the MAH received 5 serious cases (5 events) of myocarditis and pericarditis following the receipt of elasomeran/imelasomeran. There were 4 medically confirmed cases, and no cases reported a fatal outcome for the events of myocarditis or pericarditis. A total of 2 cases (40.0%) involved males and 3 cases (60.0%) involved females. The mean age of the patients was 53.2 (SD: 19.0), with a median 50.0 years (range 33.0 to 81.0 years) There were 3 events (60.0%) reporting an outcome of "Recovered." According to the Brighton Collaboration case definition for myocarditis and pericarditis, 1 case met Level 3 definition, and 4 cases met Level 4 definition. According to the CDC working definition (Gargano 2021), 1 case was considered "Probable"; and 4 cases were considered "Unassessable." According to the WHO causality assessment, 4 cases considered "Unassessable", and 1 case was considered "Unlikely" related to the vaccine. *Myocarditis and Pericarditis Cases Involving Elasomeran/Davesomeran* During the review period, the MAH received 1 serious case (1 event) of myocarditis and pericarditis following receipt of elasomeran/imelasomeran. This case involved a female with an unknown age. The event was reported as "Not recovered." According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, the case met Level 4 definition. According to the CDC working definition, the case was considered "Unassessable." According to the WHO causality assessment, the case was considered "Unlikely" related to the vaccine. *Myocarditis and Pericarditis Cases Involving Andusomeran* During the review period, the MAH received 33 serious cases (34 events) of myocarditis and pericarditis following the receipt of andusomeran. There were no cases reporting a fatal outcome for the events of myocarditis or pericarditis. A total of 17 cases (51.5%) involved males, 15 cases (45.5%) involved females; 1 case (3.0%) was missing gender information. The mean age of the patients was 63.8 (SD: 22.4), with a median 70.0 years (range 12.0 to 90.0 years). There were 15 events (44.1%) reporting an outcome of "Recovered/ Recovering."

	According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, 1 case met Level 1 definition, 7 cases met Level 2 definition, 2 cases met Level 3 definition, 22 cases met Level 4 definition, and 1 case met Level 5 definition. According to the CDC working definition, 9 cases were considered "Probable", 23 cases were considered "Unassessable" and 1 case was considered "Not a case" of myocarditis. According to the WHO causality assessment, 6 cases was considered "Possible", 19 cases were considered "Unassessable", 7 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 SARS-CoV-2 JN.1 mRNA During the review period, the MAH received 2 serious non-medically confirmed cases (2 events) of myocarditis and pericarditis following the receipt of SPIKEVAX 2024-2025 Formula. There were no cases reporting a fatal outcome for the events of myocarditis or pericarditis. One case involved a 32-year-old male, and the other case involved a 73-year-old female. The mean age of the patients was 52.5 (SD: 29.0), with a median 52.5 years (range 32.0 to 73.0 years). Both events reported an outcome of "Not Recovered/ Not Resolved." According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, both cases met Level 4 definition. According to the CDC working definition both cases were considered "Unassessable." According to the WHO causality assessment, both cases were considered "Unassessable." Myocarditis and Pericarditis Cases Involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula During the review period, no cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula were received. Myocarditis and Pericarditis Cases Involving SPIKEVAX (NOS) During the review period, the MAH received 18 serious cases (18 events) of myocarditis and pericarditis following the receipt of Spikevax (NOS). There were 16 medically confirmed cases and there were no cases with a fatal outcome for the events of myocarditis or pericarditis. A total of 8 cases (44.4%) involved males, 4 cases (22.2%) involved females; 6 cases (33.3%) was missing gender information. The mean age of the patients was 49.1 (SD: 26.2), with a median 51.0 years (range 17.0 to 84.0 years); 9 cases were missing age data. There were 2 events (20.0%) reporting an outcome of "Recovered." According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, 1 case met Level 2 definition, 17 cases met Level 4 definition.

	According to the CDC working definition, 1 case was considered "Probable", and 17 cases were considered "Unassessable." According to the WHO causality assessment, 1 case was considered "Possible", and 17 cases were considered "Unassessable." Review of the Literature article requested by EMA: "Myocardial injury safety signal for mRNA COVID-19 vaccines (MACiV study findings)" The authors of the "MACiV Multicentre Study" provided an exploration of the clinical characteristics, myocardial injury, and outcomes of COVID-19 vaccine-associated myocarditis (C-VAM) in paediatric and young adult populations. The study addresses the gaps in understanding mid- and longterm myocardial health outcomes for these patients. The study population included patients <=30 years of age, and C-VAM occurred in adolescent males (91%) with a mean age of 15.7 years. Most of the patients (95%; n=306) were vaccinated with Pfizer vaccine, 5% received Moderna vaccine (n=16), and only 1 patient received Johnson& Johnson Vaccine. Symptoms, primarily chest pain, typically appear within 3 days of vaccination, often following the second dose of an mRNA vaccine. Hormonal differences, particularly the proinflammatory role of testosterone and the cardioprotective effects of oestrogen, likely contribute to the observed age and sex disparities. Most of this cohort of patients (96%) presented with elevated troponin levels, indicative of targeted myocardial injury rather than systemic inflammation, as systemic inflammatory markers were generally low. Late gadolinium enhancement (LGE) on cardiac MRI, a marker of myocardial injury, was present in 82% of cases, resembling patterns observed in viral myocarditis. Despite these findings, the initial clinical course was mild for most patients, with only 2% requiring inotropic support. At a median follow-up of 178 days, no cardiac deaths or heart transplantations were reported, underscoring the generally favourable mid-term prognosis of C-VAM. Persistent LGE was observed in 60% of patients at follow-up, though the severity was reduced, suggesting ongoing myocardial fibrotic remodelling. The authors speculated that persistence of LGE may raise concerns about potential long-term risks, such as dilated cardiomyopathy, arrhythmias, and ventricular dysfunction. Notably, most patients recovered from left ventricular ejection fraction (LVEF), and some patients continued to experience mild symptoms such as chest pain or fatigue. While the MACiV study provides valuable insights, its retrospective design introduces potential biases. The lack of endomyocardial biopsy data limits the ability to confirm the underlying pathology. The study did not directly compare C-VAM with SARS-CoV-2 myocarditis, although findings, such as LGE and myocardial fibrosis, resemble patterns in viral myocarditis. Additionally, the median follow-up period of 178 days is insufficient to fully assess long-term outcomes. **Conclusion**

	The MAH considered that the MACiV study (FDA funded study) showed most patients with myocarditis after COVID-19 vaccination experience a mild clinical course and demonstrate favourable short- to medium-term outcomes. The MACiV study reinforces that C-VAM has significantly better outcomes compared to viral myocarditis. Key findings highlight that C-VAM predominantly affects young males, often after the second dose of an mRNA vaccine, and is characterised by localised myocardial injury rather than systemic inflammation. The authors theorised that persistent cardiac MRI abnormalities, such as LGE, may raise concerns about potential long-term risks, including myocardial fibrotic remodelling and future cardiac dysfunction, and indicated that these findings emphasise the importance of continued surveillance and follow-up to assess long-term myocardial health and outcomes. The study seems to have several strengths such as large sample size and multicenter design, comprehensive data collection (such as imaging data echocardiography, cardiac MRI), biomarker (such as troponin, c-reactive protein), use of advanced diagnostics such as Cardiac MRI (LGE to detect myocardial injury), comparison of C-VAM to multisystem inflammatory syndrome, and well defined primary and secondary outcomes. However, there are several limitations with this study such as retrospective design which could introduce biases (potential selection bias), lack of long-term follow-up data, absence of biopsy data, did not directly compare C-VAM with SARS-CoV-2 myocarditis, and the study primarily focuses on younger patients, limiting the applicability of findings to older adults. These limitations necessitate cautious interpretation of findings. The MAH acknowledges that there is limited long-term follow-up data on C-VAM. Of note it should be noted that, as part of additional pharmacovigilance activities, the MAH already has an ongoing PASS study mRNA-1273-P911 for the evaluation of long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA). The primary objective of the study is to characterise presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of SPIKEVAX. The secondary objective of the study is to compare presentation, clinical course, and long-term outcomes of vaccine-associated myocarditis with those of non-vaccine myocarditis, including myocarditis arising in COVID-infected individuals, and to characterise possible risk factors for adverse long-term outcomes of vaccine-associated myocarditis including demographic factors, lifestyle factors, and medical history. Results of the study will be shared once the study is completed. In conclusion, myocarditis is a rare adverse event and is adequately addressed in all mRNA COVID vaccine labels. The overall benefits of vaccination in preventing severe COVID-19 outcomes, including hospitalisation and death, far outweigh the risks. Long-term monitoring and research remain critical to addressing knowledge gaps and ensuring optimal management of affected individuals.

Discussion	A review of the data received during this reporting period showed there is a consistent decrease in reported cases of myocarditis and pericarditis across all vaccine formulations over time. The mean age varied across formulations was noted, and this probably could be due to potential differences in the populations receiving each vaccine formulation. Elasomeran: Mean age of 42.7 years. Andusomeran: Older population, mean age of 63.8 years. SPIKEVAX 2024-2025 Formula: Mean age of 52.5 years Consistent male predominance is observed in cases involving myocarditis/pericarditis, across all formulations. Overall, the review showed that of the 244 cases: 147 (60%) cases were assessed as "Unassessable;" 46 cases (19%) were assessed as "Unlikely;" 46 (19%) cases were assessed as "Possible" and 5 cases (2%) were assessed as "Not a case of myocarditis/pericarditis". Review of these cases did not identify any significant safety issues of concern. Review of the article suggested by the pharmacovigilance risk assessment committee (PRAC) did not identify any significant safety issue of concern. However, there are critical gaps in understanding mid and long-term myocardial health outcomes as data on long-term follow-up after vaccine induced myocarditis are very limited. Of note, as part of additional pharmacovigilance activities, the MAH continues to monitor this identified risk through an ongoing PASS study mRNA-1273-P911 (Longterm outcomes of myocarditis following administration of SPIKEVAX [COVID-19 vaccine mRNA]). Based on the analysis of all the safety data available as of 17 December 2024, 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. Please refer to [PSUR] Section 8 for results from the PASS study on the evaluation 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. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including PASS to further characterise them. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has presented data from the latest review period, 18 December 2023 through 17 December 2024, regarding the association between myocarditis and pericarditis and use of Moderna's mRNA-vaccines targeting SARS-CoV-2. Myocarditis and pericarditis are known as very rare adverse events to these vaccines. Although seen in both genders and all age groups and with different TTO and in relation to different dose number, the overall pattern is, that both myocarditis and pericarditis particularly affect adolescents and young males, commonly within a week after vaccination, and typically after second dose.

The MAH has presented data from a new literature search and the MAH's global safety database.

Results

Literature:

The MAH retrieved 195 new articles of which one (1) was considered to contribute new and significant safety information: Jain SS et al. (2024)[1].

The article presented a large observational US multicentre study which aimed to describe the initial clinical and cardiac imaging characteristics of COVID-19 vaccine-associated myocarditis (C-VAM), explore possible risk factors for myocardial injury as evidenced by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging and evaluate cardiovascular outcomes, in a large cohort of children, adolescents and young adults diagnosed with C-VAM. The 333 patients with C-VAM were compared to 100 patients with multisystem inflammatory syndrome in children (MIS-C); this is an interesting comparison as MIS-C is a serious complication of COVID-19 with common cardiac dysfunction while C-VAM is a rare complication to COVID-19 vaccines administered to prevent (severe) COVID-19.

Among results from the study were that the odds of LGE in C-VAM was found to be 3.28 times higher for males than females, 2.74 times higher for young adults and adolescents older than 15 years of age than in younger patients. Furthermore, it seemed dose-related, and the odds was 7.18 times higher for C-VAM after 1st dose and 4.5 times higher after 2nd dose compared to 3rd dose.

MIS-C patients were younger and sicker, were more likely to require intensive care management and had higher prevalence and degree of systemic inflammatory markers and cardiac dysfunction.

C-VAM patients in this cohort study were predominantly males who presented with chest pain and elevated troponin. The clinical course was generally mild and with a low prevalence of cardiac dysfunction, but myocardial injury was common as evidenced by higher troponin levels and LGE (seen in 82%).

The pattern and distribution of LGE found in the C-VAM patients resembled findings from viral myocarditis, and were in contrast to MIS-C, where LGE was rare and, when present, mild in comparison.

The new possible safety concern from this study is the finding of LGE on CMR imaging as LGE in a variety of cardiac conditions is associated with a propensity for arrhythmias, heart failure, and sudden cardiac death. Likewise, in adults with viral myocarditis LGE at presentation is a predictor of long-term major adverse cardiovascular events, even if cardiac function is preserved. As a greater extent of LGE in these different conditions confers a higher risk for adverse outcomes, it is therefore considered if this also applies to C-VAM patients, and whether persistence of LGE at follow-up may call for continued clinical surveillance of patients. Hence, the study raises a possible concern for long-term effects in individuals with C-VAM and LGE on CMR presentation. The assessor acknowledges this as a possible concern which emphasizes the relevance of long-term follow-up in patients after C-VAM following any vaccine targeting SARS-CoV-2.

The MAH has also referred to the US multicentre study and has correctly included key findings and the authors concerns that persistent CMR abnormalities with LGE may be indicative of a potential long-term risk.

Global Safety Database:

Within the latest period, the MAH received 244 cases (255 events) reporting myocarditis and/or pericarditis. Elasomeran accounted for 185 cases (195 events), Elasomeran/Imelasomeran for five (5) cases (five (5) events), Elasomeran/Davesomeran for one (1) case (one (1) event), Andusomeran for 33 cases (34 events), the JN.1 variant for 2 cases (2 events), and 18 cases (18 events) were reported for variants of the vaccine not otherwise specified.

All 244 cases were assessed according to the Brighton Collaboration Criteria (BCC). In total, 71 cases were defined within BCC levels 1-3, which according to diagnostic findings are definitive, probable or possible cases, 168 cases were categorized as level 4 which are cases with insufficient evidence to meet level 1-3 and hence cases of diagnostic uncertainty, and five (5) reported cases were BCC level 5 and therefore not cases according to the diagnostic criteria.

The 239 cases categorized as BCC level 1, 2, 3 or 4 were causality assessed according to the WHO-UMC standard. Causal association was found possible in 46 cases, unassessable in 148 cases, and unlikely in 45 cases.

Two (2) cases were reported as fatal, however, they are suspected duplicates leaving one (1) fatal case, in which there were serious health confounders, and causality associated with vaccination with Elasomeran was found unlikely.

Mean age varied across vaccine formulations, which may reflect differences in population groups receiving the different formulations. Gender distribution varied across vaccine formulations too, but across all formulations the majority of cases were in males.

Conclusion:

Myocarditis and/or pericarditis are known as very rare side effects to all mRNA vaccines against SARS-CoV-2 including the different vaccine formulations from Moderna. There is a higher risk for these events in males than in females, and in particular in adolescents and young adults compared to adults and elderly. The data collected from the global safety database for the latest review period was consistent with the known safety profile and did not reveal any new safety concern.

However, a new multicentre study (Jain SS et al. [2024]) of COVID-19 vaccine-associated myocarditis presented new data, of which some results supported the known safety profile, while other results presented new findings of LGE on CMR at presentation and at follow-up in patients with C-VAM. This may give rise to concerns about potential long-term cardiac risks in these patients despite a mild initial clinical course. In accordance with the known safety profile, the likelihood for developing LGE was higher in males than in females, higher in younger adults and adolescents >15 years of age compared to patients younger than 15 years, and higher in those who developed C-VAM after the 1st or 2nd dose of the mRNA vaccine compared to those who developed C-VAM after 3rd dose or booster dose. Due to the possible concern about the long-term safety it is suggested to ensure extended long-term follow-up safety studies in individuals who developed C-VAM.

As part of additional pharmacovigilance activities, the MAH has an ongoing PASS study mRNA-1273-P911 for the evaluation of long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA). The final study report is expected in October 2028.

The wording of the current SmPC is considered adequate and sufficient given the present data.

References

1. Jain SS et al. Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicentre study. EClinicalMedicine 2024;76:102809.

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 important potential risks of IgA Nephropathy for marketed Moderna vaccines targeting SARS-CoV-2 has not identified any clinically relevant new safety information for this topic. The characterisation of this important potential risk as described in [PSUR] Section 16.4, remains valid. IgA Nephropathy is monitored in accordance with a request from a Health Authority.

Table 22: IgA Nephropathy

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)

Source of new information	• Moderna GSDB
	• Literature Sources
	  o Search Criteria Applied: Appendix 13.4
	  o Retrieved: 61
	  o New and Significant Safety Information: None (0).

Background	Following review of PBRER#4, a Health Authority requested the following information on IgAN: • The reporting of IgA Nephropathy is rare, and 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 characterisation in PBRER section 16.3 and 16.4, respectively.
Methods	Neither the Brighton Collaboration 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 utilising the WHO-UMC standard causality assessment.
Results	Refer to [PSUR] Appendix 12.9 for information about the medical topic. During the review period, the MAH received 21 reports (24 events) that had PTs within the HLT of Glomerulonephritis and Nephrotic Syndrome (note: the following case [redacted] was captured for both elasomeran and

	SPIKEVAX BIVALENT.214 [elasomeran/imelasomeran]). Of the 20 remaining cases, 10 cases involved elasomeran, 8 cases involved SPIKEVAX (NOS) and 1 case each involved, elasomeran/davesomeran, and andusomeran. There were no reports involving SARSCo-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA. All 20 reports were medically reviewed. Seven cases were classified as confirmed IgA nephropathy and one was classified as antineutrophil cytoplasmic antibodies (ANCA) due to the clinical presentation and a positive ANCA test, with the reporter noting that IgAN was a possible diagnosis due to haematuria (no confirmatory biopsy was ever done due to the underlying severity of disease); the remaining 12 cases involved other types of nephropathy or other conditions (e.g., glomerulonephritis minimal lesion, glomerulonephritis membranous, nephrotic syndrome, glomerulonephritis rapidly progressive, and C3 glomerulopathy). According to the WHO causality assessment, 4 cases considered "Unassessable", 3 cases considered "Unlikely" related to the vaccine, and 13 cases were not assessed as they were not considered cases of IgA Nephropathy. Out of the 7 cases involving true IgA nephropathy by definition, no cases involved fatal outcomes. Of these 7 cases, the majority (4 cases) involved SPIKEVAX NOS, 2 cases involved elasomeran and 1 case involved mRNA-1273 BIVALENT .222. All of these 7 cases were serious. Six (6) cases were new onset (de novo) of IgA nephropathy, and 1 case was considered a IgA nephropathy flare because the patient was reported to have experienced exacerbation of IgA nephropathy that had been diagnosed prior to vaccination at age 18. More numbers of cases in females (6 cases; 85.7%) when compared to males (1 cases; 14.3%) were reported. The mean age was 50.3 years (SD: 15.2) and median age was 53.0 years (range: 27.0 to 67.0 years).
Discussion	During the reporting period in the MAH's GSDB, there were 7 (one case more likely ANCA with +ANCA test) cases of IgA nephropathy that were identified through medical review. Most of these cases (4 cases) were on SPIKEVAX NOS, 2 (2) cases involved elasomeran and one (1) case involved mRNA-1273 BIVALENT.222. Of the 7 cases of IgA nephropathy, 6 cases involved new onset (de novo) IgA nephropathy. None of these cases were considered WHO possible, 4 cases were unassessable due to confounding factors, underlaying condition and limited information, finally the remaining 3 cases, the WHO causality assessment was considered unlikely due to the long TTO of 3, 5 and 2 1/2 months. No new patterns were observed with regard to IgA nephropathy for marketed Moderna vaccines targeting SARS-CoV-2. Based on the analysis of all the safety data available as of 17-Dec-2024, 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 outweigh 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 the reports does not differ from the

	known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to monitor events of IgA Nephropathy using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

During the review period 18 December 2023 through 17 December 2024, the MAH received 21 cases (24 events) within the HLT 'Glomerulonephritis and Nephrotic Syndrome'. One case was a duplicate leaving 20 unique cases.

Neither the BCC nor the CDC has a diagnostic definition of IgA nephropathy. The MAH had the 20 cases medically reviewed, and considered it a case of IgA nephropathy (IgAN) if the case included a report of renal biopsy with findings of IgAN, or if IgAN was reportedly diagnosed. According to this, seven (7) of the 20 cases were classified as confirmed IgAN; six (6) cases were of new onset and one (1) a flare. It is noted by the assessor that six (6) of the seven (7) cases were in females and only one (1) was a male. This equals 85.3% being females which is in contrast to the knowledge that IgAN usually affects males at least twice as often as females. Due to low number and hence statistical uncertainty the inverse distribution by gender is not defined as a significant pattern.

The cases were causality assessed according to the WHO-UMC. However, 13 of the 20 cases were not considered a case and therefore not assessed. Of the seven (7) cases that were defined as IgAN, three (3) were categorized as 'unlikely' and four (4) cases as 'unassessable'.

Conclusion:

Overall, the data for this review period is vague and cannot be used to describe patterns for IgAN following one of the mRNA vaccines against SARS-CoV-2 distributed by Moderna.

As the reporting of IgAN has previously been described as rare, with uncertain diagnoses in many reported cases and no clear pattern observed, presenting data from only one-year periods is unlikely to be very informative. In future reviews, a cumulative analysis that includes distribution by age and gender may provide more meaningful insights.

Continued monitoring through routine surveillance is endorsed.

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 the known important missing information risks of marketed Moderna vaccines targeting SARS-CoV-2 before and during pregnancy has not identified any clinically relevant new safety information for this topic. The characterisation of these important risks as described in the approved RMP as of the DLP of this PBRER and in [PSUR] Table 16-14 remains valid.

Table 23: Use in pregnancy

Missing information	Use in pregnancy
Source of new information	• Moderna GSDB • Literature Sources

	- Search Criteria Applied: - Pregnancy Methods of Evaluation: Literature Search Methodology - Articles of Reference for Pregnancy with Company Comment o Retrieved: 992 o New and Significant Safety Information: Four (4) articles.
Background	Use of marketed Moderna vaccines targeting SARS-CoV-2 (SPIKEVAX Original [elasomeran], SPIKEVAX Bivalent .214 Original/BA.1 [elasomeran/imelasomeran], SPIKEVAX Bivalent .222 Original/BA.4/5 [elasomeran/davesomeran], SPIKEVAX 2023-2024 Formula [andusomeran]), SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA 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 marketed Moderna vaccines targeting SARS-CoV-2 will be used in women of child-bearing age, pregnancy exposures are likely to occur. Additionally, at the request of regulatory authorities, the use of marketed Moderna vaccines targeting SARS-CoV-2 before and 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 [PSUR] Appendix 12.10 for Methods of Evaluation
Results	Refer to [PSUR] Appendix 12.10 for additional information. **Overview of Pregnancy Cases Who Received Elasomeran** During the review period, the MAH received 52 pregnancy cases (540 events) with 41 serious cases (198 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. A total of 33 cases were medically confirmed, and 4 cases reported a fatal outcome. During the review period, a larger proportion (78.8%) of cases were reported as "serious" compared to cumulative data (35.5%). Among the serious cases, there were cases which simply report "maternal exposure during pregnancy" in addition to known events that reflect expected reactogenicity and are reported as "serious" cases. Serious cases should be interpreted with caution as many do not meet the true definition of "serious" (death, life-threatening, hospitalisation, 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 regardless of case medical information. Serious cases will be presented in the Serious Pregnancy-specific Events-Elasomeran and Fatal Pregnancy Cases-Elasomeran sections below. Most (24; 45.3%) pregnancy-specific cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and consistent with what has been observed in previous review periods. During the review period, the most frequently reported PTs (4 events or more) indicating an adverse event/outcome for pregnancy cases were COVID-19

	infection, pyrexia, headache, pain in extremity, fatigue, arthralgia, dizziness, hypertension, abortion spontaneous, cognitive disorder, myalgia, nausea, pain, vomiting, asthenia, thrombosis, and atrial septal defect. Most reported events reflect expected reactogenicity, were comparable with cumulative data, and consistent with the product safety profile for all marketed Moderna vaccines targeting SARS-Cov-2. During the review period, 4 pregnancy cases reported events of myocarditis and/or pericarditis after receipt of elasomeran. 2 (2) of these cases were reported in the prior reporting period but had updates made to the narrative during this review period. During this review period, case [redacted] had diagnostic data, concomitant medication, and event onset updates made to the narrative and case [redacted] had medical history and event updates made to the narrative. The MAH's original causality assessments for those 2 cases were not affected by the new information added during this review period. The remaining cases ([redacted] and [redacted]) have been reviewed in the Myocarditis/Pericarditis Section 16.3.1.2. Pregnancy-specific Events – Elasomeran) During the review period, of the 52 pregnancy cases received by the MAH, 48 cases reported a pregnancy-specific event 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). Of these 48 pregnancy cases (74 events) reporting a pregnancy-specific event, 37 cases were serious (48 serious events), 3 cases reported a fatal outcome, and 30 cases were medically confirmed. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome ("Maternal exposure during pregnancy," "Exposure during pregnancy," "Drug exposure during pregnancy," "Maternal exposure before pregnancy," "Foetal exposure during pregnancy," and "Maternal exposure timing unspecified"), the most frequently reported pregnancy-specific PT's that indicated an adverse pregnancy-specific clinical event/outcome were "Abortion spontaneous" (5 events) and "Atrial septal defect" (4 events). Consistent with cumulative data, the PT "Abortion spontaneous" has been the most frequently reported pregnancy-specific PT that indicates an adverse pregnancy-specific clinical event/outcome. (Refer to Spontaneous abortions, Stillbirths, and Foetal Deaths evaluations added below). A summary of all pregnancy outcomes associated with elasomeran exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. Serious Pregnancy-specific Events– Elasomeran During the review period, of the 41 serious pregnancy cases reported, when restricted to pregnancy cases reporting only pregnancy-specific events/outcomes, 29 serious cases (48 events) were identified. A total of 22 cases were medically confirmed, and 3 cases reported a fatal outcome.

	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 adverse event, diagnostics, treatment, and outcome. Where data were available, confounding factors for spontaneous abortion/foetal deaths and complications of pregnancy [including advanced maternal age, concomitant medications, comorbidities (such as hypothyroidism, increased blood pressure, or tobacco abuse) and previous relevant obstetric history including foetal loss] were present. Fatal Pregnancy Cases– Elasomeran During the review period, 3 pregnancy cases were coded as fatal following receipt of elasomeran. Case [redacted] concerns a 33-year-old female with a medical history of cardiomegaly, who experienced the fatal event of pericarditis constrictive. However, this case appears to be misclassified as a pregnancy case given that no information regarding obstetric medical history (e.g., LMP, delivery date/neonate outcome) was provided that would suggest a recent pregnancy associated with elasomeran (this case has been reviewed in the Myocarditis/Pregnancy Section 16.3.1.2). The remaining 2 fatal cases are summarised below: [redacted]: This RA case by a health-care professional concerns a neonate of unknown gender who experienced the fatal event of foetal hydrops approximately 4 months after maternal exposure to elasomeran (Reported as the second dose in the mother's COVID-19 vaccination schedule). As reported, the patient's mother was admitted approximately 3 months after vaccination due to the presentation of uterine contractions. Pregnancy of 28.6 gestational weeks was confirmed by ultrasound. The pregnancy was considered "uncontrolled" until gestational week 25. Venereal Disease Research Laboratory (VDRL) test was positive for syphilis at 25 weeks gestational age and treatment was initiated with intramuscular benzathine penicillin G 2,400,000 (3 doses) at 1 dose per week. An ultrasound performed at 3 months and 1 week after vaccination, indicated probable foetal hydrops that was later confirmed with a diagnosis of foetal malformation incompatible with life. Co-suspect products were reported, including MMR (measles, mumps and rubella) and DT (diphtheria and tetanus) vaccines which were administered to patient's mother at an unspecified date. The mother was discharged from obstetrics and re-admitted one day after with pre-eclampsia (blood pressure: 160/120). Vital foetus positive uterine dynamics. Magnesium Sulfate infusion was prescribed. The decision was made to terminate the pregnancy, but then an emergency caesarean section was performed: Live foetus was born, weighing 1,760 grams, Apgar score 3/6, with foetal hydrops. Newborn died in Neonatal Intensive Care Unit (NICU) [hours of life was not reported]. Underlying maternal syphilis, other viral infections (Parvovirus B19-Herpes, but with no pathological confirmation provided) and rhesus incompatibility were suggested by the reporter as important confounders. No pathology reports regarding the placenta or neonatal autopsy were provided

	that confirmed characteristic findings in foetus and placenta suggestive of syphilis and placental vasculopathy. MAH Comment: This case was assessed as "Unlikely" given the lack of biological plausibility and underlying maternal syphilis as a potential alternative aetiology for the event. This case was also potentially confounded by maternal exposure to the co-suspect products MMR and DT; and the possibility of rhesus incompatibility and/or exposure to maternal viral infection (Parovirus B19 Herpes virus-CMV). [redacted]: This RA case concerns a female neonate of unknown age, who experienced unexpected events of neonatal asphyxia, encephalopathy neonatal and neonatal behavioural syndrome that resulted in death. The events occurred almost 2 years after a dose of elasomeran (reported as the second dose in the mother's COVID-19 vaccination schedule). The mother of the baby had an emergency caesarean section at 33 and 4/7 weeks of amenorrhea from a bichorial-biamniotic twin pregnancy for placental abruption and foetal bradycardia. The mother had haemorrhagic shock due to placental detachment. The neonate was initially hospitalized in neonatology on continuous positive airway pressure (CPAP). Blood tests indicated poor neonatal adaptation with pHs of 6.79 and 7.04, lactates at 18, and Apgar score 0/0/1. The patient had severe asphyxia with hypoxic-ischaemic encephalopathy and multiorgan involvement. Despite immediate resuscitation and a recovery of the heart rhythm at 15 minutes of life, the clinical neurological evolution was unfavourable. The neonate died after 2 days of life. MAH Comment: This case was assessed as "Unlikely" given the long latency and etiopathogenesis of the events that were triggered by placental abruption. Foetal Deaths– Elasomeran The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA, and as stillbirth if they occur after 20 weeks gestational age. The threshold of 20 weeks is per the definitions applied in the US [19]. Spontaneous and Missed Abortions – Elasomeran During the review period, 5 serious pregnancy cases with a medical history of maternal exposure to elasomeran reported spontaneous abortion with 5 serious events. Of the 5 cases, 2 cases were medically confirmed, and no cases were coded as fatal. The mean age of the women was 35.4 years (SD: 6.6) and median age of 32.0 years (range 29.0 - 43.0 years). Analysis of event clustering by dose number and TTO was not meaningful as none of the events reported dose number and only 3 of the 5 events reported TTO. Of the events that reported TTO, 1 event was reported to occur between 7 to 13 days after an unspecified dose, 1 event was reported to occur 30 plus days after an unspecified dose, and 1 event was reported to occur prior to the first dose reported. Review of 5 cases reporting spontaneous abortion, showed 1 case reported long latency (2 years after the seconddose mRNA-1273), 2 cases reported advanced maternal age (>40 years old), and the remaining 2 cases lacked critical information required for a meaningful medical assessment

	including GA, prior maternal obstetric and medical history, concomitant medications, etc. No significant safety issues of concern were identified. Stillbirth – Elasomeran Stillbirth has varying global definitions based on GA and foetal weight. For the purposes of this PBRER, and as described above, the MAH applied a definition of stillbirth as foetal death after 20 weeks gestational age [19]. Congenital anomalies, placental dysfunction associated with foetal 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, 1 pregnancy case reported stillbirth following maternal exposure to elasomeran and is summarised below: [redacted]: This RA case concerns a 32-year-old female patient with a pregnancy history of a vaginal delivery at 38 weeks of amenorrhea in a 3100-gram boy, who experienced the serious (due to medically significant) unexpected events of foetal death, premature separation of placenta, thrombocytopenia, disseminated intravascular coagulation and drug exposure before pregnancy. The events foetal death, premature separation of placenta, thrombocytopenia and disseminated intravascular coagulation occurred almost 9 months after maternal exposure to a dose of elasomeran (reported as the second dose in the mother's COVID-19 vaccination schedule). Based on information provided, a caesarean delivery occurred in the 29th week due to amenorrhea stemming from placental detachment. It was estimated that time of conception occurred approximately 3 months after the mother received Dose 1 of elasomeran and approximately 2 months after she received Dose 2 of elasomeran. The mother also tested positive for SARS-CoV-2 infection between 4 to 5 months after the time of conception. As reported, the mother presented with severe disseminated intravascular coagulation in the context of placental abruption and thrombocytopenia. Blood loss was estimated at 3000 ml, and the pregnancy ended with a lower transverse isthmic caesarean section following intrauterine foetal death. The outcome of the events was reported as "Recovered." MAH Comment: This case was assessed as "Unlikely" given the long latency to onset of events. The maternal SARS-CoV-2 infection that occurred between 4 to 5 months GA during this pregnancy and maternal history of amenorrhea (the underlying hormonal imbalance leading to amenorrhea can potentially increase risk of pregnancy complications including stillbirth) may be considered as plausible alternate aetiologies for the events that led to stillbirth. A summary of all pregnancy outcomes associated with elasomeran exposure 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-Authorisation Data (EMEA/CHMP/ 313666/2005)," are presented by individual vaccine in [PSUR] Appendix 12.10.

Congenital Anomaly– Elasomeran

During the review period, 19 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 19 pregnancy cases, 5 cases occurred among foetuses and neonates who were maternally exposed to elasomeran in-utero and 14 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. All 5 pregnancy cases ([redacted]), reported a live birth at delivery. Of the 11 events reported in those 5 cases, the event outcomes were reported as "Recovered/Resolved" for 2 events, "Not Recovered/Not Resolved" for 4 events, and "Unknown" for 5 events.

Further review of the congenital anomalies, considering the GA at vaccination and foetal development, contributed to the assessment of causality. Many cases lacked GA at the time of vaccination and thus causality was 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 Analyses-Elasomeran:

• *Children <6 years of Age with a medical history of maternal exposure to elasomeran during pregnancy*

During the review period, the MAH received 6 serious cases (15 serious events) among children under 6 years of age with a medical history of maternal exposure to elasomeran during pregnancy.

Case [redacted] reported a fatal outcome and is described above in the *Fatal Pregnancy Cases-Elasomeran* section. Cases [redacted] reported congenital anomaly and are described in Appendix 12.10. The remaining case is summarised below:

[redacted]: This spontaneous case reported by a family member or friend concerns a male infant, with no reported medical history, who experienced the serious (due to medically significant) unexpected, events of foetal growth restriction and premature baby, which occurred on an unknown date following maternal exposure to a dose of elasomeran (reported as the second dose in the mother's COVID-19 vaccination schedule). It was reported that the infant was born 31 days premature and was "very small". The reporter mentioned that the infant "stopped growing at 32 weeks old, was smaller than average, and his weight was less than average." It was also reported that the infant

	experienced a "utero growth restriction;" the child was now 2.5 years of age, and "was still wearing clothes appropriate for an infant 12-18 months of age." The event outcome for both foetal growth restriction and premature baby was reported as "Recovered/Resolved." MAH Comment: This case was considered "Unassessable" given the lack of information regarding maternal medical and obstetric history (including LMP, estimated date of delivery, and details pertaining to premature delivery), family history, diagnostic evaluation, and clinical course which precludes an informed assessment. No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period. No pregnancy cases associated with exposure to elasomeran were reported for the following subpopulations during the review period: • *Children 6 to 11 Years of Age,* • *Adolescents (12 to 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 in association with elasomeran. **Pregnancy Cases After Receiving Elasomeran/Imelasomeran** During the review period, no pregnancy cases were reported for individuals who received or had a medical history of maternal exposure to a BD of elasomeran/imelasomeran. **Pregnancy Cases After Receiving Elasomeran/Davesomeran** During the review period, no pregnancy cases were reported for individuals who received or had a medical history of maternal exposure to a BD of elasomeran/davesomeran. **Pregnancy Cases After Receiving Andusomeran** During the reporting period, the MAH received 15 pregnancy cases (49 events) with 2 serious cases (2 serious events) among individuals who received or had a medical history of maternal exposure to andusomeran. A total of 12 cases were medically confirmed, and no cases reported a fatal outcome. Most (10; 66.7%) of these pregnancy cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and consistent with what has been observed with marketed Moderna vaccines targeting SARS-Cov-2 in previous review periods. During the reporting period, the most frequently reported PTs continued to be events that reflect expected reactogenicity; this is comparable with cumulative data and consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2. However, during the reporting period, there also was an increase in number of events related to administration error, specifically administration of expired product (7 events; 14.3%). To date, no pregnancy cases associated with exposure to andusomeran have reported events of myocarditis and/or pericarditis.

	Pregnancy-specific Events – Andusomeran During the reporting period, The MAH received 15 pregnancy cases (2 serious cases) reporting 49 events (2 serious events) associated with exposure to andusomeran. Of the 49 events reported, only 15 events reported a pregnancy-specific PT. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome ("Maternal exposure during pregnancy" and "Foetal exposure during pregnancy") the only remaining PT that indicated a pregnancy-specific adverse clinical event/outcome was: "Jaundice neonatal." A summary of all pregnancy outcomes associated with andusomeran exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. *Serious Pregnancy-specific Events– Andusomeran* Of the 2 serious pregnancy cases reported during the reporting period, when restricted to pregnancy cases reporting only serious pregnancy-specific events, only 1 of those serious cases identified a serious pregnancy-specific event. Case [redacted] reported a 34-year-old female who experienced the serious PT "Jaundice neonatal." This case appears to be misclassified as a pregnancy case given that no obstetric medical history (e.g., LMP, delivery date/neonate outcome) was provided to suggest a recent pregnancy. Additionally, no information was reported that linked this case to a case involving a neonate who may have experienced this event. *Fatal Pregnancy Cases– Andusomeran* During the reporting period, no pregnancy case reported a fatal outcome in association with exposure to andusomeran. *Foetal Deaths– Andusomeran* The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [19]. *Spontaneous and Missed Abortions – Andusomeran* During the reporting period, no pregnancy cases with a medical history of maternal exposure to andusomeran reported events of spontaneous or missed abortion. *Stillbirth – Andusomeran* No pregnancy cases reported stillbirth following maternal exposure to andusomeran. *Congenital Anomaly– Andusomeran* No pregnancy cases reported congenital anomaly following maternal exposure to andusomeran. **Subpopulation Analyses-Andusomeran:**

No pregnancy cases associated with exposure to andusomeran 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 associated with exposure to andusomeran have been identified.

Pregnancy Cases After Receiving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

Since its approval in August 2024, the MAH has received 5 non-serious pregnancy cases (16 events) among individuals who received or had a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Four (4) of the 5 cases were medically confirmed.

When age was reported, the pregnancy cases (2; 40.0%) occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been observed with marketed Moderna vaccines targeting SARS-Cov-2.

Most of the PTs reported in these cases were related to errors in product administration and included: "Wrong product administered" (2 events), "Accidental overdose" (1 event), "Product administration error" (1 event), and "Underdose" (1 event).

To date, no pregnancy cases associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have reported events of myocarditis and/or pericarditis.

Pregnancy-specific Events – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

The MAH has received 5 non-serious pregnancy cases reporting 16 events associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Of the 16 events reported, only 5 events reported a pregnancy-specific PT. All 5 events reported the PT "Maternal exposure during pregnancy." There were no additional PTs reported that indicated a pregnancyspecific adverse event/outcome.

A summary of all pregnancy outcomes associated with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10.

Serious Pregnancy-specific Events– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

	No serious pregnancy cases associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have been reported. Fatal Pregnancy Cases– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases have reported a fatal outcome in association with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Foetal Deaths– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [19]. Spontaneous and Missed Abortions – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases with a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have reported events of spontaneous or missed abortion. Stillbirth – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases have reported stillbirth following maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Congenital Anomaly– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases have reported congenital anomaly following maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. **Subpopulation Analyses- SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula:** No pregnancy cases associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have been reported for the following subpopulations during the review period: • Children <6 years of Age with a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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 associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have been identified. **Pregnancy Cases After Receiving SARS-CoV-2 JN.1 mRNA** Since its approval in September 2024, the MAH has received 5 pregnancy cases (20 events) with 1 serious case (1 serious event) among individuals who received or had a medical history of maternal exposure to SARS-CoV-2 JN.1 mRNA. Three of the 5 cases were medically confirmed, and no case has reported a fatal outcome.

	Most of the cases did not report mother's age (4; 80.0%). The remaining case concerned a woman in the 25 to 39-year age group which is consistent with typical childbearing age and what has been observed with marketed Moderna vaccines targeting SARS-CoV-2 in previous review period. Most of the PTs reported predominantly reflect expected reactogenicity, consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2 and comparable with events reported for these vaccines in the prior review period. In addition, there were also reported PTs related to product storage and quality: "Product temperature excursion issue" (3 events; 15.0%) and "Poor quality product administered" (1 event; 5.0%). To date, no pregnancy cases associated with exposure to SARS-CoV-2 JN.1 mRNA have reported events of myocarditis and/or pericarditis. Pregnancy-specific Events – SARS-CoV-2 JN.1 mRNA The MAH has received 5 non-serious pregnancy cases reporting 20 events associated with exposure to SARS-CoV-2 JN.1 mRNA. Of the 20 events reported, only 5 events reported a pregnancy-specific PT. All 5 events reported the PT "Maternal exposure during pregnancy." There were no additional PTs reported that indicated a pregnancy-specific adverse event/outcome. A summary of all pregnancy outcomes associated with SARS-CoV-2 JN.1 mRNA exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in [PSUR] Appendix 12.10. Serious Pregnancy-specific Events– SARS-CoV-2 JN.1 mRNA One serious pregnancy case has been reported in association with exposure to SARS-CoV-2 JN.1 mRNA and is summarised below: [redacted]: This spontaneous retrospective pregnancy case reported by a consumer concerns a female patient of unknown age with no reported medical or obstetric history who experienced the serious (due to medically significant) event of arthralgia among other non-serious events (Gait disturbance, Motor dysfunction, and Pain in extremity). The event was reported to occur 1 day following receipt of SARS-CoV-2 JN.1 mRNA (reported as the 6th dose in the patient's COVID19 vaccination series). Concomitant medication included sertraline. LMP and estimated date of delivery were not provided. Delivery occurred on an unknown date and was reported as "normal pregnancy outcome." No pregnancy-specific adverse outcomes were reported. The event outcome for arthralgia was reported as "Not Recovered/Not Resolved." MAH Comment: This case was considered "Unassessable" given the limited information provided regarding the age of the patient, maternal medical and obstetric history (including LMP, estimated date of delivery, and details associated with delivery), maternal family history, diagnostic/laboratory evaluation and results, as well as clinical course. Concomitant use of sertraline was also considered a potential confounder.

	Fatal Pregnancy Cases– SARS-CoV-2 JN.1 mRNA No pregnancy case has reported a fatal outcome in association with exposure to SPIKEVAX 2024-2025 Formula (JN.1). Foetal Deaths– SARS-CoV-2 JN.1 mRNA The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [19]. Spontaneous and Missed Abortions – SARS-CoV-2 JN.1 mRNA No pregnancy cases with a medical history of maternal exposure to SARS-CoV-2 JN.1 mRNA has reported events of spontaneous or missed abortion. Stillbirth – SARS-CoV-2 JN.1 mRNA No pregnancy cases have reported stillbirth following maternal exposure to SARS-CoV-2 JN.1 mRNA. Congenital Anomaly– SARS-CoV-2 JN.1 mRNA No pregnancy cases have reported congenital anomaly following maternal exposure to SARS-CoV-2 JN.1 mRNA. **Subpopulation Analyses- SARS-CoV-2 JN.1 mRNA:** No pregnancy cases associated with exposure to SARS-CoV-2 JN.1 mRNA have been reported for the following subpopulations: • Children <6 years of Age with a medical history of maternal exposure to SARS-CoV-2 JN.1 mRNA 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 associated with exposure to SARS-CoV-2 JN.1 mRNA have been identified. **Pregnancy Cases After Receiving SPIKEVAX (NOS)** It is important to note that for better attribution of case reports to marketed Moderna vaccines targeting SARS-CoV-2, 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, andusomeran, SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA. During the review period, the MAH received 8 pregnancy cases (36 events) with 5 serious cases (22 serious events) among individuals who received a vaccine classified as SPIKEVAX (NOS). A total of 6 cases were medically confirmed, and 1 case reported a fatal outcome. Most pregnancy cases (6; 75.0%) occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been observed

	with marketed Moderna vaccines targeting SARS-CoV-2 in the previous review period. Similar to the previous reporting period, many of the PTs reported predominantly reflect expected reactogenicity, consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2 and consistent with events reported for these vaccines in the prior review period. *Pregnancy-specific Events – SPIKEVAX (NOS)* During the reporting period, the MAH received 8 cases (5 serious) reporting 12 events (5 serious) associated with exposure to a vaccine classified as SPIKEVAX (NOS). All 12 events reported a pregnancy-specific PT. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome ("Maternal exposure during pregnancy" and Maternal exposure before pregnancy") the remaining PTs that indicated a pregnancy-specific adverse event/outcome were: "Abortion induced," "Foetal death," "Foetal malformation," "heart disease congenital," and "Peripartum cardiomyopathy." A summary of all pregnancy outcomes associated with exposure to vaccines classified as SPIKEVAX (NOS), 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. Serious Pregnancy-specific Events– SPIKEVAX (NOS) During the reporting period, the MAH received 5 serious pregnancy cases reporting 22 serious events following receipt or maternal exposure to a vaccine classified as SPIKEVAX (NOS). Case [redacted] reported maternal death and is summarised below in the *Fatal Pregnancy Cases-SPIKEVAX (NOS)* section. Case [redacted] reported stillbirth and is summarised below in the *Stillbirth-SPIKEVAX (NOS)* section. Cases [redacted] and [redacted] reported events of congenital anomaly and are summarised below in the *Congenital Anomaly-SPIKEVAX (NOS)* section. The remaining serious case is summarised below: [redacted] This spontaneous retrospective pregnancy case reported by a patient concerns a female of unknown age and no reported maternal medical, family, or obstetric history who experienced the serious (due to medically significant) unexpected AESI of peripartum cardiomyopathy and the serious (due to medically significant) unexpected event of ascites, among other non-serious events. The events occurred on an unknown date following receipt of a vaccine classified as SPIKEVAX (NOS) (reported as the third dose in the patient's COVID vaccination schedule. The patient received the first and second dose of "Moderna vaccine" in 2020). LMP and estimated date of delivery were not provided; as per the reporter, who was the patient, she estimated she was probably between 3 to 4 weeks pregnant at the time she received the booster. She reported that she found out that she was pregnant at the 7th week and had not exhibited any symptoms. She also reported that after the booster shot, she experienced the same muscle soreness and heaviness that she experienced with first and second shot. A week after giving birth, she

	experienced shortness of breath and was bloated, which lasted for a few months. Initial diagnosis was postpartum cardiomyopathy. Soon after, she had ascites which was addressed with unspecified diuretics. Additional information about clinical course, supportive diagnostic procedures, and treatment were not provided. The outcome of both serious events was reported as "Recovered." MAH Comment: This case was considered "Unassessable" given the limited information provided regarding the age of the patient, maternal medical and obstetric history (including LMP, estimated date of delivery, and details associated with delivery), maternal family history, concomitant medications, diagnostic/laboratory evaluation and results, as well as clinical course. Fatal Pregnancy Cases– SPIKEVAX (NOS) During the review period, the MAH received 1 fatal case that reported a maternal death following exposure to a vaccine classified as SPIKEVAX [NOS]. This case is summarised below: [redacted]: This spontaneous prospective pregnancy case reported events associated with maternal exposure during pregnancy. This case concerns a 39-year-old female patient with no reported medical or obstetric history, who died on an unknown date following a dose of a vaccine classified as SPIKEVAX [NOS] (reported as a BD in the patient's COVID-19 vaccination schedule). It was reported that "a pregnant woman received a booster, had side-effects, and died." No information was reported regarding LMP, estimated date of delivery, or pregnancy outcome. No cause of death was provided, and it is unknown if an autopsy was performed. MAH Comment: This case was considered "Unassessable" given the limited details provided for medical review. Latency could not be established as the event onset date was not reported. No cause of death was reported, and it is unknown if an autopsy was performed. Additionally, limited information was provided regarding maternal medical and obstetric history (including LMP and estimated date of delivery), maternal family history, diagnostic/ laboratory evaluation and results, as well as clinical course. *Foetal Deaths– SPIKEVAX (NOS)* The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the US [19]. *Spontaneous and Missed Abortions – SPIKEVAX (NOS)* During the review period, 1 serious pregnancy case with a medical history of maternal exposure to a vaccine classified as SPIKEVAX (NOS) reported spontaneous abortion with 1 serious event. Case [redacted] is summarised below in the *Congenital Anomaly-SPIKEVAX (NOS)*. *Stillbirth –SPIKEVAX (NOS)*

During the review period, 1 pregnancy case reported stillbirth following maternal exposure to a vaccine classified as SPIKEVAX (NOS). This case is summarised below:

[redacted] This literature-non-study case of maternal exposure during pregnancy concerns a 38-year-old female patient, with no reported medical history, who received an unspecified dose of a vaccine classified as SPIKEVAX (NOS) at 13 weeks GA and experienced the serious (medically significant) event of foetal death during the 22nd gestational week of pregnancy. It was reported that the patient's obstetric medical history did not indicate any observed events of arterial hypertension, diabetes, spontaneous miscarriage, or death in-utero. No concomitant or treatment medications were reported. No details of other vaccine doses were provided. No further clinical information was available for medical review.

MAH Comment: This case was considered "Unassessable" given the limited information provided regarding maternal medical, family and obstetric history (including LMP and/or estimated date of delivery), concomitant medications, diagnostic/laboratory evaluation and results, as well as clinical course. The patient's age could also be considered a risk factor for stillbirth.

Congenital Anomaly– SPIKEVAX (NOS)

During the reporting period, 2 cases reported events of congenital anomaly in association with maternal exposure to a vaccine classified as SPIKEVAX (NOS). However, 1 case [redacted] appears to be misclassified as a pregnancy case given that the reported event of congenital heart disease was diagnosed in an adult patient. The remaining case describes an elective medical termination of pregnancy due to congenital anomaly and is summarised below:

[redacted]: This literature-non-study case of maternal exposure during pregnancy concerns a 42-year-old female patient, with the concurrent medical condition of diabetes mellitus, who underwent an elective medical termination of pregnancy due to congenital anomaly (foetal malformation). The medical termination of pregnancy was reported to occur 13 weeks following maternal vaccination with a vaccine classified as SPIKEVAX (NOS). No other information regarding the patient's obstetric history or treatment was reported. No further clinical information was available for medical review.

MAH Comment: This case was considered "Unassessable" given the limited information provided regarding maternal medical, family, and obstetric history (including LMP and/or estimated date of delivery), concomitant medications, diagnostic/laboratory evaluation and results, or clinical course; as well, history of foetal malformations in the family. The patient's age and concurrent medical condition of diabetes mellitus could also be considered risk factors for foetal malformation.

Subpopulation Analyses-SPIKEVAX (NOS):

	During the review period, no pregnancy cases associated with exposure to a vaccine classified as SPIKEVAX (NOS) were reported for the following subpopulations: • Children <6 years of Age with a medical history of maternal exposure to a vaccine classified as SPIKEVAX (NOS) 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 associated with vaccines classified as SPIKEVAX (NOS) have been identified.
Discussion	During the reporting period, the MAH received a total of 85 pregnancy cases (661 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 related with the administration of marketed Moderna vaccines targeting SARS-CoV-2 with no other causal association to vaccination. 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. When data were available, it included important 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 review period, 2 cases reported stillbirth. Both cases of stillbirth had clear alternate aetiologies with no observed pattern or clear TTO cluster. This is consistent with cumulative data concerning stillbirth reported thus far for marketed Moderna vaccines targeting SARS-CoV-2. Published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth following 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 21 cases reporting congenital anomalies following maternal exposure to elasomeran (19 cases) and vaccines classified as SPIKEVAX [NOS)] (2 cases) during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunisation with marketed Moderna vaccines targeting SARS-CoV-2.

	During the reporting period, the only reports concerning children under 6 years of age exposed to marketed Moderna vaccines targeting SARs-CoV-2 were reported in association with elasomeran. Review of these 6 serious cases did not identify unusual patterns or safety concerns. During the reporting period, no pregnancy cases associated with exposure to marketed Moderna vaccines targeting SARS-CoV-2 were reported concerning children 6 to 11 years of age. Additionally, no pregnancy cases among adolescents associated with exposure to marketed Moderna vaccines targeting SARS-CoV-2 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. During the review period, in August 2024, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new variant KP.2. The new formulation was labelled SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Since that approval, the MAH has received 5 pregnancy cases reporting events after exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Review of all pregnancy-specific events and non-pregnancy-specific events for all pregnancy cases received following exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccination did not identify any new safety concerns. There were no cases that reported pregnancy-specific complications related with the administration of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. No unusual patterns or pregnancy-specific safety concerns have been identified with use during pregnancy. The current safety profile of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is consistent with the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to review cases involving exposure to the SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccine using routine surveillance. The most frequently reported PTs following SPIKEVAX 2024-2025 Formula (KP.2) vaccination were related to errors in product administration ("Wrong product administered," "Accidental overdose," "Product administration error," and "Underdose"). The other PTs reported were predominantly reactogenicity events, which is consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2 and consistent with events reported for those vaccines in prior review periods. No pregnancy-specific events indicating an adverse clinical outcome following SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccination have been reported. No pregnancy cases following SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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. 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. During the review period, in September 2024, the EMA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new

	variant JN.1. The new formulation was labelled SARS-CoV-2 JN.1 mRNA. Since that approval, the MAH has received 5 pregnancy cases reporting events after exposure to SARS-CoV-2 JN.1 mRNA. Review of serious pregnancy-specific events and non-pregnancy-specific events for all pregnancy cases involving exposure to SARS-CoV-2 JN.1 mRNA vaccination has not identified any new safety concerns. Overall, cases of pregnancy-specific complications were temporally related with the administration of SARS-CoV-2 JN.1 mRNA 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 SARS-CoV-2 JN.1 mRNA is consistent with the safety profile of marketed Moderna vaccines targeting SARSCoV-2. The MAH will continue to review cases involving exposure to SARS-CoV-2 JN.1 mRNA vaccine using routine surveillance. The most frequently reported PTs following SARS-CoV-2 JN.1 mRNA vaccination were related to product storage and quality ("Product temperature excursion issue" and "Poor quality product administered"). The other PTs reported were predominantly reactogenicity events, which is consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2 and consistent with events reported for those vaccines in prior review periods. No pregnancy specific events indicating an adverse clinical outcome following SARS-CoV-2 JN.1 mRNA vaccination have been reported. No pregnancy cases following SARS-CoV-2 JN.1 mRNA 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. 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 immunisation with marketed Moderna vaccines targeting SARS-CoV-2. Furthermore, published literature has reported that there is transfer of maternal antibodies, reduction in SARSCoV- 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 SARS-CoV-2 infection may be more serious and cause complications for both the mother and the foetus. Four (4) articles published during the reporting period provided additional evidence supporting the use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy. A prospective cohort study from [20] demonstrated that both SARS-CoV-2 infection and COVID-19 vaccine (including marketed Moderna vaccines targeting SARS-CoV-2) exposure in-utero were not associated with an increased risk of adverse neurodevelopmental outcomes in infants up to 12 months of age. Similarly, a prospective study conducted by [21] in the United States suggested that the use of COVID-19 vaccines (including mRNA vaccines) was safe during pregnancy from the perspective of infant neurodevelopment up to 18 months of age. [22] conducted an observational population-based cohort study in Sweden and Norway which indicated that vaccination of pregnant individuals with mRNA COVID-19

	vaccines was not associated with an increased risk of neonatal AEs in their infants. Lastly, [23] conducted a population-based retrospective cohort study and sibling matched analysis that demonstrated that mRNA COVID-19 vaccines (including marketed Moderna vaccines targeting SARS-CoV-2) given during the first trimester of pregnancy were not associated with an increased risk for major congenital anomalies in offspring, overall or grouped by organ system (for a summary of these articles please refer to Articles of Reference for Pregnancy with Company comment). Published literature supports the favourable benefit/risk profile of maternal immunisation 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-authorisation studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has presented information regarding use of Moderna's mRNA-vaccines targeting SARS-CoV-2 in relation to pregnancy. According to the MAH, animal studies have not indicated direct nor indirect harmful effects with respect to pregnancy; neither regarding the development of the embryo or foetus, parturition, or postnatally. There is no information from clinical trials, as no CTs were performed among pregnant women. Use of the vaccines include administration to women of child-bearing age.

The MAH has presented data from the latest review period, 18 December 2023 through 17 December 2024, based on evidence achieved from the MAH's global safety database and from a new literature search.

Results

Literature:

The MAH has performed a literature search and retrieved 992 papers of which four were considered to contain new and significant safety information. These were observational studies of which two found that vaccines targeting SARS-CoV-2 were not associated with increased risk of adverse neurodevelopmental outcomes, this for infants up to 12 months of age according to one paper and for infants up to 18 months according to the other. A third paper found that vaccination with mRNA-vaccines against SARS-CoV-2 was not associated with increased risk of neonatal adverse events; while a fourth paper demonstrated that administration of the vaccines in pregnant women during first trimester was not associated with increased risk of major congenital abnormalities.

Global Safety Database:

During the latest reporting period, the MAH received a total of 85 pregnancy-related cases (661 events). Overall, cases of pregnancy-specific complications are temporally related with the administration of the vaccine with no other causal association to vaccination. Review of serious pregnancy-specific events and non-pregnancy-specific events during the review period did not identify any new safety concerns.

Elasomeran:

During the review period, the MAH received 52 pregnancy cases (540 events) with 41 serious cases (198 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. Four (4) cases reported a fatal outcome, and 33 cases were medically confirmed.

The majority of reported events reflect expected immunological reactogenicity including milder and benign events as headache, fever, pain in extremities, but also myocarditis and/or pericarditis were reported.

In total, 48 cases (74 events) were pregnancy-specific event. Among these, three (3) cases were reported as fatal. Of these, one was misclassified as pregnancy-related, and both of the other cases were unlikely causally related to the vaccine as one had a TTO of app. two (2) years, and in the last case which presented foetal malformation incompatible with life there were other more plausible explanations. There was one (1) case reported as stillbirth and this was not counted in among the fatal cases. With a TTO of app. 9 months this case was unlikely vaccine-related.

There were 19 cases of reported congenital anomaly of which many were unassessable due to lack of information. However, the MAH has also considered the cumulative data regarding congenital anomaly, and no significant patterns or safety concerns were identified.

The most frequently reported pregnancy-related outcome was spontaneous abortion.

Elasomeran/Imelasomeran and Elasomeran/Davesomeran:

During the review period, no pregnancy cases were reported regarding these two vaccines.

Andusomeran:

During the reporting period, the MAH received 15 pregnancy cases (49 events) with two (2) serious cases (2 serious events) among individuals who received or were maternally exposed to a booster dose of Andusomeran. None had a fatal outcome. Most events reflected expected reactogenicity. No new safety concerns were identified.

SARS-CoV-2 KP.2 mRNA (COVID-19 vaccine, mRNA) 2024-2025 Formula:

This vaccine was approved in August 2024, and the reporting period for this specific vaccine only covers a part of the latest one-year review period. From August 2024 through 17 December 2024 the MAH received 5 non-serious pregnancy cases (16 events) among individuals who received or were maternally exposed to this vaccine. None had a fatal outcome. Among the 16 events, five (5) were related to administration error. No new safety concerns were identified.

SARS-CoV-2 JN.1 mRNA:

This vaccine was approved in September 2024, and the reporting for this specific vaccine only covers the period from September 2024 through 17 December 2024. During this period, the MAH received five (5) pregnancy cases (20 events) among individuals who received or were maternally exposed to this vaccine. None had a fatal outcome. No new safety concerns were identified.

SPIKEVAX NOS:

During the one-year review period, the MAH received 8 pregnancy cases (36 events) reported in

individuals who received or had a medical history of maternal exposure to an unspecified mRNA vaccine against COVID-19 from Moderna. There were 5 cases with adverse events defined as serious, of these one was misclassified and 4 were unassessable. No significant patterns or safety concerns were identified.

Conclusion:

During the latest reporting period, the MAH received a total of 85 pregnancy-related cases (661 events). Overall, cases of pregnancy-specific complications are temporally related with the administration of the vaccine with no other causal association to vaccination. Information from the global safety database did not show any unusual patterns during the reporting period, and review of serious events reported within the latest review period did not raise any new safety concerns.

This findings from the global safety database were supported by a new literature search presented by the MAH. According to observational studies presented, vaccines targeting SARS-CoV-2 were not associated with increased risk of adverse neurodevelopmental outcomes infants or increased risk of neonatal adverse events or increased risk of major congenital abnormalities.

The MAH will continue to monitor events for pregnancy-specific outcomes using routine surveillance and on-going post-authorization studies.

2.3.1.3.2. Use while breastfeeding

Evaluation of information received during the PBRER reporting interval relating to the missing information safety concern of all marketed Moderna vaccines targeting SARS-CoV-2 during breastfeeding has not identified any additional clinically relevant new safety information for this topic. The characterisation 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 24: Use while Breastfeeding

Missing information	Use while Breastfeeding
Source of new information	• Moderna GSDB • Literature Sources o Search Criteria Applied: [PSUR] Appendix 13.4 o Retrieved: 992 New and Significant Safety Information: None (0)
Background	Use of marketed Moderna vaccines targeting SARS-CoV-2 while breastfeeding 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 while breastfeeding have been identified.
Methods	Refer to [PSUR] Appendix 12.11 for Methods of Evaluation
Results	Refer to [PSUR] Appendix 12.11 for additional information.

	During the reporting period of this PBRER, a total of 36 lactation cases (137 events) were reported among individuals who received a marketed Moderna vaccine targeting SARS-CoV-2. No cases were reported among children under 6 years of age exposed via breastmilk from mothers vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2. There were no reports of adolescent mothers (12-17 years age group) who received a marketed Moderna vaccine targeting SARS-Cov-2 and were breastfeeding their newborn/infants. **Overview of Lactation Cases Who Received Elasomeran** During the review period, the MAH received 29 lactation cases (94 events) with 2 serious cases (2 serious events) among individuals who received elasomeran. A total of 26 cases were medically confirmed, and no cases reported a fatal outcome. Similar to the prior reporting period, the majority (27; 93.1%) of cases reported were non-serious. During the reporting period, no meaningful changes were observed in the age distribution of the cases of lactating women and their breastfeeding children. The majority of lactation cases (24; 82.8%) reported concerned individuals in the 25 to 39-year age group which is consistent with the expected age of lactating women. During the review period, the most frequently reported PTs (2 or more events; >2.0%) among individuals who received elasomeran were "Maternal exposure during breast-feeding," "Pyrexia," "Pain in extremity," "Fatigue," "COVID-19," "Headache," and "Nasopharyngitis." Most of the remaining reported events predominantly reflect expected events consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2. After the exclusion of PTs that do not indicate a lactation-specific event (including "Maternal exposure during breast-feeding") the only reported PT's indicating a lactation-specific clinical adverse/outcome were "Lactation disorder" and "Lactation puerperal increased." There was no 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, the MAH received 2 serious lactation cases following receipt of elasomeran. Neither case [redacted] or [redacted]) reported a serious lactation specific event indicating a clinical adverse event/outcome for an infant/child or lactating woman. The only lactation-specific PT reported in both cases was "Maternal exposure during breastfeeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. Please note: Case [redacted] reported an event of spontaneous abortion, was medically reviewed, and presented as part of the

	analysis of cases reporting spontaneous or missed abortions in Section 16.3.5.1 (Use in Pregnancy). Similar to cumulative data, these cases lacked critical information required for a meaningful medical assessment including paediatric medical history, concurrent clinical events, evaluation and clinical course, as well as event outcome. However, 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. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with elasomeran or adolescent mothers (12-17 years age group) who received elasomeran and were breastfeeding their newborn/infants in association with exposure to elasomeran. No unusual patterns or lactation-specific safety concerns were identified in association with exposure to elasomeran. **Lactation Cases After Receiving BD 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 elasomeran/imelasomeran. **Lactation Cases After Receiving BD with Elasomeran/Davesomeran** 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 elasomeran/davesomeran. **Lactation Cases After Receiving BD with Andusomeran** During the reporting period, the MAH received 5 lactation cases (3 serious) reporting 29 events (13 serious) among individuals who received a BD of andusomeran. One (1) case was medically confirmed, and no cases reported a fatal outcome. During the reporting period, no meaningful changes were observed in the age distribution of the cases of lactating women and their breastfeeding children. Most reported lactation cases (3; 60.0%) concerned adult women in the 25 to 39-year age group which is consistent with the expected age of lactating women. The other 2 cases involved a 43-year-old woman and a woman of unknown age. During the review period, the most frequently reported PTs (2 or more events; >6.0%) among individuals who received andusomeran were "Maternal exposure during breastfeeding," "Injection site pain," "nausea," and issues related to product administration ("Discontinued product administered"). The remaining reported events predominantly reflect expected reactogenicity. These events were comparable to cumulative data and are consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2. When restricted to lactation-specific events, the only PTs reported were "Maternal exposure during breast-feeding." No other PTs indicating a lactation-specific clinical adverse/outcome were reported.

	When compared to cumulative data, there was no significant change in the pattern of PTs reported. During the review period, the MAH received 3 serious lactation cases among women who received andusomeran. None of the 3 cases [redacted] reported a serious lactation-specific event indicating a clinical adverse event/outcome for an infant/child or lactating woman. The only lactation-specific PT reported in all 3 cases was "Maternal exposure during breastfeeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with andusomeran or adolescent mothers (12-17 years age group) who received andusomeran and were breastfeeding their newborn/infants in association with exposure to andusomeran. No unusual patterns or lactation-specific safety concerns were identified in association with exposure to andusomeran. **Lactation Cases After Receiving SPIKEVAX 2024-2025 Formula (KP.2)** The MAH received 1 medically confirmed non-serious case reporting 4 events involving a 65-yearold female who received a dose of SPIKEVAX 2024-2025 Formula (KP.) [reported as 8th dose in her COVID-19 vaccination series]. The only lactation-specific PT reported was "Maternal exposure during breastfeeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. This case appears to be misclassified as a lactation case given the individual's age (65 years old). The MAH requested further clarification for this case report. At the time of this PBRER, no response to this query had been received. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with SPIKEVAX 2024-2025 Formula (KP.2) or adolescent mothers (12-17 years age group) who received SPIKEVAX 2024-2025 Formula (KP.2) and were breastfeeding their newborn/infants in association with exposure to SPIKEVAX 2024-2025 Formula (KP.2). No unusual patterns or lactation-specific safety concerns were identified in association with exposure to SPIKEVAX 2024-2025 Formula (KP.2). **Lactation Cases After Receiving SPIKEVAX 2024-2025 Formula (JN.1)** The MAH received 1 serious lactation case reporting 10 serious events involving a 38-year-old female who received a dose of SPIKEVAX 2024-2025 Formula [JN.1] (reported as the second dose in her COVID-19 vaccination schedule). The only lactation-specific PT reported was "Maternal exposure during breast-feeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with SPIKEVAX 2024-2025 Formula (JN.1) or adolescent mothers (12-17 years age group) who received SPIKEVAX 2024-2025 Formula (JN.1) and were breastfeeding their newborn/infants in association with exposure to SPIKEVAX 2024-2025 Formula (JN.1).

	No unusual patterns or lactation-specific safety concerns were identified in association with exposure to SPIKEVAX 2024-2025 Formula (JN.1). **Lactation Cases After Receiving SPIKEVAX (NOS)** No lactation cases associated with exposure to vaccines classified as SPIKEVAX (NOS) have been reported. There were no lactation-specific events reported in children in association with exposure to vaccines classified as SPIKEVAX (NOS).
Discussion	During the reporting period of this PBRER, a total of 36 lactation cases (137 events) were reported among individuals who received a marketed Moderna vaccine targeting SARS-CoV-2. No cases were reported among children under 6 years of age exposed via breastmilk from mothers vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2. There were no reports of adolescent mothers (12-17 years age group) who received a marketed Moderna vaccine targeting SARS-Cov-2 and were breastfeeding their newborn/infants. There were 6 serious lactation cases received during the reporting period. However, no serious lactation-specific events were reported. The only lactation-specific PT reported in all 6 cases was "Maternal exposure during breastfeeding." 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 AEs 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 [24] [25] [26]. Similar to the prior reporting period, the most frequently reported PT was "Maternal exposure during breast-feeding." The only other lactation-specific PTs indicating a clinical adverse event/outcome were "Lactation disorder" and "Lactation puerperal increased." These were mild transient events which occurred within 2 days after vaccination. No clustering by dose or TTO or concerning patterns or notable trends of events reported were identified. The pattern of reports remains generally consistent when compared with cumulative data and no new safety concerns were identified. 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 [25] [27] [28]. 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 SARSCoV-2 in this population through routine pharmacovigilance [29] [30] [31]. 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 SARSCoV-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 postauthorisation 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 information regarding use of Moderna's mRNA-vaccines targeting SARS-CoV-2 while breastfeeding. The use of the vaccines among breastfeeding women has been an area of missing information. However, real world evidence and previous literature have shown that the vaccines are well tolerated by breastfeeding women and their children, and that adverse effects seem to be similar to adverse effects in the general population. The MAH has presented data from the latest review period, 18 December 2023 through 17 December 2024, based on data achieved from the MAH's global safety database and from a new literature search.

Results

Literature:

The MAH performed a new literature search and retrieved 992 manuscripts. However, the MAH did not find any new and significant safety information in these.

Global Safety Database:

Lactation cases:

During the one-year review period there were a total of 36 lactation cases (137 events) reported after receiving a Moderna vaccine targeting SARS-CoV-2. Of these, 29 cases (94 events) were reported for Elasomeran, 5 cases (29 events) for Andusomeran, 1 case (4 events) for SPIKEVAX 2024-2025 Formula KP.2, and 1 case (10 events) for SPIKEVAX 2024-2025 Formula JN.1. There were no cases reported for Elasomeran/Imelasomeran or Elasomeran/Davesomeran.

For both lactating women and breastfed infants and children there were symptoms consistent with well-known and milder side effects reflecting immunological reactogenicity. Lactation-specific events such as lactation disorders were also reported.

Conclusion

In the review period 18 December through 17 December 2024, 36 new breastfeeding cases (137

events) were reported after receiving one of Moderna's mRNA vaccines against COVID-19. There was no indication of a certain pattern regarding dose number or TTO among the cases, and symptoms are mainly consistent with milder side effects to vaccination and/or to breastfeeding difficulties. The findings from the global safety database are consistent with previously reported data, and do not raise new concerns. Likewise, the MAH's literature review did not identify any manuscripts of new information or concern.

Lactation cases will continue to be monitored by routine surveillance.

2.3.1.3.3. Long-term safety

Table 25: Long-term Safety

Missing information	Long-term Safety
Source of new information	As of the DLP of this PBRER, there have been 25 CTs, including 19 sponsored by ModernaTx, Inc., of which 5 CT (P203, P204, P205, P304, and P305) were completed during the reporting period, assessing the safety of mRNA-1273 and its variant containing vaccines. Cumulatively, 64,409 subjects have been or estimated to be exposed to either elasomeran, or its variants (mRNA 1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA 1273.617, mRNA 1273.617.2, mRNA-1273.529, mRNA-1273.231, 712, and mRNA-1273.815), and participants exposed to mRNA-1273 (or its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 active licensed sFLU vaccines, or mRNA-1345 in the mRNA clinical development programme sponsored by ModernaTx, Inc. The total count of 64,409 represents unique subjects (Subjects enrolled in both trials mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total).
Background	Per protocols, the clinical development programme had a safety follow-up period of 12 months or more in the ongoing studies that assessed long-term safety: mRNA-1273-P306, and the completed studies mRNA-1273-P301, mRNA-1273-P203, mRNA-1273-P204, and mRNA-1273-P205. Post-authorisation safety studies in real-world that evaluate long-term safety include ongoing studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911.
Methods of evaluation	The long-term safety profile remains to be characterised through continued trial follow-up, routine pharmacovigilance, and PASS as indicated in the current RMP. **Study mRNA-1273-P203** Study mRNA 1273 P203, completed during the current review period of this PBRER, was a Phase 2/3 clinical study that aimed to extend the age indication of mRNA-1273 to adolescents 12 to 17 years of age. In Part 1A and 1B, in the mRNA-1273 group Safety Set (N=2486), the median duration of follow-up was

	347 days (range: 30 to 791 days) after Dose 1 and 316 days (range: 1 to 749 days) after Dose 2 (in participants who received Dose 2). In the placebo mRNA-1273 group, (N=96), the median duration of follow-up was 213 days (range: 46 to 505 days) after Dose 1 and 182 days (range: 37 to 471 days) after Dose 2 (in participants who received Dose 2). In the mRNA-1273-Part 1C-1 (booster group) Safety Set (N=1357), the median duration of follow-up was 365 days (range: 2 to 562 days) after the BD. In the placebo mRNA-1273-booster group, (N=51), the median duration of follow-up was 363 days (range: 192 to 381 days) after the BD. In Part 1C-2, in the Safety Set (N=155), the median duration of follow-up after the heterologous booster was 363 days (range: 179 to 463 days). In Part 2, in the Safety Set (N=52), 52 participants received Dose 1 and 50 participants received Dose 2. The median duration of follow-up after Dose 1 was 473 days (range: 29 to 520 days) and the median duration of follow-up after Dose 2 was 442 days (range: 0 to 492 days). **Study mRNA-1273-P204** Study mRNA 1273 P204, was a Phase 2/3, dose-escalation, age de-escalation, 3 parts study (Part 1, open-label) and randomised, observer-blind, placebo-controlled expansion study (Part 2) to evaluate the safety, reactogenicity, and effectiveness of mRNA 1273 (primary series and BD) and safety of mRNA 1273.214 (BD) in children 6 months through 11 years of age, assessing up to 3 dose levels (25, 50, and 100 µg) of mRNA 1273 in the primary series. Part 3 (open-label) evaluated an alternative primary series regimen of mRNA 1273 in the primary series (2 doses of mRNA 1273 25 µg on Days 1 and 29 followed by Dose 3 of mRNA 1273 25 µg at least 3 months and up to 5 months after Dose 2) in children 6 years through 11 years of age. Part 3 data are not in scope for this application. **mRNA-1273-P204 Primary series (Part 2)** In the 6 years through 11 years age group, during the Blinded Phase, the median duration of followup for participants who received the mRNA 1273 50 µg primary series (N=3007) was 78.0 days from Dose 1 and 48.0 days from Dose 2. The duration of follow-up was similar in the placebo group. In the long-term analysis (encompassing a period that covers the Blinded Phase and Open-Label Phase [ie, after study unblinding] up to the receipt of a BD, EOS, or database lock [17 May 2024], whichever occurred first), the median duration of follow-up for participants who received the mRNA 1273 50 µg primary series (including those in the placebo mRNA 1273 group) (N=3708) was 290.0 days from Dose 1 and 260.0 days from Dose 2. A total 3612 (97.4%) participants and 1042 (28.1%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety follow-up after Dose 2 of mRNA 1273, respectively. In the 2 years through 5 years age group, during the Blinded Phase, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (N=3031) was 217.0 days from Dose 1 and 186.0 days from Dose 2. The duration of follow-up was similar in the placebo group. In the long-term analysis, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (including those in the placebo mRNA 1273 group) (N=3671) was 362.0 days from Dose 1 and 330.0 days

from Dose 2. A total 3116 (84.9%) participants and 1752 (47.7%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety follow-up after Dose 2 of mRNA 1273, respectively.

In the 6 months through 23 months age group, during the Blinded Phase, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (N=1994) was 213.0 days from Dose 1 and 183.0 days from Dose 2. The duration of follow-up was similar in the placebo group. In the long-term analysis, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (including those in the placebo mRNA 1273 group) (N=2438) was 345.0 days from Dose 1 and 314.0 days from Dose 2. A total 1968 (80.7%) participants and 956 (39.2%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety followup after Dose 2 of mRNA 1273, respectively.

mRNA 1273 BD (Study P204 Parts 1 and 2, 6 Years Through 11 Years)

A total of 2519 participants in the 6 years through 11 years age group received the mRNA 1273 25µg BD following the mRNA 1273 50 µg 2 dose primary series in Study P204. The median interval between Dose 2 of mRNA 1273 in the primary series and the BD was 235.0 days. The median duration of follow-up after the BD was 369.0 days. A total of 2447 (97.1%) participants and 2262 (89.8%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety follow-up after the BD, respectively.

mRNA 1273.214 BD (Study P204 Parts 1 and 2, 6 Months Through 11 Years)

In the 6 months through 5 years age group, in Study P204 Part 2 (N=2766), the median interval between Dose 2 of mRNA 1273 in the primary series and the BD was 317.0 days. The median duration of follow-up after the BD was 184.0 days. A total of 2658 (96.1%) participants had ≥6 months (ie, ≥168 days) of safety follow-up after the BD.

In the 6 years through 11 years age group, for Study P204 participants who received the mRNA 1273.214 BD (N=184), the median interval between Dose 2 of mRNA 1273 in the primary series and the BD was 385.0 days. The median duration of follow-up after the BD was 186.5 days. A total of 180 (97.8%) participants had ≥6 months (ie, ≥168 days) of safety follow-up after the BD.

Study mRNA-1273-P205

Study mRNA-1273-P205 was an open-label, Phase 2/3 study with multiple, sequentially enrolled cohorts to evaluate the immunogenicity, safety, and reactogenicity of variant containing formulations of mRNA-1273 administered as BDs in adults aged 18 years and older. Across all study parts, a total of 5161 participants received a single BD of mRNA 1273 or its variant containing formulations in the study.

Exposure and duration of follow-up details of mRNA 1273 and its variant containing formulations administered as a single BD in each study part are as follows:

Part A.1: 300 participants received the mRNA-1273.211 50 µg single BD, and 593 participants received the mRNA1273.211 100 µg single BD. The median duration of follow-up after the BD was 373.0 days in the mRNA-1273.211 50

	µg arm and 357.0 days in the mRNA1273.211 100 µg arm. Most participants (>95.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.211 BD. **Part A.2:** 135 participants received the mRNA-1273.214 50 µg single BD. The median duration of follow-up after the second BD was 177.0 days in the mRNA1273.214 50 µg arm. Most participants (>96.0%) had ≥5 months of safety follow-up after the mRNA-1273.214 second BD. **Part B:** 305 participants received the mRNA-1273 100 µg single BD. The median duration of followup after the BD was 358.0 and most participants (>93.0%) had ≥10 months of safety follow-up after the mRNA-1273 BD. **Part C:** 581 participants received the mRNA-1273.617.2 50 µg single BD, and 586 participants received the mRNA-1273.617.2 100 µg single BD. The median duration of follow-up after the BD was 360.0 days in the mRNA-1273.617.2 50 µg arm and 357.0 days in the mRNA-1273.617.2 100 µg arm. Most participants (>95.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.617 BD. **Part D:** 327 participants received the mRNA-1273.213 50 µg single BD, and 583 participants received the mRNA-1273.213 100 µg single BD. The median duration of follow-up after the BD was 359.0 days in the mRNA-1273.213 50 µg arm and 358.0 days in the mRNA-1273.213 100 µg arm. Most participants (>94.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.211 BD. **Part E:** 42 participants received the mRNA-1273.213 100 µg single BD and the median duration of follow-up after the BD was 359.5 days. All participants (100%) had ≥10 months of safety followup after the mRNA1273.213 BD. **Part F (Cohort 1):** 133 participants received the mRNA-1273.529 50 µg single BD. The median duration of follow-up after the BD was 357.0 days in the mRNA1273.529 50 µg arm. Most participants (>93.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.529 BD. **Part F (Cohort 2):** 376 participants received the mRNA-1273.529 50 µg single BD, and 375 participants received the mRNA1273 50 µg single BD. The median duration of follow-up after the second BD was 358.0 days in the mRNA1273.529 50 µg arm and 358.0 days in the mRNA-1273 50 µg arm. Most participants (>94.0% in each arm) had ≥10 months of safety follow-up after the mRNA1273.529/mRNA1273 second BD. **Part G:** 437 participants received the mRNA-1273.214 50 µg single BD and the median duration of follow-up after the second BD was 358.0 days. Most participants (>96.0%) had ≥10 months of safety follow-up after the mRNA-1273.214 second BD. **Part H:** 510 participants received the mRNA-1273.222 50 µg single BD. The median duration of follow-up after the second BD was 179.0 days in the mRNA-1273.222 50 µg arm. Most participants (>96.0%) had ≥5 months of safety follow-up after the mRNA-1273.222 second BD. **Part J:** 50 participants each received the mRNA-1273.815 50 µg single BD or mRNA-1273.231 50 µg single BD. The median duration of follow-up after the third BD was 168.0 days in the mRNA-1273.815 50 µg arm and 169.5 days in

	the mRNA1273.231 50 µg arm. Most participants (>96.0%) had ≥5 months of safety follow-up after the mRNA1273.231/mRNA-1273.815 third BD.
Results	No long-term safety concerns were identified after completion of the studies mRNA-1273-P203, P204, and P205. Post-authorisation 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 characterised. In addition to routine pharmacovigilance activities, results from the following studies will be used to evaluate long-term safety of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran. **Ongoing Studies**: • Study mRNA-1273-P904 (final CSR: 31 Mar 2025), • Study mRNA-1273-P910 (final CSR: 30 Jun 2025), • Study mRNA-1273-P911 (final CSR: 31 Oct 2028), • Study mRNA-1273-P306 (final CSR: Feb 2026). **Completed Studies:** • Study mRNA-1273-P301 (final CSR: 20 Oct 2023), • Study mRNA-1273-P203 (final CSR: 08 Jan 2024), • Study mRNA-1273-P204 (final CSR; 22 Nov 2024), • Study mRNA-1273-P205 (final CSR: 09 Oct 2024).
Conclusion	As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor in the 4 completed study (mRNA-1273-P301, P203, P204, and P205) which are being assessed to characterise long-term safety of marketed Moderna vaccines targeting SARS-CoV-2.

Rapporteur assessment comment:

Long-term Safety

According to the information provided by the MAH in this 7th PSUR, there have been 25 clinical trials as of the data lock point, and five (5) of these were completed during the reporting period. The assessor has noted that in a previous PSUR, the MAH informed about 26 ongoing clinical trials, all aiming to study long-term safety issues; if a study was withdrawn or some studies were merged, it could appropriately be mentioned together with the number of studies completed.

Initially it is mentioned that the studies P203, P204, P205, P304, and P305 were completed during the reporting period. However, as background information and also in the discussion section, only four (4) completed studies are listed, these being P203, P204, P205, and P301. It appears certain that the studies P203, P204, and P205 were completed, but not which other studies were too.

For three (3) (P203, P204, and P205) of the five (5) studies completed during the review period,

the MAH has presented information about participants (age groups and number), doses and follow-up time, and for the same three (3) studies it is reported that no long-term safety concerns were identified after completion of the studies. The assessor acknowledges the information on participants, doses and follow-up time given for these three (3) studies but will kindly emphasize that information on participants and negative results in form of no concerns identified is not sufficiently useful without information about which health outcomes were included in aim of study.

The MAH has reported that no long-term safety concerns were identified after completion of the studies P203, P204, P205.

The MAH has reported, that no findings related to long-term safety have yet been identified for the ongoing studies P904, P910, P911.

Conclusion:

Among the many clinical trials involving Moderna's variants of mRNA vaccines against SARS-CoV-2, information has been provided about selected studies of which some are ongoing and some are completed. It is unclear whether four (4) or five (5) studies were completed in the latest review period, and unclear why only data from three (3) of the studies were described. The MAH has reported that no long-term safety concerns were identified after completion of the three (3) studies P203, P204, P205; it is unclear why the last one(s) were not mentioned but if due to unprocessed data, a short statement as 'results not available yet' would be acknowledged.

In addition, the assessor will kindly emphasize that information on participants and negative results in form of 'no concerns identified' is not sufficiently useful without information about which health outcomes were included in the aim of study. It is therefore recommended to specify aim of study, for instance,

- *mRNA-1273-P904 aims to carry out signal detection and safety evaluation of identified possible signals using routinely collected health data from Denmark, Italy, Norway, Spain, and the UK.*
- *mRNA-1273-P910 aims to describe the clinical course, outcomes and risk factors for myocarditis and pericarditis using health data from Spain, Denmark, Norway, and the UK.*
- *mRNA-1273-P911 aims to evaluate patients with myocarditis for up to 5 years after elasomeran exposure compared to non-vaccine myocarditis.*

The initiative to specify study numbers and provide information on participant age groups, doses and follow-up time is acknowledged. It is recommended also to add which health outcomes are included in aim of study.

Further investigation of long-term safety in relation to Moderna's mRNA vaccines against SARS-CoV-2 can be performed using data from ongoing clinical trials as well as data collected through routine surveillance.

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.

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 A health authority.

The characterisation of the missing information within this PBRER on Use in Immunocompromised Individuals, as of the DLP of this PBRER, and in [PSUR] 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 12.12.

Table 26: Use in immunocompromised subjects (Safety concern in PBRER only)

Missing information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
Source of new information	• Moderna GSDB • Literature Sources o Search Criteria Applied: [PSUR] Appendix 13.4 o Retrieved: 215 articles 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 summarised because it is an area of missing information in 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 of evaluation	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 tumours 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": 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 12.12 for additional information. **Overview of Cases for Immunocompromised Individuals Who Received Elasomeran** During this review period, the MAH received 89 cases (489 events) with 57 serious cases (206 serious events) among immunocompromised individuals

	who received elasomeran. A total of 62 cases were medically confirmed, and 2 cases reported a fatal outcome. Similar to the prior reporting period, there were more cases involving females (53; 59.6%) compared to males (34; 38.2%), with 2 cases (2.2%) that did not report gender information. The median age of patients was 58.0 years (range: 28.0 to 87.0 years). Similar to the previous review period, the most frequently reported MedDRA PTs (8 events or more; >1.6%) in immunocompromised individuals who received elasomeran included fatigue, headache, pyrexia, nausea, pain in extremity, arthralgia, and dyspnoea. Most of the events reported reflect expected reactogenicity and were comparable to those events reported in the general population. Events of COVID-19 infection among immunocompromised individuals was the most reported event during this review period (28; 5.7%). 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, 12 cases (including 11 serious cases and 0 fatal 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)** During the review period, no cases were reported among immunocompromised individuals in these age groups who received elasomeran. **Fatal Cases in Immunocompromised Individuals – Elasomeran** During the reporting period, 2 cases reported a fatal outcome among immunocompromised individuals who received elasomeran. One case concerns a 75-year-old female patient with a relevant medical history of Rheumatoid arthritis who passed away due to asphyxia and aspiration. The asphyxiation due to aspiration of vomit occurred during SARS-CoV-2 PCR testing. The patient's elderly age and significant medical history and concurrent RA-ILD remained as potential confounders. The other case concerned a 66-year-old male patient with a medical history of Epstein-Barr virus infection, and concurrent medical condition of psoriasis that was treated with methotrexate and adalimumab. The patient experienced angioimmunoblastic T-cell lymphoma and passed away due to uncontrollable infection and disseminated intravascular coagulation. His death occurred 3 months after the second dose of elasomeran. His medical history of Epstein-Barr virus infection, and concurrent medical conditions of psoriasis treated with methotrexate and adalimumab, and angioblastic T-cell lymphoma remain as confounders for the fatal events. Using the WHO-UMC causality assessment tool, both cases were assessed as "Unlikely," considering their elderly age, prolonged TTO and

	significant medical histories, and concurrent medical conditions which could provide alternative explanation for the occurrence of the fatal events. 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 13 cases (73 events) with 5 serious cases (45 serious events) for immunocompromised individuals who received a BD of elasomeran/imelasomeran. Nine (9) cases were medically confirmed, and no cases reported a fatal outcome. Similar to the previous reporting period, there were more cases reported for females (8; 61.5%) than males (5; 38.5%). The median age of patients was 63.0 years (range: 21.0 to 77.0 years). During the review period, the most frequently reported PTs (2 or more events; >2.0%) in immunocompromised individuals who received elasomeran/imelasomeran were fatigue, rash, headache, pyrexia, pain in extremity, syncope, lethargy, gastroesophageal reflux disease, burning sensation, and condition aggravated. Most of these events reflect expected reactogenicity and were comparable to events reported in the general population receiving elasomeran/imelasomeran. Events of COVID-19 infection were the most frequently reported PT in this subpopulation during this review period (6; 8.2%). 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, 1 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 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 2 cases (4 events) with 1 serious case (2 serious events) for immunocompromised individuals who received elasomeran/davesomeran. Both cases were medically confirmed, and neither case reported a fatal outcome.

	Similar to the previous review period, there were no meaningful changes in the gender distribution of reports as a similar proportion of cases continued to be reported in both females (1; 50.0%) and males (1; 50.0%). The median patient age was 64.5 years (range: 63.0 to 66.0 years). No meaningful comparison of PTs reported during this reporting period can be made with the prior reporting period due to the significant decrease in the number of cases/events reported for immunocompromised individuals who received elasomeran/davesomeran During this reporting period, the only PTs reported in immunocompromised individuals who received elasomeran/imelasomeran were fatigue, condition aggravated, nail pigmentation, and rheumatoid arthritis. Note that during the review period, no 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, no cases were reported among immunocompromised individuals in these age groups who received elasomeran/davesomeran. 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** During the review period, the MAH received 224 cases (990 events) with 164 serious cases (554 serious events) for immunocompromised individuals who received andusomeran. A total of 46 cases were medically confirmed, and 3 cases reported a fatal outcome. Similar to the prior reporting period, there were more cases involving females (142; 63.4%) compared to males (71; 31.7%), with 11 cases (4.9%) that did not report gender information. The median age of patients was 65.0 years (range: 0.0 to 95.0 years). Similar to the previous reporting period, the most frequently reported PTs (21 events or more; >2.0%) in immunocompromised individuals who received andusomeran included fatigue, headache, pyrexia, nausea, arthralgia, chills, pain in the extremity, pain, and product expiration issues (PT: "Discontinued product administered"). Most of these events reflect expected reactogenicity and were comparable to cumulative data. These events were also comparable to events reported in the general population during this reporting period. Note that during the review period, 42 cases (34 serious cases and 0 fatal 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) – Andusomeran)** During the reporting period, the MAH received 1 serious case reporting 3 events (1 serious) involving an immunocompromised child under 12 years of age who received a dose of andusomeran. **Case** [redacted] is a health authority report that concerns a [redacted]-day-old female who experienced the serious event of vomiting as well as the non-serious events of feeling hot and chills on the same day following a dose of andusomeran (reported as the second dose in the patient's COVID-19 vaccination schedule). However, it appears this case may be misclassified as a case involving a neonate considering the events occurred after the second dose and there is no information suggesting maternal exposure to andusomeran in-utero. Additionally, the patient's concurrent medical conditions (which included chronic kidney disease stage 5, diabetes, and immunodeficiency) are not compatible with reported age and seem to indicate that these events may have occurred in an older individual. **Use in Immunocompromised Adolescents (12-17 years old) – Andusomeran)** During the reporting period, the MAH received 1 non-serious case involving an immunocompromised 15-year-old female with a medical history of immunodeficiency who received an unspecified dose of andusomeran. It was reported that the wrong product was administered ("no drug effect") at the pharmacy where she received the vaccine. No other AEs or outcomes were reported. **Fatal Cases in Immunocompromised Individuals – Andusomeran** During the review period, 3 cases reported a fatal outcome among immunocompromised individuals following receipt of andusomeran. All 3 cases concerned individuals 75 years of age or older. According to the WHO causality assessment, all 3 cases were assessed as "Unlikely" given the patient's elderly age and significant medical history (1: Pulmonary embolism, deep vein thrombosis, plasma cell myeloma; 2): Type II diabetes, hypertension, myasthenia gravis; 3): Diffuse large B-cell lymphoma on chemotherapy) which provided alternative explanation for the fatal events. 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 SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** It is important to note that during the review period, in August 2024, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new variant KP.2. The new formulation was labelled SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Therefore, this will be the first PBRER review period where cases for immunocompromised

	individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula will be reviewed. Since its approval, the MAH has received 7 cases (15 events) including 1 serious case (1 serious event) for immunocompromised individuals who received a dose of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Five (5) cases were medically confirmed, and no cases reported a fatal outcome. There have been fewer cases reported for females (3; 42.9%) than males (4; 57.1%). The median age of patients was 66.5 years (range: 25.0 to 79.0 years). Fifteen (15) PTs (1 event each) have been reported in immunocompromised individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. These PTs included anaphylactic reaction, contusion, COVID-19 infection, diarrhoea, gastrointestinal disorder, heart rate increased, lethargy, peripheral swelling, secretion discharge, skin haemorrhage, urticaria, vaccination site pain, as well as issues related to product quality and product storage. No specific pattern/trend were noted among the events reported for these cases. Note that no 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) – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval, no cases have been reported among immunocompromised individuals in these age groups who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. **Overview of Cases for Immunocompromised Individuals Who Received SARS-CoV-2 JN.1 mRNA** Since its approval, the MAH has received 12 cases (39 events) including 6 serious cases (17 serious events) for immunocompromised individuals who received a dose of SARS-CoV-2 JN.1 mRNA. Six (6) cases were medically confirmed, and 1 case reported a fatal outcome. More cases have been reported for females (9; 75.0%) than males (3; 25.0%). The median age of patients was 59.5 years (range: 16.0 to 84.0 years). The most frequently reported PTs (2 events or more; >5.0%) in immunocompromised individuals who received SARS-CoV-2 JN.1 mRNA included pyrexia, dizziness, erythema, malaise, pain in extremity, and syncope. Most of these events reflect expected reactogenicity and were

	comparable to events reported in the general population who received SARS-CoV-2 JN.1 mRNA. Note that 2 cases (1 serious case, no fatal 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) – SARS-CoV-2 JN.1 mRNA** Since its approval, no cases have been reported among immunocompromised individuals in this age group who received SARS-CoV-2 JN.1 mRNA. **Use in Immunocompromised Adolescents (12-17 years old) – SARS-CoV-2 JN.1 mRNA** Since its approval, the MAH has received 1 non-serious case involving an immunocompromised 16-year-old female with a medical history of rheumatoid arthritis who received. The only reported PT was "Product selection error (Incorrect dose selected)." The event outcome was reported as "Unknown," and no other adverse events/outcomes were reported. **Fatal Cases in Immunocompromised Individuals – SARS-CoV-2 JN.1 mRNA** Since its approval, the MAH has received 1 case reporting a fatal outcome among an immunocompromised individual following receipt of SARS-CoV-2 JN.1 mRNA. This case concerns an 84-year-old male who experienced cerebral infarction and passed away approximately a month after the second dose of SARS-CoV-2 JN.1 mRNA. The patient's medical history included unspecified immunodeficiency and unspecified concomitant medications. According to WHO causality assessment, the case was considered "Unassessable" given the lack of information pertaining to adequate medical history, concomitant medications, diagnostics tests, clinical course of the events, etc., required for a meaningful medical assessment. The patient's elderly age and medical history could be considered as significant risk factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received SARS-CoV-2 JN.1 mRNA. **Overview of Cases for Immunocompromised Individuals Who Received a Vaccine Classified as SPIKEVAX (NOS)** It is important to 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 marketed Moderna vaccines targeting SARS-CoV-2. During this review period, the MAH received 17 cases (43 events) with 8 serious cases (14 serious events) among immunocompromised individuals who received a vaccine classified as SPIKEVAX (NOS). Thirteen cases (13) cases were medically confirmed, and reported a fatal outcome.

	Unlike the previous reporting period, there were fewer cases reported for females (5; 29.4%) when compared to males (11; 64.7%) during this reporting period and 1 case (5.9%) that did not report gender information. The median age of patients was 65.0 years (range: 32.0 – 79.0 years). Similar to the previous reporting period, most events predominantly reflect expected reactogenicity. During the reporting period, the most frequently reported PTs (2 events or more; >4.0%) were pain and pain in the extremity. Additionally, events of COVID-19 infection continued to be the most reported event for this subpopulation (5; 11.6%) when compared to cumulative data as well as the general population (122; 8.2%) during this review period. This may be due to an already exiting COVID-19 infection prior to vaccination, decreased immunogenicity of vaccination, and/or the susceptibility to constantly changing variants. Note that during the review period, 1 serious non-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 Analyses:** **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 classified as SPIKEVAX (NOS). **Fatal Cases in Immunocompromised Individuals – SPIKEVAX NOS** During the review period, 1 case reported a fatal outcome following receipt of a vaccine classified as Spikevax NOS. This case concerns a 42-year-old male with a medical history of myeloma (vincristine, doxorubicin [Adriamycin], Dexamethasone treatment), hypopharyngeal cancer (10 years post-transplant) allogeneic peripheral haematopoietic stem cell transplant and pharyngectomy, who died on unknown date after receiving an unspecified dose of a vaccine reported as Spikevax (NOS). The cause of death was not provided. According to WHO causality assessment, this case was assessed as "Unassessable", given the lack of information provided including cause of death, circumstances leading up to death, supportive diagnostic procedures and treatment, autopsy details, latency, etc. which precluded an adequate medical assessment. However, the conditions outlined in the patient's medical history were considered significant risk factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received a vaccine classified as SPIKEVAX (NOS).

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 AEs observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population were generally similar. Epidemiological studies have not indicated any increased risk of AEs in immunocompromised individuals following vaccination with a marketed Moderna vaccine 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. During the review period, there were 2 cases reported in adolescents. One (1) case was reported for a child 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 either strongly confounded by multiple comorbidities that provided alternate aetiologies or lacked key data elements required for a meaningful medical assessment.
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 regarding 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 vaccines 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

The MAH has presented information regarding use of Moderna's mRNA-vaccines targeting SARS-CoV-2 in immunocompromised subjects. This has been an area of missing information. The MAH has presented data from the latest review period, 18 December 2023 through 17 December 2024, based on data achieved from the MAH's global safety database and from a new literature search. No new and significant safety information was identified for use in immunocompromised individuals.

The MAH defined an immunocompromised subpopulation by searching the global safety database for individuals with a medical history of previous hematological malignant tumors SMQ, transplantation, innate or acquired immunodeficiency syndromes, and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs.

For comparison, all individuals in the global safety database for Moderna's mRNA vaccines against SARS-CoV-2 were defined as a background population.

Results

Literature:

The MAH has performed a literature search and retrieved 215 papers but none were considered to contain new and significant safety information.

Global Safety Database:

During the latest reporting period, the MAH received a total of 364 cases (1,653 events) reported in immunocompromised. Overall, most events reflected expected reactogenicity with milder symptoms.

Elasomeran:

During the review period, the MAH received 89 cases (489 events) with 57 serious cases (206 serious events) in immunocompromised individuals who received or had a medical history of exposure to Elasomeran. Two (2) cases reported a fatal outcome, both were assessed as unlikely according to the WHO-UMC causality assessment. The majority of reported events reflected expected immunological reactogenicity including milder and benign events as headache, fever, pain in extremities, joint pain. There were no cases in children or adolescents younger than 18 years of age.

Elasomeran/Imelasomeran

There were 13 cases (73 events) with 5 serious cases (45 serious events) following Elasomeran/Imelasomeran. None were fatal. Most events reflected expected reactogenicity. There were no cases in children or adolescents younger than 18 years of age.

Elasomeran/Davesomeran:

During the review period, there were 2 cases (4 events) with 1 serious case (2 serious events) in immunocompromised individuals after exposure to Elasomeran/Davesomeran. None were fatal. There was no specific pattern in the reported adverse events other than that several seemed possibly related to underlying disorder. There were no cases in children or adolescents younger than 18 years of age.

Andusomeran:

During the reporting period, the MAH received 224 cases (990 events) with 164 serious cases (554 serious events) among immunocompromised individuals exposed to Andusomeran. Three (3) were fatal, however, all three (3) were causality assessed as 'Unlikely' due to more plausible causes being present including severe underlying disease. Most events reflected expected reactogenicity. For Andusomeran there were two (2) cases reported in children and adolescents, however, one (1) was possibly misclassified and the other related to administration error and of unknown outcome and unassessable.

SARS-CoV-2 KP.2 mRNA (COVID-19 vaccine, mRNA) 2024-2025 Formula:

This vaccine was approved in August 2024, and the reporting period for this specific vaccine only covers August 2024 through 17 December 2024, in which the MAH received 7 cases (15 events) among immunocompromised individuals. None were fatal. The PTs varied from milder (increased heart rate, vaccination site pain) to more severe (anaphylactic reaction, peripheral swelling, skin haemorrhage), nevertheless, the number of cases was small and no specific pattern was seen. There were no cases in children or adolescents younger than 18 years of age.

SARS-CoV-2 JN.1 mRNA:

This vaccine was approved in September 2024, and the reporting for this specific vaccine only covers the period from September 2024 through 17 December 2024. During this period, the MAH received 12 cases (39 events) in immunocompromised individuals. One (1) had a fatal outcome; however, this was WHO-UMC causality categorized as unassessable. One (1) case was reported in the age group younger than 18 years of age; the reported event was dose-related, health-related outcome was unknown, and the case is considered unassessable.

SPIKEVAX NOS:

The MAH received 17 cases (43 events) reported in immunocompromised individuals who had been exposed to an unspecified mRNA vaccine against COVID-19 from Moderna. There were 8 cases (14 events) with adverse events defined as serious. One (1) was fatal; this was found unassessable. Most events reflected expected reactogenicity. There were no cases in children or adolescents younger than 18 years of age.

Conclusion:

During the latest one-year reporting period, the MAH received 364 cases (1,653 events) reported in immunocompromised. Most events reflected expected reactogenicity, and data from the global safety database did not identify any unusual patterns during the reporting period. The review did not raise any new safety concerns. The MAH will continue to monitor events among immunocompromised individuals using routine surveillance and ongoing post-authorization studies.

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 relation to the frail subpopulation has not identified any additional clinically relevant new safety information for this subpopulation.

It is important to note that the use of marketed Moderna vaccines targeting SARS-Cov-2 in frail subjects with unstable health conditions and co-morbidities is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a

request from a health authority. The characterisation of the risk for this missing information as of the DLP of this PBRER and in Section 16.4, below, remains valid.

Table 27: Use in frail subjects

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	• Moderna GSDB • Literature Sources o Retrieved: 26 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 hospitalisations 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 characterising safety through post-marketing routine monitoring of AEs in this special subpopulation. It is important to note that the use of marketed Moderna vaccines targeting SARS-Cov-2 in frail subjects with unstable health conditions and co-morbidities is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a request from a health authority. No specific safety concerns have been identified.
Methods of evaluation	The ModernaTx, Inc. GSDB was queried for reports of frail individuals using "Frail" custom search as defined in the Moderna SSP (see Appendix 12.13), 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 12.13 for more information. **Overview of Frail Cases Reported for Elasomeran:** During the review period, the MAH received 657 cases (4,161 events) with 453 serious cases (1,571 serious events) among frail individuals who received elasomeran. A total of 351 cases were medically confirmed, and 23 cases reported a fatal outcome. The majority of cases (638; 97.1%) received during this period were spontaneous reports. Similar to the prior reporting period, more cases were reported in females (357, 54.3%) compared to males (292, 44.4%) with 8 cases (1.2%) that did not report gender. The median patient age was 56.0 years (range: 18.0 to 100.0 years). Similar to the previous reporting period, a high proportion of reported cases in frail individuals was among the elderly (198, 30.1%). The most frequently reported MedDRA PTs (45 events or more; >1.0%) were fatigue, headache, pyrexia, dyspnoea, pain, pain in extremity, myalgia, arthralgia, asthenia, dizziness, and issues related to the interchange of vaccine products. These events were comparable to those reported in the general

	population and most events reflect expected reactogenicity. Events of COVID-19 infection were also frequently reported during this review period (98; 2.4%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. **Subpopulation Analyses:** **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – Elasomeran)** During the review period, no cases were reported among frail individuals in these age groups who received elasomeran. **Fatal Cases in Frail Individuals – Elasomeran** During the reporting period, the MAH received 23 cases (3.5%) that reported a fatal outcome among frail individuals following receipt of elasomeran. Most cases (15; 65.2%) involved individuals over the age of 65 years. Using the WHO-UMC causality assessment, most of the cases (20; 87.0%), were assessed as "Unlikely" due to the patient's medical history, comorbidities, or concurrent medical conditions that provided alternate aetiologies. Three (3) cases (13.0%) were considered "Unassessable" given the lack of information (e.g. cause of death, autopsy details, circumstances surrounding the event, clinical course, diagnostic tests, etc.) required for a meaningful medical assessment. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received elasomeran. **Overview of Frail Cases reported for Elasomeran/Imelasomeran:** During the review period, the MAH received 24 cases (98 events) with 17 serious cases (59 serious events) among frail individuals who received elasomeran/imelasomeran. A total of 10 cases were medically confirmed, and 1 case reported a fatal outcome. Similar to the prior reporting period, cases were almost equally distributed across gender, with a similar number of cases reported in females (11 cases, 45.8%) compared to males (12 cases, 50.0%) and with 1 case (4.2%) that did not report gender. The median patient age was 63.0 years (range: 42.0 to 90.0 years). Similar to the previous reporting period, a high proportion of reported cases in frail individuals was among the elderly (7, 29.2%). The most frequently reported PTs (3 or more events; >3.0%) were fatigue, dyspnoea, headache, pyrexia, and pain in extremity. Most reported events reflect expected reactogenicity and were comparable to cumulative data reported for this subpopulation. These events were also comparable to those observed in the general population during this reporting period. Events of COVID-19 infection were also frequently reported during this review period (5 events; 6.9%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. **Subpopulation Analyses:** **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – Elasomeran/Imelasomeran)**

	During the review period, no cases were reported among frail individuals in these age groups who received elasomeran/imelasomeran. **Fatal Cases in Frail Individuals – Elasomeran/Imelasomeran** During the review period, the MAH received 1 case reporting a fatal outcome among a frail individual following receipt of elasomeran/imelasomeran. This case concerns a 90-year-old male with a medical history of heart failure, cardiac pacemaker insertion, ruptured abdominal aortic aneurysm, chronic kidney disease, who passed away following receipt of a dose of elasomeran/imelasomeran (reported as his fifth dose in his COVID-19 vaccine schedule). The cause of death was reported as natural cause along with multiple events. According to WHO-UMC causality assessment, this case was assessed as "Unlikely." The patient's elderly age (90 years old) and significant medical history were considered important confounding factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received elasomeran/imelasomeran. **Overview of Frail Cases Reported for Elasomeran/Davesomeran:** During the review period, the MAH received 24 cases (72 events) with 13 serious cases (24 serious events) among frail individuals who received elasomeran/davesomeran. A total of 20 cases were medically confirmed, and 1 case reported a fatal outcome. Similar to the prior reporting period, more cases were reported in females (15; 62.5%) compared to males (8; 33.3%) with 1 case (4.2%) not reporting gender. The median patient age was 73.0 years (range: 7.0 to 87.0 years). Similar to the previous reporting period, a high proportion of reported cases in frail individuals was among the elderly (13, 54.2%). During the reporting period, the most frequently reported PTs (3 events or more; >4.0%) for frail individuals who received elasomeran/davesomeran were pyrexia, fatigue, myalgia, and swelling. Most events reported during this reporting period reflect expected reactogenicity and were comparable to cumulative data for this subpopulation. Additionally, these events were also comparable with events reported in the general population. **Subpopulation Analyses:** **Use in Frail Children (<12 years old)-Elasomeran/Davesomeran** During the reporting period, the MAH received 1 non-serious case (6 events) concerning a 7-yearold male with a medical history of asthma, who received Elasomeran/Davesomeran, and experienced reactogenicity events. **Use in Frail Adolescents (12-17 years old) – Elasomeran/Davesomeran)** During the review period, no cases were reported among frail adolescents who received elasomeran/davesomeran. **Fatal Cases in Frail Individuals – Elasomeran/Davesomeran**

	During the review period, the MAH received 1 case reporting a fatal outcome in a frail individual following receipt of elasomeran/davesomeran. This case concerns a 70-year-old male with a medical history that indicated multiple comorbidities (hyperlipidaemia, overweight, atrial fibrillation, and peripheral vascular disorder). Information including the cause of death, circumstances leading up to death, whether an autopsy was performed or not, details regarding previous vaccination dates and doses received, clinical symptoms, and concomitant medications were not provided. According to WHO-UMC causality assessment, this case was considered "Unassessable." The patient's elderly age and significant medical history could be considered as risk factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received elasomeran/davesomeran. **Overview of Frail Cases Reported for Andusomeran:** During the review period, the MAH received 546 cases (2,069 events) with 273 serious cases (871 serious events) among frail individuals who received andusomeran. A total of 291 cases were medically confirmed, and 18 cases reported a fatal outcome. Similar to the prior reporting period, more cases were reported in females (329; 60.3%) compared to males (198; 36.3%) with 19 cases (3.5%) not reporting gender. The median patient age was 75.0 years (range: 0.0 to 98.0 years). Similar to the prior reporting period, a high proportion of reported cases in frail individuals was among the elderly (340, 62.3%). During the reporting period, the most frequently reported PTs (43 events or more; >2.0%) in frail individuals who received andusomeran included fatigue, headache, pyrexia, nausea, pain in extremity, as well as issues related to product expiration and discontinued product administration. Most of the reported events reflect expected reactogenicity and were comparable to cumulative data reported for this subpopulation. Additionally, these events were also comparable to events reported in the general population during this review period. **Subpopulation Analyses:** **Use in Frail Children (<12 years old)-Andusomeran** During the review period, the MAH received 10 cases (21 events) with 1 serious case (1 serious event) among frail children less than 12 years of age who received or had a medical history of maternal exposure to andusomeran. A total of 9 cases were medically confirmed, and no cases reported a fatal outcome. There was no meaningful comparison by gender as there were an equal number of cases reported in females (5; 50.0%) and males (5; 50.0%). The median patient age was 6.0 years (range: 0.0 to 10.0 years). The 1 serious case (**Case** [redacted]) was a health authority report that concerns a [redacted]-day-old female who experienced the serious event of vomiting as well as the non-serious events of feeling hot and chills on the same day following a dose of andusomeran (reported as the second dose in the patient's COVID-19 vaccination schedule). However, it appears this case may be misclassified as a

	case involving a neonate considering the events occurred after the second dose and there is no information suggesting maternal exposure to andusomeran in-utero. Additionally, the patient's concurrent medical conditions (which included chronic kidney disease stage 5, diabetes, and immunodeficiency) are not compatible with reported age and seem to indicate that these events may have occurred in an older individual. **Use in Frail Adolescents (12-17 years old) – Andusomeran)** During the review period, the MAH received 5 cases (10 events) with 1 serious case (1 serious event) among frail adolescents 12 to 17 years of age who received andusomeran. All 5 cases were medically confirmed, and no cases reported a fatal outcome. There was no meaningful comparison by gender as there were a similar number of cases reported in females (2; 40.0%) and males (3; 60.0%). The median patient age was 14.0 years (range: 12.0 to 17.0 years). The 1 serious case concerned a 12-year-old female with a medical history of asthma who experienced the serious event of chest pain 1 day after receiving Dose 1 of andusomeran. The event outcome was reported as "Resolved." **Fatal Cases in Frail Individuals – Andusomeran** During the reporting period, the MAH received 18 cases (3.3%) that reported a fatal outcome among frail individuals following receipt of andusomeran. The majority of cases (16; 89%) concerned individuals over the age of 65 years. Using the WHO-UMC causality assessment, most of the cases (14; 89%), were assessed as "Unlikely" due to the patient's medical history, comorbidities, or concurrent medical conditions that provided alternate aetiologies, Three (3) cases were considered "Unassessable" given the lack of information (including cause of death, autopsy details, circumstances surrounding the event, clinical course, diagnostic tests, etc.) required for a meaningful medical assessment. One (1) case was assessed as "Possible," however, the patient's medical history could be considered as an important risk factor. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received andusomeran. **Overview of Cases for Frail Individuals Who Received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval in August 2024, the MAH has received 45 cases (172 events) with 10 serious cases (24 serious events) among frail individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. A total of 35 cases were medically confirmed, and no cases reported a fatal outcome. More cases have been reported in females (27; 60.0%) compared to males (17; 37.8%). The median patient age was 64.0 years (range: 0.6 to 93.0 years). Additionally, a high proportion of cases in frail individuals was among the elderly (21, 46.7%). The most frequently reported PTs (4 or more events; >2.0%) in frail individuals who have received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula were fatigue, headache, malaise, myalgia, pain in

	extremity, pyrexia, as well as administration issues related to underdosing. Most of the reported events reflect expected reactogenicity and were comparable with events reported during this review period in the general population. **Subpopulation Analyses:** **Use in Frail Children (<12 years old)- SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval for EUA for use in children 6 months to <12 years of age, the MAH has received 6 non-serious medically confirmed cases (13 events) among frail children less than 12 years of age who received or had a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The median patient age was 5.5 years (range: 0.6 to 10.0 years). Five of these cases reported PTs indicating issues related to product administration (wrong product administered, overdose, or expired product administered). No additional adverse events/outcomes were reported in these cases. The remaining case reported only the non-serious event of urticaria in a 6-year-old male with a medically history of eczema, drug sensitivity, and allergy. **Use in Frail Adolescents (12-17 years old) – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval, the MAH has received 2 cases (10 events) with 1 serious case (8 serious event) among frail adolescents 12 to 17 years of age who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Both cases were medically confirmed, and neither case reported a fatal outcome. There was no meaningful comparison by gender as there was an equal number of cases reported in females (1; 50.0%) and males (1; 50.0%). The median patient age was 15.0 years (range: 14.0 to 16.0 years). The 1 serious case concerned a 14-year-old female with a medical history of asthma, Type 1 diabetes mellitus, and coeliac disease who experienced the serious events of blood glucose increased, blood ketone body increased, headache, peripheral coldness, pyrexia, vaccination site cellulitis, vaccination site inflammation, and vomiting on the same day following Dose 1 of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula) [reported as the fourth dose in patient's COVID-19 vaccine schedule. Previous doses were Pfizer's Comirnaty vaccine]. The event outcome was reported as "Recovering/Resolving." Potential confounders for this case include the patient's medical history of Type 1 diabetes mellitus as well as the concurrent vaccination with Prevnar in the same arm on the same day. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula **Overview of Cases for Frail Individuals Who Received SARS-CoV-2 JN.1 mRNA** Since its approval in Sep 2024, the MAH received 60 cases (198 events) with 26 serious cases (60 serious events) among frail individuals who received

	SARS-CoV-2 JN.1 mRNA. A total of 36 cases were medically confirmed, and 3 cases reported a fatal outcome. More cases were reported in females (33; 55.0%) compared to males (27; 45.0%). The median patient age was 73.0 years (range: 32.0 to 94.0 years). Additionally, a high proportion of reported cases in frail individuals was among the elderly (35, 58.3%). The most frequently reported PTs (4 events or more; >2.0%) in frail individuals who received SARSCoV- 2 JN.1 mRNA were dyspnoea, pyrexia, arthralgia, fatigue, dizziness, headache, nausea, pain in extremity, as well as issues related to product expiration. Most of the reported events reflect expected reactogenicity and were comparable with events reported during this review period in the general population. **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – SARS-CoV-2 JN.1 mRNA** Since its approval, no cases have been reported among frail individuals in these age groups who received SARS-CoV-2 JN.1 mRNA. **Fatal Cases in Frail Individuals – SARS-CoV-2 JN.1 mRNA** Since its approval, the MAH has received 3 cases reporting a fatal outcome among frail individuals following receipt of SARS-CoV-2 JN.1 mRNA. 2 (2) cases concerned individuals who were older than 65 years of age. The remaining case concerned an individual who was 64 years old. According to the WHO-UMC causality assessment, 2 cases were assessed as "Unlikely" due to the patient's medical history, comorbidities, or concurrent medical conditions that provided alternate aetiologies. The remaining case was considered "Unassessable" given the lack of information provided including additional medical history, concomitant medications, diagnostic/laboratory tests, circumstances surrounding the events, event details, cause of death, autopsy details etc. The patient's underlying history of COPD and previous strokes were considered significant risk factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received SARS-CoV-2 JN.1 mRNA. **Overview of Frail Cases Reported for a Vaccine Classified as SPIKEVAX (NOS):** It is important to 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 marketed Moderna vaccines targeting SARS-CoV-2. During the review period, the MAH received 47 cases (185 events) with 20 serious cases (50 serious events) among frail individuals who received a vaccine classified as SPIKEVAX (NOS). A total of 25 cases were medically confirmed, and 2 cases reported a fatal outcome.

	When compared to the prior reporting period, there was a slightly higher proportion of cases reported in females (24; 51.1%) than males (19; 40.4%) with 4 cases (8.5%) that did not report gender. The median patient age was 66.0 years (range: 28.0 to 89.0 years). Similar to the prior reporting period, a high proportion of reported cases in frail individuals was among the elderly (19, 40.4%). During the reporting period, the most frequently reported PTs (3 or more events; >1.6%) reported among frail individuals who received a vaccine classified as SPIKEVAX (NOS) were fatigue, illness, pain, immunisation reaction, pain in extremity, peripheral swelling, dizziness, hypersensitivity, syncope, as well as issues related to interchange of vaccine products. Most of the reported events reflect expected reactogenicity and were comparable to cumulative data for this subpopulation. Additionally, these events were also comparable to events reported in the general population during this review period. Similar to the prior reporting period, events of COVID-19 infection continued to be the most frequently reported event during this reporting period (10; 5.4%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – SPIKEVAX (NOS)** During the review period, no cases were reported among frail individuals in these age groups who received a vaccine classified as SPIKEVAX (NOS). **Fatal Cases in Frail Individuals – SPIKEVAX (NOS)** During the review period, 2 cases reported a fatal outcome among frail individuals following receipt of a vaccine classified as SPIKEVAX (NOS). Both cases were reported for individuals over 75 years of age. Using WHO-UMC causality assessment, both cases were assessed as "Unlikely" due to the patient's medical history, comorbidities, or concurrent medical conditions that provided alternate aetiologies. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received a vaccine classified as SPIKEVAX (NOS).
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. During the reporting period, there were 17 cases reported among frail children and 7 cases reported among frail adolescents in association with exposure to marketed Moderna vaccines targeting SARSCoV-2. There was no clustering or trends among these cases that revealed any new or unusual pattern of events or safety concerns. Cases reporting a fatal outcome among frail individuals during the reporting period (3.4%) were either strongly confounded by advanced age and multiple comorbidities that provided alternate aetiologies or lacked key data elements required for a meaningful medical assessment.
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 SARSCoV-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 frailsubpopulation. 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 theadministration 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:

Use in frail subjects is no longer considered missing information within the RMP, but was included in this PSUR according to request from a health authority. The term 'frail subjects' includes individuals of all ages with unstable health conditions and comorbidities including COPD, HIV, diabetes, chronic neurological disease and cardiovascular disorders. Frail subjects have been of certain interest as they are considered at higher risk of complications to COVID-19 including hospitalization and death.

The MAH has presented data from the latest review period, 18 December 2023 through 17 December 2024, based on a literature search and data achieved from the MAH's global safety database.

Results

Literature:

In a literature search, the MAH retrieved 26 manuscripts and did not find any new and significant safety information in these.

Global Safety Database:

During the latest review period, the MAH received 1,403 cases (6,955 events) reporting adverse events in frail subjects. Of these, 812 cases (2,659 events) were serious, and 48 were fatal.

In tota,l 17 cases (40 events) were in children younger than 12 years of age, and seven (7) cases

(20 events) were in adolescents who were 12 – 17 years of age. None of the cases in children and adolescents were fatal.

All cases were causality assessed according to WHO-UMC.

Cases by vaccine:

During the review period 18 December 2023 through 17 December 2024, the MAH received 657 cases (4,161 events) in frail subjects following exposure to Elasomeran. Of these, 453 cases (1,571 events) were serious. There were 24 cases (98 events) for Elasomeran/Imelasomeran of which 17 cases (59 events) were serious. For Elasomeran/Davesomeran, the MAH received 24 cases (72 events) of which 13 cases (24 events) were serious. For Andusomeran, 546 cases (2,069 events) were reported in frail subjects, and 273 cases (871 events) were serious. The MAH received 45 cases (172 events) following SARS-CoV-2 KP.2 mRNA with 10 serious cases (24 serious events), and 60 cases (198 events) following SARS-CoV-2 JN.1 mRNA with 26 serious cases (60 serious events). Furthermore, 47 cases (185 events) were reported for not otherwise specified vaccines from Moderna against SARS-CoV-2, of which 20 cases (50 events) were serious. Overall, the age distribution corresponded to what has previously been seen cumulatively, and most events represented symptoms related to expected reactogenicity to the vaccines and reflected symptoms also seen in the general population.

Cases in children and adolescents:

Among the cases received by the MAH within the latest review period there were 17 cases in frail children and seven (7) cases in frail adolescents. One (1) case (6 events) was a child < 12 years following Elasomeran/Davesomeran. In children < 12 years there were also 10 cases (21 events) reported after Andusomeran which also accounted for 5 cases (10 events). For the KP.2 variant, 6 cases (13 events) were reported in children < 12 years, and two (2) cases (10 events) in adolescents. No fatal cases were reported among children and adolescents.

Fatal cases:

The 48 cases reported in total in the review period were 23 fatal cases related to Elasomeran, one (1) case related to each of Elasomera/Imelasomeran and Elasomeran/Davesomeran, 18 fatal cases related to Andusomeran, three (3) cases were reported following SARS-CoV-2 JN.1 mRNA, and two (2) cases following SPIKEVAX NOS. Overall, the reported fatal cases among frail subjects were, of course, confounded by comorbidities. According to causality assessment, causal association to the vaccinations were found unlikely or unassessable in most cases, yet for one (1) case related to Andusomeran causal association was found possible.

Conclusion:

During the latest one-year reporting period, the MAH received 1,403 cases (6,955 events) reporting adverse events in frail subjects, among these 17 cases (40 events) in children less than 12 years of age and seven (7) cases (20 events) in adolescents aged 12 – 17 years. In total, 48 cases were fatal but none among children and adolescents. Most events reflected expected reactogenicity. For cases with fatal outcome, one (1) was found possible and others were unlikely or unassessable. The data from the latest review did not raise any new safety concerns. The MAH will continue to monitor events among frail subjects using routine surveillance.

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 the missing information of all marketed Moderna vaccines targeting SARS-CoV-2 in relation to individuals with known history of autoimmune and inflammatory disorders (MedHx AI/ID), has not identified any additional clinically relevant new safety information for this population.

Use in subjects with AI/ID is no longer considered missing information in the approved RMP. It is presented here as per request from a health authority. The characterisation of this missing information as described in this PBRER and in [PSUR] Section 16.4, below, remains valid. The number of cases received during reporting period are presented by product in [PSUR] Table 16-19. Refer to [PSUR] Appendix 12.14 for further information on fatal cases.

Table 28: Use in Subjects with autoimmune or inflammatory disorders (AI/ID)

Missing information	Use in subjects with autoimmune or inflammatory disorders (Safety concern in PBRER only)
Source of new information	• Moderna GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 1056 o New and Significant Safety Information: None (0).
Background	To date, CTs, and post-authorisation safety data have not identified any safety risks in individuals with AI/ID. 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 additional doses 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. 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 of evaluation	The ModernaTx, Inc GSDB was queried for valid spontaneous reports for marketed Moderna vaccines targeting SARS-CoV-2 in people with a medical history of autoimmune and/or inflammatory disease, received for the review period (18 Dec 2023 to 17 Dec 2024). Reports from individuals with a MedHx AI/ID were identified from MAH GSDB using Immunemediated/autoimmune disorder SMQ "Immune-mediated/autoimmune disorders SMQ" PTs identified in past medical history. Company causality assessment is provided utilising the WHO-UMC standardised case causality assessment.
Results	Refer to [PSUR] Appendix 12.14 for additional information. **Overview of MedHx AI/ID Cases Reported for Elasomeran** During this reporting period, 279 cases (184 serious, 151 medically confirmed, 7 fatal cases) with 1,920 events (590 serious) were reported in individuals

	with a known MedHx AI/ID after receiving elasomeran. Majority of cases (202; 72.4%) were reported in females compared to males (74 cases; 26.5%), with a small proportion of cases (3; 1.1%) having no gender reported. The mean patient age was 51.7 years (SD: 13.8) and median age was 50.0 years (range: 14.0 to 90.0 years). Of note, 13 cases (4.7%) were missing age-related information. The most frequently reported (>1%) serious events during this reporting period were COVID-19; Asthenia; Dyspnoea; and Fatigue. **Subpopulation Analysis:** **Use in Children <18 Years of Age with MedHx AI/ID (Elasomeran)** During this reporting period, there was 1 non-serious follow-up case reported in a 14-year-old male, who had inappropriate schedule of product administration (First dose was administered on 18 Feb 2021 and second dose was administered on 03 Mar 2021). There were no AEs reported. On 29 Jan 2024: Follow-up received during this PBRER reporting period was non-significant. No adverse event was added. **Fatal Cases in Individuals with MedHx AI/ID (Elasomeran)** During this reporting period, 7 cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran. Most of these cases (4 out of 7) were assessed as Unassessable due to limited information and remaining 3 cases were assessed as Unlikely. Refer to Appendix 12.14 for further information. **Overview of MedHx AI/ID Cases Reported for Elasomeran/Imelasomeran** During the reporting period, 10 cases (7 serious, 4 medically confirmed, 0 fatal) with 35 events (17 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 (6 cases; 60.0%) and males (4 cases; 40.0%). The mean patient age was 62.4 years (SD:6.5) and median age was 62.0 years (range: 56.0 to 77.0). Of note, 1 case (10.0%) was missing age-related information. During this reporting period, Syncope, and Myocardial injury were reported in 2 cases, (11.8%), and all other serious events, each were reported once (5.9%) in individuals each 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, 10 cases (5 serious, 7 medically confirmed, 0 fatal) with 35 events (8 serious) reported in individuals with known MedHx of AI/ID after receiving elasomeran/davesomeran. The majority of cases were reported in females (8 cases; 80.0%) compared to males (2 cases; 20.0%). The mean patient age was 57.5 years (SD:15.0) and median age was 61.0 years (range: 27.0 to 75.0 years). All 10 cases report age related information. During this reporting period, the following serious events were reported Anaphylactic reaction; Acute macular neuroretinopathy; Aneurysm; Coagulopathy; Myasthenia gravis; Retinal vascular occlusion; TIA; and Ventricular tachycardia. Each event was reported once (12.5%) in individuals 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, 261 cases (181 serious, 61 medically confirmed, 6 fatal case) with 1114 events (573 serious) were reported in individuals with a known MedHx AI/ID after receiving andusomeran. The majority of cases (187; 71.6%) were reported in females compared to males (67 cases; 25.7%), with a small proportion of cases (7; 2.7%) having no gender reported. The mean patient age was 62.9 years (SD: 14.0) and median age was 64.0 years (range: 27.0 to 93.0 years). Of note, 33 cases (12.6%) did not provide age related information. The most frequently reported serious events during this reporting period reflected expected reactogenicity events, such as pyrexia, headache, and fatigue. This is 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, 6 cases with fatal outcome was reported in an individual with known MedHx AI/ID who received andusomeran. Refer to Appendix 12.14 for further information. **Overview of MedHx AI/ID Cases Reported for SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula.** During this reporting period, 11 cases (2 serious, 9 medically confirmed, with no fatal case) with 61 events (9 serious events) were reported in individuals with a known MedHx AI/ID after receiving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The majority of cases (9; 81.8%) were reported in females compared to males (2 cases; 18.2%). The mean patient age was 53.4 years (SD: 25.6) and median age was 62.0 years (range: 5.0 to 79.0 years). There was no frequently reported serious events during this reporting period. None of the serious events were reported for the first time and most of the events were reactogenicity events (such as pyrexia, headache, etc). These are consistent with cumulative reporting. **Subpopulation Analysis:** **Use in Children <18 Years of Age with MedHx AI/ID with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula**: During this review period, there was one non-serious case (MOD-2024-776023) involving a 14-year-old female administered SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula reported in children <18 years of age. **Fatal Cases in Individuals with MedHx AI/ID with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula:** During this reporting period, there were zero (0) case with fatal outcome who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. **Overview of MedHx AI/ID Cases Reported for SARS-CoV-2 JN.1 mRNA** During this reporting period, 13 cases (6 serious, 6 medically confirmed, 0 fatal case) with 41 events (13 serious events) were reported in individuals with a known MedHx AI/ID after receiving SARSCoV-2 JN.1 mRNA. The majority of cases (10; 76.9%) were reported in females compared to males (3 cases; 23.1%). The mean patient age was 58.0 years (SD: 21.7) and median age was 62.5 years (range: 16.0 to 91.0 years). Of note, 1 case (12.9%) did not provide age related information. There was no frequently reported serious events during this reporting period and none of the serious events reported more than once. None of the serious events were reported for the first time and most of these were reactogenicity events. This is consistent with cumulative reporting. **Subpopulation Analysis:** ***Use in Children <18 Years of Age with MedHx AI/ID with SARS-CoV-2 JN.1 mRNA***

	During this review period, there was one non-serious case involving a 16-years-old female involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula were reported in children <18 years of age. ***Fatal Cases in Individuals with MedHx AI/ID with SARS-CoV-2 JN.1 mRNA*** During this reporting period, there were zero (0) cases with fatal outcome who received SARS-CoV-2 JN.1 mRNA. **Overview of MedHx AI/ID Cases Reported for SPIKEVAX (NOS):** 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 marketed Moderna vaccine targeting SARS-CoV-2. During this reporting period, 27 cases (18 serious, 19 medically confirmed, 0 fatal) with 80 events (28 serious) were reported in individuals with a known MedHx AI/ID after receiving SPIKEVAX (NOS). The majority of the cases involved females (20 cases, 74.1%) compared to males (7 cases, 25.9%). The mean patient age was 59.6 years (SD: 12.3) and median age was 61.0 years (range: 38.0 to 79.0 years). Of note, 2 cases (7.41%) did not provide age related information. During this reporting period, Rheumatoid arthritis was the only serious event reported more than once (14.3%). All remaining events were reported once each (3.6%) in individuals with known MedHx AI/ID receiving SPIKEVAX (NOS). **Subpopulation Analysis:** ***Use in Children <18 Years of Age with MedHx AI/ID (SPIKEVAX [NOS])*** During this review period, no cases involving SPIKEVAX (NOS) 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 SPIKEVAX NOS.
Discussion	Based on the analysis of all the safety data available as of 17-Dec-2024, 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 outweigh any possible vaccine-associated risks. Review of the literature for use in AI/ID individuals did not identify any new safety concerns and support the positive benefit/risk profile of marketed Moderna vaccines targeting SARS-CoV-2. 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, in addition to their underlying autoimmune diseases, the cases had common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, and hyperlipidaemia, 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 reported AEs and administration of marketed Moderna vaccines targeting SARS-CoV-2 in individuals with AI/ID. Information presented in the reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARSCoV-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 vaccines 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:

Clinical trials and cumulative post-authorisation safety data have not identified any safety concerns for use in subjects with AI/ID. It is no longer considered missing information within the RMP, but was included in this PSUR according to request from a health authority.

The MAH has presented data from the latest review period, 18 December 2023 through 17 December 2024, based on a literature search and data achieved from the MAH's global safety database.

Results

Literature:

In a literature search, the MAH retrieved 1,056 articles of which none were considered to provide any new and significant safety information. The MAH highlights that many articles discuss decreased or waning effectiveness of the vaccines in AI/ID subjects.

Global Safety Database:

During the latest review period, the MAH received 611 cases (3,286 events) reporting adverse events in subjects with AI/ID. Of these, 403 cases (1,238 events) were serious, and 13 were reported as fatal.

In accordance with previous data within this area there were more cases in females than in males, and most cases in adults or elderly. There were no cases in children younger than 12 years and three (3) cases in adolescents aged 12 – 17 years. None of the cases in children and adolescents were fatal.

A majority of cases presented symptoms compatible with expected reactogenicity and flares. All cases were causality assessed according to WHO-UMC, and overall cases were causality assessed as unlikely or unassessable.

Cases by vaccine:

During the review period, the MAH received 279 cases (1,920 events) in AI/ID subjects following exposure to Elasomeran, of which seven (7) were fatal. There were 10 cases (35 events) for Elasomeran/Imelasomeran, none were fatal. For Elasomeran/Davesomeran, there were 10 cases (35 events) and none fatal. For Andusomeran, 261 cases (1,114 events) were reported of which six (6) had a fatal outcome. There were 11 cases (61 events) following SARS-CoV-2 KP.2 mRNA, none were fatal, and 13 cases (41 events) following SARS-CoV-2 JN.1 mRNA, none were fatal. Finally, 27 cases (80 events) were reported for not otherwise specified vaccines from Moderna against SARS-CoV-2, none of these were fatal. Among cases in children and adolescents, there were no cases in children < 12 years but three (3) in adolescents aged 12 – 17 years with one (1) case following Elasomeran, one (1) after the KP.2 vaccine variant and one (1) after the JN.1 variant, and none of these were fatal.

Conclusion:

The data from the latest review did not reveal new patterns in symptoms, by age groups or by gender, and did not raise any new safety concerns for use in subjects with AI/ID. The MAH will continue monitoring using routine surveillance.

2.4. Characterisation of risks

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

Rapporteur assessment comment:

The safety concerns remain unchanged

3. Benefit evaluation

Marketed Moderna COVID-19 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 marketed Moderna vaccines targeting SARS-CoV-2, from data in clinical studies and post licensure data with more than 1.8 billion doses of distributed worldwide and more than 1 billion doses estimated to have been administered globally as of 17 Dec 2024. Further, safety for bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran), as well with the 2023-2024 monovalent variant vaccine (andusomeran), SARS-CoV2 JN.1, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula has been demonstrated in adults including young adults (18 to < 25 years) in clinical studies and postauthorisation settings.

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. 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).

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 programme, 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.

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

4. Benefit-risk balance

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

There has been no change or re-characterisation in the safety concerns. Based on the evaluation of cumulative safety data and the benefit-risk analysis, no changes to the additional risk minimization activities are warranted.

New and significant data was presented for the important identified risk myocarditis and pericarditis. A new multicentre study (Jain SS et al. [2024]) of COVID-19 vaccine-associated myocarditis presented new data, of which some results supported the known safety profile, while other results presented new findings of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging at presentation and at follow-up in patients with COVID-19 vaccine-associated myocarditis (C-VAM). This may raise concerns about potential long-term cardiac risks in these patients despite an initially mild clinical course. In accordance with the known safety profile, the likelihood of developing LGE was higher in males than in females, higher in younger adults and adolescents >15 years of age compared to patients younger than 15 years, and higher in those who developed C-VAM after the 1st or 2nd dose of the mRNA vaccine compared to those who developed C-VAM after 3rd dose or booster dose. Due to this possible concern about the long-term safety it is suggested to ensure extended long-term follow-up safety studies in individuals who developed C-VAM. As part of additional pharmacovigilance activities, the MAH has an ongoing PASS study mRNA-1273-P911 for the evaluation of long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA). The final study report is expected in October 2028. At present, no SmPC updates are considered warranted.

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, andusomeran, SARS-Co-V-2 KP.2 mRNA, and SARS-CoV-2 JN.1 mRNA in the approved indications.

5. Rapporteur Request for supplementary information

Data in summary tabulations

Request 1

Based on the prior issues with data classification, the MAH is requested, within this procedure, to clarify whether or not the issue of missing data in the summary of tabulations has been corrected. If relevant, the updated annexes should be submitted within this PSUSA procedure.

Request 2

Within this procedure, the MAH is requested to specify which corrective actions have been taken to ensure individual case safety reports (ICSRs) downloaded from EudraVigilance (EV) are properly processed in the Global Safety Database (GSDB). Furthermore, the MAH should confirm if all relevant cumulative tables have been updated.

Signal evaluation

Request 3

Within this procedure, for five of the presented signals (cerebral venous thrombosis, erectile dysfunction, ischaemic stroke, dermatitis allergic, and hypotension), the MAH is requested to discuss the impact of the cumulative reviews on the current information in the EU SmPC.

Request 4

To avoid any misunderstandings the MAH is requested to clarify in this PSUSA procedure, whether the SFDA requested the topic of "dermatitis allergic" to be presented, as the same text is presented in section 2.2.7 for the signal "hypotension" or if the signal of dermatitis allergic was triggered by another source.

6. MAH responses to Request for supplementary information

Data in summary tabulations

Request 1

Based on the prior issues with data classification, the MAH is requested, within this procedure, to clarify whether or not the issue of missing data in the summary of tabulations has been corrected. If relevant, the updated annexes should be submitted within this PSUSA procedure.

MAH response to request 1

The MAH acknowledges the prior concerns raised regarding data classification in the summary of tabulations and confirms that the issue has been addressed and resolved.

As part of this PSUSA procedure, the MAH has reviewed and verified the relevant outputs. Where tabulations or annexes contain no data, this reflects the absence of individual case safety reports (ICSRs) corresponding to those specific parameters during the reporting period. These outputs were intentionally included to demonstrate that the relevant searches were conducted in the safety database, and that the absence of data is due to a lack of reportable cases, rather than an oversight or omission.

To enhance clarity and avoid potential misinterpretation, the MAH respectfully requests confirmation from the PRAC on whether the inclusion of such null outputs is considered appropriate, or if it would be preferable to omit them in future submissions, with a textual note indicating that no relevant cases were identified.

Rapporteur assessment comment:

The MAH has confirmed that tables with null outputs have been reviewed and verified as such. This is acknowledged.

In future submissions, it would be preferable to omit null outputs and indicate any relevant annex as not applicable, with a textual note indicating that no relevant cases were identified.

Issue resolved.

Request 2

Within this procedure, the MAH is requested to specify which corrective actions have been taken to ensure individual case safety reports (ICSRs) downloaded from EudraVigilance (EV) are properly processed in the Global Safety Database (GSDB). Furthermore, the MAH should confirm if all relevant cumulative tables have been updated.

MAH response to request 2

The MAH implemented several corrective actions to ensure proper processing of ICSRs downloaded via EVWEB. The impact of this incident was recorded as a Quality Event in the Moderna Quality Management System, and a Corrective and Preventive Action (CAPA) plan was developed. The corresponding actions were addressed in several CAPAs implemented by the MAH:

- A full review and impact assessment for the 15,044 rejected reports was completed on 17-Sep-2024. All rejected reports which qualified for case processing were processed and submitted to the respective Regulatory Authorities as of 28-Oct-2024.
- The EV Web download process and associated guidance document have been updated, and relevant case processing personnel received training as of 16-Dec-2024.
- On 17-Mar-2025, iTriage (tool used for downloading reports) was decommissioned. The MAH confirms that all relevant cumulative tables presented in this procedure have been updated accordingly.

Rapporteur assessment comment:

The MAH has specified that a Corrective and Preventive Action (CAPA) plan was developed to ensure proper processing of ICSRs downloaded via EudraVigilance (EV). All relevant cumulative tables in the PSUR have been updated accordingly.

Issue resolved.

Signal evaluation

Request 3

Within this procedure, for five of the presented signals (cerebral venous thrombosis, erectile dysfunction, ischaemic stroke, dermatitis allergic, and hypotension), the MAH is requested to discuss the impact of the cumulative reviews on the current information in the EU SmPC.

MAH response to request 3

As discussed in this procedure, the MAH conducted signal evaluations of the five validated signals requested by various health authorities (Australian health authority (Therapeutic Goods Administration (TGA)), Saudi FDA(SFDA), Rwanda HA) and the Advisory Committee on Immunisation Practices (ACIP)).

Results from the cumulative review of all the information available to the MAH did not identify a causal relationship between SPIKEVAX and these events. Therefore, based on these results an update to the EU SmPC is not warranted. The MAH remains committed to continuous routine pharmacovigilance and will reassess the need for updates to the product information should new evidence emerge.

Rapporteur assessment comment:

The response from the MAH is noted and it is agreed that the review of cumulative data regarding the five signals does not indicate any causality, and updates of the product information are therefore not considered appropriate at this point in time. The MAH is reminded to consider these issues upfront and to state clearly the relevant conclusions in future PSUSA procedures.

Issue resolved.

Request 4

To avoid any misunderstandings the MAH is requested to clarify in this PSUSA procedure, whether the SFDA requested the topic of "dermatitis allergic" to be presented, as the same text is presented in section 2.2.7 for the signal "hypotension" or if the signal of dermatitis allergic was triggered by another source.

MAH response to request 4

Both signals "Dermatitis allergic" and "Hypotension" were received by the MAH as part of the same request from Saudi FDA to present Dermatitis allergic and Hypotension in the next Spikevax PSUR (covering reporting period from 18-Dec-2023 to 17-Dec-2024). SFDA mentioned in their request that both signals were identified from medical literature with elasomeran, but after requesting additional information for this request, the agency did not provide the literature information that was considered the source for this request.

Rapporteur assessment comment:

The MAH has confirmed that the two signals "Dermatitis allergic" and "Hypotension" were received as part of the same request from Saudi FDA. This is noted and the reference to "hypotension" in the signal review for "dermatitis allergic" under the headline "source" will be considered a typo going forward.

Issue resolved.

7. Comments from Member States

MS1: We fully endorse the PRAC Rapp assessment, and have no further comments

Member states' comments:

The endorsement from MS1 is acknowledged.

MS2: The thorough assessment carried out by the PRAC Rapporteur's team is fully supported, including the recommendations detailed in the report.

Minor note: According to GVP Module VII (EMA/816292/2011 Rev 1), a summary of important safety concerns at the beginning of the reporting interval should be provided in PSUR sub-section "Summary of safety concerns".

Member states' comments:
MS2 has pointed out that a summary of important safety concerns at the beginning of the reporting interval should be provided in PSUR sub-section "summary of safety concerns", according to GVP module VII. This is acknowledged.

SEVENTH 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), **Andusomeran** (SPIKEVAX XBB.1.5, mRNA-1273.815, SPIKEVAX 2023-2024 Formula), **SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** (SPIKEVAX KP.2, mRNA-1273.712), and **SARS-CoV-2 JN.1 mRNA** (SPIKEVAX JN.1, mRNA-1273.167)

ATC CODE(S): J07BN01 (previously J07BX03)
MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Products	Dates of Worldwide Authorisation	Marketing Authorisation Holder
SPIKEVAX (mRNA-1273; elasomeran/ COVID-19 mRNA Vaccine [nucleoside-modified])	06 Jan 2021	Moderna Biotech Spain S.L. Or Moderna TX Inc.
SPIKEVAX Bivalent.214 Original/ BA.1 (mRNA-1273.214; elasomeran/imelasomeran)	12 Aug 2022	
SPIKEVAX Bivalent.222 Original/ BA.4/5 (mRNA-1273.222; elasomeran/davesomeran)	31 Aug 2022	
SPIKEVAX XBB.1.5 (mRNA-1273.815; SPIKEVAX 2023-2024 Formula, andusomeran)	11 Sep 2023	
SPIKEVAX KP.2 (mRNA-1273.712; SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula)	22 Aug 2024	
SPIKEVAX JN.1 (mRNA-1273.167; SARS-CoV-2 JN.1 mRNA)	02 Sep 2024	

AUTHORISATION PROCEDURE in the European Union (EU): Centralised

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12 Feb 2025

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Health Canada	1

EXECUTIVE SUMMARY

This Seventh Periodic Safety Update Report (PSUR) (referred to as Periodic Benefit-Risk Evaluation Report [PBRER] throughout the report) on SPIKEVAX™ (elasomeran ; 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), SPIKEVAX XBB.1.5 (andusomeran; mRNA1273.815; SPIKEVAX 2023-2024 Formula), SPIKEVAX KP.2 (SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula; mRNA-1273.712) and SPIKEVAX JN.1 (SARS-CoV-2 JN.1 mRNA; mRNA 1273.167) was compiled for regulatory authorities in the PBRER format detailed in the European Medicines Agency (EMA) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)E2C guidelines (Good pharmacovigilance Practice guideline Module VII PSURs, 2012 and ICHE2C[R2]). Throughout the PBRER, the term "SPIKEVAX NOS" is used to categorise the case reports received by ModernaTx, Inc when insufficient details were reported to determine the exact SPIKEVAX product that was utilised. Also, throughout the PBRER, "marketed Moderna vaccines targeting SARS-CoV-2" is used where appropriate instead of listing all currently approved/authorised mRNA-1273 vaccines (elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA).

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).

The International Birth date of elasomeran is 18 Dec 2020. The product was authorised in 47 unique countries, regions, and unions/areas for active immunisation 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 UK on 12 Aug 2022. Elasomeran/davesomeran was granted Emergency Use Authorisation (EUA) status by the US Food & Drug Administration (FDA) on 31 Aug 2022.

Andusomeran was granted authorisation for individuals ≥12 years of age and EUA status for individuals 6 months to 11 years of age by the US FDA on 11 Sep 2023. SARS-CoV-2 JN.1 mRNA was granted authorisation for individuals 6 months of age and older by the Pharmaceuticals and Medical Devices Agency (PMDA) for Japan on 23 Aug 2024. SARS-Co-V-2 KP.2 mRNA

(COVID-19 Vaccine, mRNA) 2024-2025 Formula was granted authorisation for individuals 12 years of age and older, and EUA for individuals 6 month to 11 years of age by the US FDA on 22 Aug 2024.

As of June 2023, the MAH discontinued distribution of elasomeran worldwide. As of Nov 2023, the MAH discontinued distribution of elasomeran/imelasomeran and elasomeran/davesomeran worldwide.

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#7 is 18 Dec 2023 to 17 Dec 2024. Currently, the marketed Moderna vaccines targeting SARS-CoV-2 PBRER is on an annual submission schedule based on the European Union reference dates (EURD).

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; SARS-CoV-2). As per the Company Core Data Sheet (CCDS) (v19.0, dated 13 Jun 2024), elasomeran is authorised as a suspension for injection for active immunisation to prevent COVID-19 caused by SARSCoV2 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 months of age and older 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-CoV2 in individuals 6 months of age and older. SARS-CoV-2 JN.1 mRNA and SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula are indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

Elasomeran is a 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 2 proline residues to stabilise the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of 4 lipids: heptadecan-9-yl 8((2hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102); cholesterol; 1,2distearoyl-sn-glycero-3-phosphocholine (DSPC); and one monomethoxypolyethyleneglycol 2,3dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000DMG). Imelasomeran contains mRNA, 5'-capped, encoding a full-length, codon

optimised prefusion stabilised conformation variant (K983P and V984P) of the SARSCoV2 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). SARS-CoV-2 JN.1 mRNA (mRNA-1273.167) 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 (JN.1). SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains nucleoside-modified mRNA encoding the pre-fusion stabilised spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage KP.2.

During this reporting period, ModernaTx, Inc. was in pharmacovigilance (PV) agreement with the following cosponsors: 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 210012, 22-0004 (DMID/NIAID sponsored), 000115 (NCI Sponsored), COVID-19 Version 2.0 (UCLA sponsored), mRNA1273P508 (SAMRC sponsored), V110-911-00 and V503-076-00 (MSD sponsored), and RHM MED1781 (University of Southampton sponsored).

Elasomeran, was formulated as a dispersion for injection supplied in a multidose vial or in a pre-filled syringe and was administered intramuscularly (IM). Elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, and SARS-CoV-2 JN.1 are formulated as a dispersion for injection supplied in a single dose vial, a multidose vial or a single use pre-filled syringe. SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is formulated as a dispersion for injection supplied in a single use prefilled syringe.

- Elasomeran 0.2 mg/mL dispersion for injection.

Elasomeran is supplied as a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each. One dose (0.5 mL) contains 100 µg of elasomeran, a COVID19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

- Elasomeran 0.1 mg/mL dispersion for injection.

Elasomeran was supplied as a multidose vial that contains 5 doses of 0.5 mL each or a maximum of 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 25 µg of elasomeran, a COVID19 mRNA Vaccine (embedded in LNPs).

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

Elasomeran was 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 was 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.

Elasomeran/imelasomeran was 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 was 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).

- Elasomeran/davesomeran (25 μg/25 μg)/mL dispersion for injection.

Elasomeran/davesomeran was supplied as a single dose 0.5 mL vial (blue flip-off cap) containing 1 doses of 0.5 mL. One dose (0.5 mL) contains 25 μg of elasomeran and 25 μg of davesomeran, 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 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 was supplied as a multi-dose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Andusomeran 50 μg dispersion for injection.

Andusomeran was 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 COVID19 mRNA Vaccine (embedded in lipid nanoparticles).

- SARS-CoV-2 JN.1 mRNA, 0.1 mg/mL dispersion for injection.

SARS-CoV-2 JN.1 mRNA is supplied as a multi-dose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 50 μg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- SARS-CoV-2 JN.1 mRNA, 50 μg dispersion for injection.

SARS-CoV-2 JN.1 mRNA is supplied as a single dose 0.5 mL vial (blue flip-off cap) and prefilled syringe. Each contains 1 dose of 0.5 mL for single use. One dose (0.5 mL) contains 50 μg of mRNA-1273.167, a COVID19 mRNA Vaccine (embedded in lipid nanoparticles).

- SARS-CoV-2 JN.1 mRNA, 25 μg dispersion for injection.

SARS-CoV-2 JN.1 is supplied as a single dose 0.25 mL pre-filled syringe. Each 0.25 mL dose contains 25 mcg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles).

- SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, 50 µg dispersion for injection.

SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is supplied as single dose pre-filled syringes containing either 0.5 mL or 0.25 mL. Each 0.5 mL dose of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 50 mcg mRNA-1273.712, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles). Each 0.25 mL dose of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 25 mcg mRNA-1273.712, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles).

Elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran posology: Primary series, a third dose in severely immunocompromised and booster is provided below in Table 1-1, **andusomeran** posology is provided in Table 1-2, **andusomeran** posology for immunocompromised individuals is provided in Table 1-3, **SARS-CoV-2 JN.1 mRNA** posology is provided in Table 1-4, **SARS-CoV-2 JN.1 mRNA** posology for immunocompromised individuals is provided in Table 1-5, **SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** posology. Individuals 6 Months Through 23 Months of Age by Number of Previous Doses of Moderna COVID-19 Vaccine Received is provided in Table 1-6, and **SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** posology. Individuals 2 Years of Age and Older Irrespective of COVID-19 Vaccination Status is provided in Table 1-7:

Table 1-1 Elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran Posology

Concentration	Vaccination type	Age(s)	Dose	Recommendations
Spikevax 0.2 mg/L dispersion for injection	Primary series	Individuals 12 year of age and older	2 (2) (0.5 mL each, containing 100 micrograms mRNA)	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 years through 11 years of age	2 (2) doses (0.25 mL each, containing 50 micrograms mRNA, which is half of the primary dose for individuals 12 years and older)	
	Third dose in severely immuno-compromised individuals	Individuals 12 year of age and older	1 (one) dose of 0.5 mL, containing 100 micrograms mRNA	A third dose may be given at least 28 days after the second dose.
		Children 6 years through 11 years of age	1 (one) dose of 0.25 mL containing 50 micrograms mRNA	
	Booster dose	Individuals 12 year of age and older	1 (one) dose of 0.25 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary

Concentration	Vaccination type	Age(s)	Dose	Recommendations
				series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Spikevax 0.1 mg/L dispersion for injection and Spikevax 50 micrograms dispersion for injection in pre-filled syringe*	Primary series†	Children 6 years through 11 years of age	2 (2) doses (0.5 mL each, containing 50 micrograms mRNA each)	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age	2 (2) doses (0.25 mL each, containing 25 micrograms mRNA each, which is half of the primary dose for children 6 years through 11 years of age)*	
	Third dose in severely immuno-compromised individuals‡	Children 6 years through 11 years of age	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA	A third dose may be given at least 28 days after the second dose.
		Children 6 months through 5 years of age	1 (one) dose of 0.25 mL, containing 25 micrograms mRNA*	
	Booster dose	Individuals 12 year of age and older	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 6 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
		Children 6 years through 11 years of age	1 (one) dose (0.25 mL each, containing 25 micrograms mRNA)*	

* Do not use the pre-filled syringe to deliver a partial volume of 0.25 mL.
† 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 individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.

Table 1-2 Andusomeran Posology

Age(s)	Dose	Additional recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS-CoV-2 infection	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 any Spikevax vaccine, one dose of Spikevax XBB.1.5 should be administered to complete the 2 dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly*	Spikevax XBB.1.5 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 Andusomeran Posology for immunocompromised individuals

Age(s)	Dose	Additional recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly*	A third 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 single dose vial or prefilled syringe to deliver a partial volume of 0.25 mL.

Table 1-4 SARS-CoV-2 JN.1 mRNA Posology

Age(s)	Dose	Additional recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS-CoV-2 infection	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 any Spikevax vaccine, one dose of Spikevax JN.1 should be administered to complete the 2 dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly*	Spikevax JN.1 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 prefilled syringe to deliver a partial volume of 0.25 mL.

Table 1-5 SARS-CoV-2 JN.1 mRNA Posology for immunocompromised individuals

Age(s)	Dose	Additional recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly*	A third 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 COVID19 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 single dose vial or prefilled syringe to deliver a partial volume of 0.25 mL.

Table 1-6 SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Posology. Individuals 6 Months Through 23 Months of Age by Number of Previous Doses of Moderna COVID-19 Vaccine Received

Number of Previous Doses of Moderna COVID-19 Vaccine(s)[a]	SPIKEVAX (2024-2025 Formula) Dosing Regimen, Dose and Schedule
0[b]	2 doses,[c] 0.25 mL each Dose 1: month 0 Dose 2: month 1
1	Single dose, 0.25 mL One month after receipt of a previous dose of Moderna COVID-19 vaccine[a]
≥2	Single dose, 0.25 mL ≥2 months after receipt of the last previous dose of Moderna COVID-19 vaccine[a]

[a] Previous dose refers to a dose of any prior Moderna COVID-19 Vaccine that is no longer authorised for use in the United States.
[b] Not previously vaccinated with any COVID-19 vaccine.
[c] Individuals turning from 23 months to 2 years of age during the vaccination series should receive both doses with SPIKEVAX (2024-2025 Formula).

Table 1-7 SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Posology. Individuals 2 Years of Age and Older Irrespective of COVID-19 Vaccination Status

Age	SPIKEVAX (2024-2025 Formula) Dosing Regimen, Dose and Schedule
2 years through 11 years	Single dose, **0.25 mL**
12 years and older	Single dose, **0.5 mL**

If previously vaccinated with any COVID-19 vaccine, administer the dose ≥2 months after the last dose of COVID-19 vaccine.

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, there was a total of 11 ModernaTx, Inc. sponsored clinical trials (CTs) with mRNA-1273 completed (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P304, mRNA-1273-P305, mRNA-1273-P401, mRNA-1283-P101, mRNA-1283-P201, mRNA-1073-P101, mRNA-1083-P301, and mRNA-1230-P101). There were 4 ongoing ModernaTx, Inc. sponsored CTs with mRNA-1273 (mRNA-1273-P206, mRNA-1273-P306, mRNA-1273-P403, and mRNA-1273-P404), and 4 ongoing CTs that include mRNA-1273 treatment arm as active control (mRNA-1283-P301, mRNA-1083-P101, mRNA-1345-P302, and mRNA-CRID-001).

Cumulatively, 64,409 subjects have been exposed to either mRNA-1273, or its variants (mRNA1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA1273.617, mRNA1273.617.2, mRNA-1273.529, mRNA-1273.231, mRNA-1273.712, and mRNA1273.815), and participants exposed to mRNA-1273 (including its variants) in CTs using the fixed combination compound mRNA-1283 (including its variant mRNA-1283.211); also in CTs in which mRNA-1273 was coadministered with mRNA-1010 or mRNA-1345; and in CTs in which mRN-1273 was co-administered with active licensed sFLU vaccines (Fluzone High-Dose or Fluarix) in clinical development programmes sponsored by ModernaTx, Inc. The total count of 64,409 represents unique subjects (Subjects enrolled in both trials mRNA-1273-P301 and mRNA1273P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total).

During the reporting period, 4,601 subjects were estimated to be exposed to either mRNA-1273, or its variants (mRNA-1273.167, mRNA-1273.214, mRNA-1273.222, SPIKEVAX KP.2, and mRNA-1273.815), and subjects exposed to mRNA-1273 (or its variants) co-administered active licensed sFLU vaccines in the mRNA clinical development programme sponsored by ModernaTx, Inc.

As of data lock point (DLP), 12,946 subjects were exposed to mRNA-1273 and its variants from ongoing CTs sponsored by licensing partners. Out of 12,946 subjects, 423 subjects were exposed to mRNA-1273 in CTs sponsored by DMID, 19 subjects from a CT sponsored by NCI, 12,342 subjects from a CT sponsored by SAMRC, 162 subjects from CTs sponsored by MSD. Cumulatively, 493 subjects were enrolled in ongoing investigator-initiated trials.

Cumulatively, a total of 1,850,065,554 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered to countries worldwide. For the current reporting period, a total of 73,758,211 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered.

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 2024) and used for this report is the CCDS v19.0 (dated 13 Jun 2024). During this reporting period, the RSI (CCDS) was updated from v18.0 (dated 12 Oct 2023) to v19.0 (dated 13 Jun 2024).

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, authorised as a suspension for injection for active immunisations 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-authorisation

non-interventional studies conducted to date support the positive safety and efficacy profile of mRNA-1273.

During the reporting period, no safety-related actions were taken.

Seven signals were closed by the MAH during the reporting period. Based on scientific evaluation of the available information, all 7 closed signals were refuted, they were: Cerebral venous thrombosis; Dermatitis allergic; Erectile dysfunction; Hypotension; Ischaemic stroke; Pre-eclampsia, gestational hypertension and gestational diabetes; and Renal Failure.

The important identified and potential risks as per Risk Management Plan (RMP) version 9.1 dated 05 Sep 2024 valid at the end of this PBRER/PSUR reporting period are:

Important Identified Risks:

- Myocarditis,
- Pericarditis.

Important Potential Risk:

- None.

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:

- Immunoglobulin (IgA) Nephropathy.

Review of Missed ICSRs and Misattributed Cases During the Reporting Period:

During the reporting period, the MAH discovered an issue related to a number of individual case safety reports (ICSRs) downloaded from EudraVigilance (EV) database for Spikevax, which remained in the intake tool and were not processed in the Global Safety Database (GSDB). A review was completed to assess the potential impact of the 5,543 missed on the safety profile of Spikevax. Of the 5,543 cases, 2,057 cases were serious, and 99 cases were reported with a fatal outcome.

A retrospective ad hoc signal detection review was conducted on the missed ICSRs, focusing on potential impacts on previously closed signals throughout the lifecycle of Spikevax. This review also addressed safety concerns, adverse events of special interest, standard topics, and the identification of any new potential signals. The findings confirmed that these cases did not reveal any new safety information beyond the existing knowledge of Spikevax's safety profile.

It is important to note that because these cases were included in EVDAS, they were already considered in the MAHs ongoing signal detection activities, since January 2021, and that any disproportionately reported among the cases in EVDAS would have been promptly reviewed through proactive routine signal detection activities. The benefit-risk profile of Spikevax remains unaffected by this review of the missed cases.

- Also of note, during the review period, the MAH noticed that after SARS-CoV-2 JN.1 mRNA approval, the MAH continued to receive andusomeran cases from a Regulatory Authority (RA). Upon further investigation the RA reporting site had not been updated to include the JN.1 product as an option for selection for reporters. The RA informed that their sites had been updated approximately 1 month after SARS-CoV-2 JN.1 mRNA approval to include JN.1 as a selection. In total 428 cases were mistakenly reported by the RA as related to andusomeran instead of SARS-CoV-2 JN.1 mRNA. In 367 of these cases, MAH added the event of "Discontinued product administered" for purposes of identification.

Conclusion: 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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Acronym	Definition
ACIP	Advisory Committee on Immunisation Practices
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
AKI	Acute Kidney Injury
AR	Adverse Reaction
ANCA	Antineutrophil Cytoplasmic Antibodies
ATC	Anatomical Therapeutic Chemical
BAT	Basophil Activation Test
BC	Brighton Collaboration
BCC	Brighton Collaboration Criteria
BD	Booster dose
BLA	Biologics License Application
CCDS	Company Core Data Sheet
CDC	Centres for Disease Control
CEAC	Clinical Events Adjudication Committee
CI	Confidence Interval
CMQ	Certified in Medical Quality
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CMR	Cardiac magnetic resonance
CMV	Cytomegalovirus
CPAP	Continuous Positive Airway Pressure
CT	Clinical Trial(s)
CU	Chronic urticaria
CVST	Cerebral venous sinus thrombosis
CVT	Cerebral venous thrombosis
DA	Dermatitis allergic
DCM	Dilated Cardiomyopathy
DMID	Division of Microbiology and Infectious Diseases
DSUR	Development Safety Update Reports
DSPC	1,2-Distearoyl-sn-glycero-3-phosphocholine

Acronym	Definition
DT	Diphtheria and tetanus
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECDC	European Centre for Disease Prevention and Control
ED	Emergency Department
EHR	Electronic Health Record
EMA	European Medicines Agency
ERR	Expected Recovery Rate
EUA	Emergency Use Authorisation
EURD	European Union Reference Date
EU	European Union
ESRD	End-stage renal disease
EVDAS	EudraVigilance system
FFS	Fee-For-Service
GA	Gestational age
GD	Gestational diabetes
GMC	Geometric Mean Concentration
GMT	Geometric mean titres
GRM	Geometric Mean Ratio
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
GSDB	Global Safety Database
HA	Health Authority
HCP	Healthcare Professional
HELLP	Haemolysis, Elevated Liver Enzymes, And Low Platelets
HHS	Health and Human Services
HLT	High Level Term
HIV	Human Immunodeficiency Virus
HIRD	HealthCare Integrated Research Database
HI	Hemagglutination inhibition
HR	Hazard Ratio
HTN	Hypertension
IB	Investigator's Brochure
IBD	International Birth Date

Acronym	Definition
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
ICMR	Indian Council of Medical Research
IgAN	Immunoglobulin A Nephropathy
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILD	Interstitial Lung Disease
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IPTW	Inverse probability of treatment weighting
JMDC	Japan Medical Data Centre
LGE	Late gadolinium enhancement
LMP	Last Menstrual Period
LNP	Lipid Nanoparticle
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorisation Holder
MACiV	Myocarditis After COVID Vaccination
MCM	Major Congenital Malformations
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MHRA	Medical and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MIN	Minute(s)
MMR	Measles, mumps and rubella
MRI	Myocardial injury
MSD	Merck, Sharp and Dohme
NCI	National Cancer Institute
NHIS	National Health Insurance Services
NIAID	National Institute of Allergy and Infectious Diseases
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health

Acronym	Definition
NIS	Non-Interventional Study
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PASS	Post-authorisation safety studies
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PEG	Polyethylene Glycol
PI	Product information
PIL	Package information Leaflet
PMS	Post-Market Surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PASC	Post-Acute Sequelae Of COVID-19
PSS	Potential Safety Signal
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
PY	Person-years
QoL	Quality of Life
RA	Regulatory Authority
RCT	Randomised Controlled Trials
RMP	Risk Management Plan
RMST	Restricted Mean Survival Time
ROC	Revenue Operating Committee
RSV	Respiratory syncytial Virus
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAMRC	South Africa Medical Research Council
SARS	Severe acute respiratory syndrome
SCRI	Self-controlled risk interval
SD	Standard Deviation
SDV	Single dose vial
SFDA	Saudi Food & Drug Authority
SER	Signal Evaluation Reports

Acronym	Definition
SHA	Singapore Health authority
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOT	Solid Organ Transplant
SRR	Seroresponse Rates
SMQ	Standard MedDRA Query
TEAE	Treatment Emergent Adverse Event
TGA	Therapeutics Goods Administration
TIA	Transient Ischaemic Attack
TTO	Time to onset
UCLA	University of California, Los Angeles
UK	United Kingdom
USA/US	United States of America/United States
VAERS	Vaccine AEs Reporting System
VDH	Virginia Department of Health
VDRL	Venereal Disease Research Laboratory
VE	Vaccine effectiveness
VITT	Vaccine Induced Thrombotic Thrombocytopenia
VOC	Variants of concern
VOI	Variants of interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee
V	Version
vs	Versus
VSD	Vaccine Safety Datalink
VUM	Variants under monitoring
WHO	World Health Organisation
XEC	Recombinant Variant
Y	Year(s)

1. INTRODUCTION

This Seventh Periodic Safety Update Report (PSUR) (referred to as Periodic Benefit-Risk Evaluation Report [PBRER] throughout the report) on SPIKEVAX™ (elasomeran ; 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), SPIKEVAX XBB.1.5 (andusomeran; mRNA-1273.815; SPIKEVAX 2023-2024 Formula), SPIKEVAX KP.2 (mRNA-1273.712; SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula) and SPIKEVAX JN.1 (mRNA 1273.167; SARS-CoV-2 JN.1 mRNA) was compiled for regulatory authorities in the PBRER format detailed in the EMA and the International Council for Harmonisation 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 categorise the case reports received by ModernaTx, Inc when insufficient details were reported to determine the exact SPIKEVAX product that was utilised. Also, throughout the PBRER, "marketed Moderna vaccines targeting SARS-CoV-2" is used where appropriate instead of listing all currently approved/authorised mRNA-1273 vaccines (elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA).

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#7 is 18 Dec 2023 to 17 Dec 2024. Currently, the marketed Moderna vaccines targeting SARS-CoV-2 PBRER is on an annual submission schedule based on the European Union (EU) reference dates (EURD).

Marketed Moderna vaccines targeting SARS-CoV-2 belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has 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 the most recent Company Core Data Sheet (CCDS) (v19.0, dated 13 Jun 2024), elasomeran was authorised as a suspension for injection for active immunisation to prevent COVID-19 caused by SARSCoV2 in individuals 6 months of age and older. Elasomeran/imelasomeran and elasomeran/davesomeran were

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-CoV2 in individuals 6 months of age and older, SARS-CoV-2 JN.1 mRNA is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

Elasomeran is a 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 2 proline residues to stabilise the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of 4 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 (PEG) of average molecular weight 2000 (PEG-2000DMG).

Imelasomeran contains mRNA, 5'-capped, encoding a full-length, codon optimised prefusion stabilised 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). Andusomeran 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.

SARS-CoV-2 JN.1 mRNA 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 JN.1 mRNA and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 50 mcg nucleoside-modified mRNA encoding the

pre-fusion stabilised Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage KP.2. Each dose also contains the following ingredients: a total lipid content of 1.01 mg (SM-102, PEG 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), 0.25 mg tromethamine, 1.2 mg tromethamine hydrochloride, 0.021 mg acetic acid, 0.10 mg sodium acetate trihydrate, and 43.5 mg sucrose.

Elasomeran, was formulated as a dispersion for injection supplied in a multidose vial or in a pre-filled syringe and was administered intramuscularly (IM). Elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, and SARS-CoV-2 JN.1 are formulated as a dispersion for injection supplied in a single dose vial, a multidose vial or a single use pre-filled syringe. SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is formulated as a dispersion for injection supplied in a single use prefilled syringe.

- Elasomeran 0.2 mg/mL dispersion for injection.

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

- Elasomeran 0.1 mg/mL dispersion for injection.

Elasomeran was supplied as a multidose vial that contains 5 doses of 0.5 mL each or a maximum of 10 doses of 0.25 mL each. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 25 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

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

Elasomeran was 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 was 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.

Elasomeran/imelasomeran was 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 was 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).

- Elasomeran/davesomeran (25 µg/25 µg)/mL dispersion for injection.

Elasomeran/davesomeran was supplied as a single dose 0.5 mL vial (blue flip-off cap) containing 1 doses of 0.5 mL. One dose (0.5 mL) contains 25 µg of elasomeran and 25 µg of davesomeran, 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 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 was supplied as a multi-dose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 50 ug of andusomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- Andusomeran 50 µg dispersion for injection.

Andusomeran was 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).

- SARS-CoV-2 JN.1 mRNA, 0.1 mg/mL dispersion for injection.

SARS-CoV-2 JN.1 mRNA is supplied as a multi-dose 2.5 mL vial (blue flip-off cap) containing 5 doses of 0.5 mL each. One dose (0.5 mL) contains 50 µg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- SARS-CoV-2 JN.1 mRNA, 50 µg dispersion for injection.

SARS-CoV-2 JN.1 mRNA is supplied as a single dose 0.5 mL vial (blue flip-off cap) and pre-filled syringe. Each contains 1 dose of 0.5 mL for single use. One dose (0.5 mL) contains 50 µg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

- SARS-CoV-2 JN.1 mRNA, 25 µg dispersion for injection.

SARS-CoV-2 JN.1 is supplied as a single dose 0.25 mL pre-filled syringe. Each 0.25 mL dose contains 25 mcg of mRNA-1273.167, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles).

- SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, 50 µg dispersion for injection.

SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is supplied as single dose pre-filled syringes containing either 0.5 mL or 0.25 mL. Each 0.5 mL dose of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 50 mcg mRNA-1273.712, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles). Each 0.25 mL dose of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula contains 25 mcg mRNA-1273.712, a COVID-19 mRNA Vaccine (embedded in liquid nanoparticles).

Elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran posology: Primary series, a third dose in severely immunocompromised and booster is provided below in Table 1-1, **andusomeran** posology is provided in Table 1-2, **andusomeran** posology for immunocompromised individuals is provided in Table 1-3, **SARS-CoV-2 JN.1 mRNA** posology is provided in Table 1-4, **SARS-CoV-2 JN.1 mRNA** posology for immunocompromised individuals is provided in Table 1-5, **SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** posology. Individuals 6 Months Through 23 Months of Age by Number of Previous Doses of Moderna COVID-19 Vaccine Received is provided in Table 1-6, and **SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** posology. Individuals 2 Years of Age and Older Irrespective of COVID-19 Vaccination Status is provided in Table 1-7:

Table 1-1 Elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran Posology

Concentration	Vaccination type	Age(s)	Dose	Recommendations
Spikevax 0.2 mg/L dispersion for injection	Primary series	Individuals 12 years of age and older	2 (2) (0.5 mL each, containing 100 micrograms mRNA)	It is recommended to administer the second dose 28 days after the first dose
		Children 6 years through 11 years of age	2 (2) doses (0.25 mL each, containing 50 micrograms mRNA, which is half of the primary dose for individuals 12 years and older)	
	Third dose in severely immuno-compromised individuals	Individuals 12 years of age and older	1 (one) dose of 0.5 mL, containing 100 micrograms mRNA	A third dose may be given at least 28 days after the second dose.
		Children 6 years through 11 years of age	1 (one) dose of 0.25 mL containing 50 micrograms mRNA	
	Booster dose	Individuals 12 years of age and older	1 (one) dose of 0.25 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Spikevax 0.1 mg/L dispersion for injection and Spikevax 50 micrograms dispersion for injection in pre-filled syringe*	Primary series†	Children 6 years through 11 years of age	2 (2) doses (0.5 mL each, containing 50 micrograms mRNA each)	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age	2 (2) doses (0.25 mL each, containing 25 micrograms mRNA each, which is half of the primary dose for children 6 years through 11 years of age)*	
	Third dose in severely immuno-compromised individuals‡	Children 6 years through 11 years of age	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA	A third dose may be given at least 28 days after the second dose.
		Children 6 months through 5 years of age	1 (one) dose of 0.25 mL, containing 25 micrograms mRNA*	
	Booster dose	Individuals 12 years of age and older	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 6 years of age and older who

Concentration	Vaccination type	Age(s)	Dose	Recommendations
		Children 6 years through 11 years of age	1 (one) dose (0.25 mL each, containing 25 micrograms mRNA)*	have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.

* Do not use the pre-filled syringe to deliver a partial volume of 0.25 mL.
† 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 individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.

Table 1-2 Andusomeran Posology

Age(s)	Dose	Additional recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS-CoV-2 infection	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 any Spikevax vaccine, one dose of Spikevax XBB.1.5 should be administered to complete the 2 dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly*	Spikevax XBB.1.5 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 Andusomeran Posology for immunocompromised individuals

Age(s)	Dose	Additional recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly*	A third 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 single dose vial or prefilled syringe to deliver a partial volume of 0.25 mL.

Table 1-4 SARS-CoV-2 JN.1 mRNA Posology

Age(s)	Dose	Additional recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS-CoV-2 infection	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 any Spikevax vaccine, one dose of Spikevax JN.1 should be administered to complete the 2 dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly*	Spikevax JN.1 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 prefilled syringe to deliver a partial volume of 0.25 mL.

Table 1-5 SARS-CoV-2 JN.1 mRNA Posology for immunocompromised individuals

Age(s)	Dose	Additional recommendations
Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly*	A third 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 COVID19 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 single dose vial or prefilled syringe to deliver a partial volume of 0.25 mL.

Table 1-6 SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Posology. Individuals 6 Months Through 23 Months of Age by Number of Previous Doses of Moderna COVID-19 Vaccine Received

Number of Previous Doses of Moderna COVID-19 Vaccine(s)[a]	SPIKEVAX (2024-2025 Formula) Dosing Regimen, Dose and Schedule
0[b]	2 doses,[c] 0.25 mL each Dose 1: month 0 Dose 2: month 1
1	Single dose, 0.25 mL One month after receipt of a previous dose of Moderna COVID-19 vaccine[a]
≥2	Single dose, 0.25 mL ≥2 months after receipt of the last previous dose of Moderna COVID-19 vaccine[a]

[a] Previous dose refers to a dose of any prior Moderna COVID-19 Vaccine that is no longer authorised for use in the United States.
[b] Not previously vaccinated with any COVID-19 vaccine.
[c] Individuals turning from 23 months to 2 years of age during the vaccination series should receive both doses with SPIKEVAX (2024-2025 Formula).

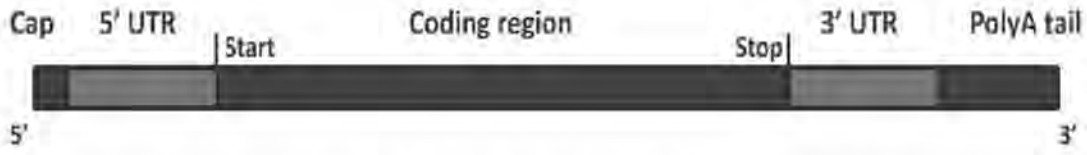
Table 1-7 SARS-CoV-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Posology. Individuals 2 Years of Age and Older Irrespective of COVID-19 Vaccination Status

Age	SPIKEVAX (2024-2025 Formula) Dosing Regimen, Dose and Schedule
2 years through 11 years	Single dose, **0.25 mL**
12 years and older	Single dose, **0.5 mL**

If previously vaccinated with any COVID-19 vaccine, administer the dose ≥2 months after the last dose of COVID-19 vaccine. 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.

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 minimise 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 2 proline substitutions within the heptad repeat one domain (S-2P) to stabilise 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 stabilised Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5. mRNA-1273.167 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. 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 recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate neutralising antibodies, which may contribute to protection against COVID-19.

Modified, variant-matched bivalent COVID-19 mRNA vaccine were developed containing equal amounts of 2 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 2 distinct spike protomers, each of which represents one of the 3 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 stabilised Spike glycoprotein (S) of the SARS-CoV-2 Omicron variant lineage XBB.1.5 (andusomeran) and SARS-CoV-2 JN.1 mRNA. 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 programme (See Table 1-8).

Table 1-8 Variants and World Health Organisation (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)

Suffix	Variants
mRNA-1273.167	SARS-CoV-2 JN.1 mRNA
mRNA-1273.712	SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

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

The expressed Spike protein of SARS-CoV-2 is then recognised 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 v19 dated 13 Jun 2024) in Appendix 1.

During this reporting period, ModernaTx, Inc. was in pharmacovigilance (PV) agreement with the following co-sponsors: the 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 210012, 22-0004 (DMID/NIAID sponsored), 000115 (NCI Sponsored), COVID-19 Version 2.0 (UCLA sponsored), mRNA-1273-P508 (SAMRC sponsored), V110-911-00 and V503-076-00 (MSD sponsored), and RHM MED1781 (University of Southampton sponsored).

2. WORLDWIDE MARKETING APPROVAL STATUS

The international birth date (IBD) of elasomeran is 18 Dec 2020. The product was authorised in 47 unique countries, regions, and unions/areas for active immunisation 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 (MHRA) for use in the United Kingdom (UK) on 12 Aug 2022. Elasomeran/davesomeran was granted Emergency Use Authorisation (EUA) status by the US Food & Drug Administration (FDA) on 31 Aug 2022. Andusomeran was granted authorisation for individuals ≥12 years of age and EUA status for individuals 6 months to 11 years of age by the US FDA on 11 Sep 2023. SARS-CoV-2 JN.1 mRNA was granted authorisation for individuals 6 months of age and older by the Pharmaceuticals and Medical Devices Agency (PMDA) for Japan on 23 Aug 2024. SARS-Co-V-2 KP.2 mRNA

(COVID-19 Vaccine, mRNA) 2024-2025 Formula was granted authorisation for individuals 12 years of age and older, and EUA for individuals 6 month to 11 years of age by the US FDA on 22 Aug 2024.

As of June of 2023, the MAH discontinued distribution of elasomeran worldwide. As of Nov 2023, the MAH discontinued distribution of elasomeran/imelasomeran and elasomeran/davesomeran worldwide.

Marketed Moderna vaccines targeting SARS-CoV are 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 2 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 3 bivalent vaccines (elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran) as well as additional periodic doses against circulating SARS-CoV-2 variants (SARS-CoV-2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula continue to expand.

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

Table 2-1 Worldwide Marketing Authorisations

List of Authorisations	Link to Table
WWMA: mRNA-1273	Table 20-1
WWMA: Bivalent Original/Omicron BA.1 (.214)	Table 20-2
WWMA: Bivalent Original/BA.4/5 (.222)	Table 20-3
WWMA: Spikevax XBB.1.5	Table 20-4
WWMA: SARS-CoV-2 JN.1 mRNA	Table 20-5
WWMA: SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula	Table 20-6

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting period, no safety-related actions were taken.

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 2024) and used for this report is the CCDS v19.0 (dated 13 Jun 2024). 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 v18.0 (dated 12 Oct 2023) to v19.0 (dated 13 Jun 2024). The safety-related changes are summarised below in Table 4-1.

Table 4-1 CCDS safety-related changes during the reporting period

Version	Date	Summary of changes
19.0	13 Jun 2024	**Sections 1, 2, 4.1, 4.2, 5.1, 6.3 and 6.6:** Addition of JN.1 variant particulars and addition of paperboard PFS and 25 mcg PFS SKUs. **Section 6.6:** Deletion of statements on 15-minute wait time per Revenue Operating Committee (ROC) request.

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative Subject Exposure in Clinical Trials

Cumulatively, 64,409 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, mRNA-1273.617.2, mRNA-1273.529, mRNA-1273.231, mRNA-1273.712, and mRNA-1273.815), and participants exposed to mRNA-1273 (including its variants) in CTs using the fixed combination compound mRNA-1283 (including its variant mRNA-1283.211); also in CTs in which mRNA-1273 was co-administered with mRNA-1010 or mRNA-1345; and in CTs in which mRN-1273 was co-administered with active licensed sFLU vaccines (Fluzone High-Dose or Fluarix) in clinical development programmes sponsored by ModernaTx, Inc. The total count of 64,409 represents unique subjects (Subjects enrolled in both trials mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total).

During the reporting period, 4,601 subjects were estimated to be exposed to either mRNA-1273, or its variants (mRNA-1273.167, mRNA-1273.214, mRNA-1273.222, SPIKEVAX KP.2, and mRNA-1273.815), and subjects exposed to mRNA-1273 (or its variants) co-administered active licensed sFLU vaccines in the mRNA clinical development programme sponsored by ModernaTx, Inc.

As of DLP, 12,946 subjects were exposed to mRNA-1273 and its variants from ongoing CTs sponsored by licensing partners. Out of 12,946 subjects, 423 subjects were exposed to mRNA-1273 in CTs sponsored by DMID, 19 subjects from a CT sponsored by NCI, 12,342

subjects from a CT sponsored by SAMRC, 162 subjects from CTs sponsored by MSD. Cumulatively, 493 subjects were enrolled in ongoing investigator-initiated trials.

Estimates of cumulative subject exposure, based upon actual exposure data from completed CTs and the enrolment/randomisation schemes for ongoing and blinded trials is provided in Table 5.1. Further details on cumulative subject exposure categorised by age, gender, racial group and ethnicity is provided in Table 5-2, Table 5-3, Table 5-4, and Table 5-5, respectively.

Table 5.1 Estimated Cumulative Subject Exposure from Clinical Trials

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P201	Placebo	42[a]
mRNA-1273-P201	mRNA-1273	558[a]
mRNA-1273-P201	mRNA-1273 Booster	344
mRNA-1273-P201	mRNA-1273.351 Booster	40[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]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	135[a]
mRNA-1273-P205	mRNA-1273.213 Booster	952[a]
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	423[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	5[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	1759[a]
mRNA-1273-P305	mRNA-1273.214 Booster	1422[a]
mRNA-1273-P305	mRNA-1273.529 Booster	367[a]
mRNA-1273-P306	mRNA-1273.214	391[a]
mRNA-1273-P306	mRNA-1273.815	598[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1273-P306	mRNA-1273.815 Booster	249[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P401	Spikevax	109[a]
mRNA-1273-P401	mRNA-1273.815	106[a]
mRNA-1273-P403	mRNA-1273.167	50[a]
mRNA-1273-P403	SPIKEVAX KP.2	50[a]
mRNA-1273-P404	Overall (SPIKEVAX KP.2 - Placebo Crossover or Placebo - SPIKEVAX KP.2 Crossover)	997[a]
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	Overall (mRNA-1273.222 or mRNA-1273.815)	7,106[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	107[a]
mRNA-1083-P101	mRNA-1273.815	41[a, b]
mRNA-1083-P301	Fluarix + Spikevax co-administration	2009[a]
mRNA-1083-P301	Fluzone HD + Spikevax co-administration	2009[a]
mRNA-1083-P302	Licensed influenza vaccine + Spikevax	1007[a, b]
mRNA-1230-P101	mRNA-1273.214	43[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1345-P302	Overall (mRNA-1273.214, or mRNA-1345 + mRNA-1273.214 co-administration)	1,710[a]

[a]= These numbers were counted for the total subject exposure in each study.
[b]= Estimated numbers per randomisation scheme as the study is currently blinded.

Table 5-2 Cumulative Subject Exposure to Investigational Drug from Completed or Unblinded/Open-label Clinical Trials by Age[a]

Age Range	mRNA-1273											mRNA-1283		mRNA-CRID	mRNA-1073	mRNA-1083		mRNA-1230	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P401	P403	P101	P201	001	P101	P101 Part 1	P301	P101	
<2 years	0	0	2,606	0	68	0	0	0	667	0	0	0	0	0	0	0	0	0	**3,227**
2 to <6 years	0	0	3,877	0	0	0	0	0	1,016	0	0	0	0	0	0	0	0	0	**4,437**
6 to <12 years	0	0	4,549	0	0	0	0	0	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	0	0	0	0	0	**2,397**
16 to <18 years	0	780	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	**781**
18 to <65 years	475	0	0	3,868	0	20,679	184	2,349	0	178	64	27	51	56	127	53	2,007	32	**27,153**
65 to <75 years	120	0	0	1,035	0	5,825	43	1,118	0	28	29	0	5	4	22	47	1,595	11	**9,052**

Age Range	mRNA-1273											mRNA-1283		mRNA-CRID	mRNA-1073	mRNA-1083		mRNA-1230	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P401	P403	P101	P201	001	P101	P101 Part 1	P301	P101	
75 to <85 years	20	0	0	236	0	1,256	7	75	0	9	7	0	1	0	1	7	399	0	**1,837**
>=85 years	3	0	0	22	0	83	0	5	0	0	0	0	0	0	0	0	17	0	**115**
Total	**618**	**3,177**	**11,032**	**5,161**	**68**	**27,843**	**234**	**3,548**	**1,683**	**215**	**100**	**27**	**57**	**60**	**150**	**107**	**4,018**	**43**	**53,548[b]**

[a]Data from Completed or Unblinded/Open-label trials till 17 Dec 2024.
[b]The Subjects enrolled in both mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total number.

Table 5-3 Cumulative Subject Exposure to Investigational Drug from Completed or Unblinded/Open-label Clinical Trials by Sex[a]

Sex	mRNA-1273											mRNA-1283		mRNA-CRID	mRNA-1073	mRNA-1083		mRNA-1230	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P401	P403	P101	P201	001	P101	P101 part 1	P301	P101	
Male	222	1,638	5,615	2,405	38	14,588	124	1,757	868	115	36	18	25	22	56	45	1,722	17	**27,017**
Female	369	1,539	5,417	2,756	30	13,255	110	1,791	815	100	64	9	32	38	94	62	2,296	26	**26,531**
Total	**618**	**3,177**	**11,032**	**5,161**	**68**	**27,843**	**234**	**3,548**	**1,683**	**215**	**100**	**27**	**57**	**60**	**150**	**107**	**4,018**	**43**	**53,548[b]**

[a]Data from Completed or Unblinded/Open-label trials till 17 Dec 2024.
[b]The Subjects enrolled in both mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total number.

Table 5-4 Cumulative Subject Exposure to Investigational Drug from Completed or Unblinded/Open-label Clinical Trials by Racial Group[a]

Race	mRNA-1273											mRNA-1283		mRNA-CRID	mRNA-1073	mRNA-1083		mRNA-1230	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P401	P403	P101	P201	001	P101	P101 Part 1	P301	P101	
White	586	2,353	8,071	4,367	44	22,131	160	3,348	821	174	19	19	47	51	122	80	2,913	39	**41,509**
Black or African American	15	253	721	391	18	2,848	39	12	339	2	78	1	6	7	19	23	924	3	**5,369**
Asian	8	151	764	208	1	1,182	13	92	37	22	3	1	3	2	5	3	75	1	**2,373**
American Indian or Alaska Native	4	15	41	22	0	213	2	0	19	0	0	0	0	0	1	0	25	0	**322**
Native Hawaiian or Other Pacific Islander	1	3	11	9	0	58	0	0	3	1	0	0	0	0	0	0	9	0	**86**
Multiple	2	134	1,152	75	5	597	3	56	115	5	0	1	1	0	2	0	25	0	**2,057**
Other	2	250	182	59	0	544	9	17	329	9	0	0	0	0	0	1	11	0	**1,359**
Not Reported	0	11	68	21	0	160	6	20	9	2	0	5	0	0	0	0	29	0	**311**
Unknown	0	7	22	9	0	110	2	3	11	0	0	0	0	0	1	0	7	0	**162**
Total	**618**	**3,177**	**11,032**	**5,161**	**68**	**27,843**	**234**	**3,548**	**1,683**	**215**	**100**	**27**	**57**	**60**	**150**	107	4,018	43	**53,548**[b]

[a]=Data from Completed or Unblinded/Open-label trials till 17 Dec 2024.
[b]=The Subjects enrolled in both mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total number.

Table 5-5 Cumulative Subject Exposure to Investigational Drug from Completed or Unblinded/Open-label Clinical Trials by Ethnicity[a]

Ethnicity	mRNA-1273											mRNA-1283		mRNA-CRID	mRNA-1073	mRNA-1083		mRNA-1230	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P401	P403	P101	P201	001	P101	P101 part 1	P301	P101	
Hispanic or Latino	44	722	1,740	668	18	5,624	22	0	695	8	0	9	11	15	17	11	658	5	**9,608**
Not Hispanic or Latino	573	2,431	9,195	4,457	50	21,966	210	0	975	178	99	17	45	45	127	96	3,297	37	**39,892**
Not Reported	1	22	71	31	0	173	2	0	6	24	1	1	1	0	4	0	57	1	**372**
Unknown	0	2	26	5	0	80	0	0	7	5	0	0	0	0	2	0	6	0	**128**
Missing	0	0	0	0	0	0	0	3,548	0	0	0	0	0	0	0	0	0	0	**3,548**
Total	**618**	**3,177**	**11,032**	**5,161**	**68**	**27,843**	**234**	**3,548**	**1,683**	**215**	**100**	**27**	**57**	**60**	**150**	**107**	**4,018**	**43**	**53,548[b]**

[a]=Data from Completed or Unblinded/Open-label trials till 17 Dec 2024.
[b]=The Subjects enrolled in both mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total number.

5.2 Cumulative and Interval Exposure from Marketing Experience

Cumulatively, a total of 1,850,065,554 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered to countries worldwide. North America, Europe, and Asia accounted for approximately 85% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed Table 5-6.

For the current reporting period (18 Dec 2023 to 17 Dec 2024), a total of 73,758,211 doses of marketed Moderna vaccines targeting SARS-CoV-2 had been delivered and an estimated total of 36,879,106 doses had been administered. North America, Latin America, Europe, and Asia accounted for approximately 95% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed Table 5-6.

Given that elasomeran, distribution was discontinued worldwide after second quarter of 2023, no new doses were distributed during this PBRER reporting period. Additionally, elasomeran/imelasomeran and elasomeran/davesomeran were discontinued in Nov 2023, there were no doses distributed between 18 Dec 2023 and 17 Dec 2024.

A total of 25,369,142 doses of andusomeran had been delivered to 23 countries and an estimated total of 12,684,571 doses had been administered. Latin America, North America, and Asia accounted for approximately 93% of doses distributed and approximately 93% of doses administered. A total of 24,771,589 doses of SARS-CoV-2 JN.1 mRNA had been delivered to 15 countries and an estimated total of 12,385,795 doses had been administered. Europe, and Asia accounted for approximately 90% of all doses delivered and administered. A total of 23,617,480 doses of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula had been distributed to USA, Canada and Japan and an estimated total of 11,808,740 doses had been administered Table 5-7.

Table 5-6 Total Doses Distributed and Administered for All Marketed Moderna Vaccines Targeting SARS-CoV-2 as of 17 Dec 2024

	Cumulative				Interval			
Region	**Distributed**	**%**	**Administered**	**%**	**Distributed**	**%**	**Administered**	**%**
** Total **	1,850,065,554	100.0	1,040,373,873	100.0	73,758,211	100.0	36,879,106	100.0
North America	699,828,236	37.83	377,606,869	36.30	26,783,092	36.31	13,391,546	36.31
US	626,478,906	33.86	338,507,107	32.54	22,184,452	30.08	11,092,226	30.08
All Europe	525,182,137	28.39	279,643,099	26.88	16,466,944	22.33	8,233,473	22.33

	Cumulative				Interval			
Region	**Distributed**	**%**	**Administered**	**%**	**Distributed**	**%**	**Administered**	**%**
European Economic Area	422,443,266	22.83	226,294,318	21.75	1,418,923	1.92	709,462	1.92
Asia	436,143,821	23.57	232,191,602	22.32	8,503,205	11.53	4,251,603	11.53
Latin America	95,305,500	5.15	50,762,130	4.88	18,180,550	24.65	9,090,275	24.65
Africa	32,474,530	1.76	17,855,749	1.72	0	0.0	0	0.0
Oceania	29,568,000	1.60	15,967,830	1.53	499,920	0.68	249,960	0.68
Middle East	31,563,330	1.71	16,914,697	1.63	3,324,500	4.51	1,662,250	4.51
International donations	.	.	49,431,898	4.75	.	.	0	0.0

*The international donations were restricted only to Spikevax original (Elasomeran). Based on data shared by the Centres for Disease Control (CDC) for the US, the MAH had estimated that approximately 15% of all Moderna doses distributed may be part of such agreements. As tracking data on the administration of doses donated after initial distribution was not available, the MAH had conservatively assumed that only 25% of these doses have been administered globally.

Table 5-7 Doses Distributed and Administered for Elasomeran/Imelasomeran, Elasomeran/Davesomeran, Andusomeran, SARS-CoV2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula as of 17 Dec 2024

Elasomeran/Imelasomeran

	Cumulative				Interval			
Region	**Distributed**	**%**	**Administered**	**%**	**Distributed**	**%**	**Administered**	**%**
** Total **	129,007,543	100.0	64,503,772	100.0	0	0.00	0	0.00
North America	10,521,450	8.16	5,260,725	8.16	0	0.00	0	0.00
US	21,600	0.02	10,800	0.02	0	0.00	0	0.00
All Europe	83,496,993	64.72	41,748,497	64.72	0	0.00	0	0.00
European Economic Area	58,739,963	45.53	29,369,982	45.53	0	0.00	0	0.00
Asia	29,554,550	22.91	14,777,275	22.91	0	0.00	0	0.00
Latin America	1,100,150	0.85	550,075	0.85	0	0.00	0	0.00
Africa	104,850	0.08	52,425	0.08	0	0.00	0	0.00
Oceania	2,891,400	2.24	1,445,700	2.24	0	0.00	0	0.00
Middle East	1,338,150	1.04	669,075	1.04	0	0.00	0	0.00

Elasomeran/Davesomeran

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	245,792,144	100.0	122,896,072	100.0	0	0.00	0	0.00
North America	69,347,234	28.21	34,673,617	28.21	0	0.00	0	0.00
US	67,846,884	27.60	33,923,442	27.60	0	0.00	0	0.00
All Europe	65,556,530	26.67	32,778,265	26.67	0	0.00	0	0.00
European Economic Area	59,256,930	24.11	29,628,465	24.11	0	0.00	0	0.00
Asia	93,671,610	38.11	46,835,805	38.11	0	0.00	0	0.00
Latin America	12,826,800	5.22	6,413,400	5.22	0	0.00	0	0.00
Africa	0	0.00	0	0.00	0	0.00	0	0.00
Oceania	1,999,970	0.81	999,985	0.81	0	0.00	0	0.00
Middle East	2,390,000	0.97	1,195,000	0.97	0	0.00	0	0.00

Andusomeran

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	108,692,842	100.0	54,346,421	100.0	25,369,142	100.0	12,684,571	100.0
North America	42,487,162	39.09	21,243,581	39.09	3,165,712	12.48	1,582,856	12.48
US	34,238,612	31.50	17,119,306	31.50	3,165,712	12.48	1,582,856	12.48
All Europe	18,731,190	17.23	9,365,595	17.23	110,120	0.43	55,060	0.43
European Economic Area	1,683,620	1.55	841,810	1.55	109,870	0.43	54,935	0.43
Asia	24,639,370	22.67	12,319,685	22.67	2,618,740	10.32	1,309,370	10.32
Latin America	18,840,550	17.33	9,420,275	17.33	17,830,150	70.28	8,915,075	70.28
Africa	0	0.00	0	0.00	0	0.0	0	0.0
Oceania	1,000,030	0.92	500,015	0.92	499,920	1.97	249,960	1.97
Middle East	2,994,540	2.76	1,497,270	2.76	1,144,500	4.51	572,250	4.51

SARS-CoV-2 JN.1 mRNA

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	24,771,589	100.0	12,385,795	100.0	24,771,589	100.0	12,385,795	100.0
North America	0	0.00	0	0.00	0	0.00	0	0.00
US	0	0.00	0	0.00	0	0.00	0	0.00
All Europe	16,356,824	66.03	8,178,413	66.03	16,356,824	66.03	8,178,413	66.03
European Economic Area	1,309,053	5.28	654,527	5.28	1,309,053	5.28	654,527	5.28
Asia	5,884,365	23.75	2,942,183	23.75	5,884,365	23.75	2,942,183	23.75
Latin America	350,400	1.41	175,200	1.41	350,400	1.41	175,200	1.41
Africa	0	0.00	0	0.00	0	0.00	0	0.00
Oceania	0	0.00	0	0.00	0	0.00	0	0.00
Middle East	2,180,000	8.80	1,090,000	8.80	2,180,000	8.80	1,090,000	8.80

SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
** Total **	23,617,480	100.0	11,808,740	100.0	23,617,480	100.0	11,808,740	100.0
North America	23,617,380	100.0	11,808,690	100.0	23,617,380	100.0	11,808,690	100.0
US	19,018,740	80.53	9,509,370	80.53	19,018,740	80.53	9,509,370	80.53
All Europe	0	0.00	0	0.00	0	0.00	0	0.00
European Economic Area	0	0.00	0	0.00	0	0.00	0	0.00
Asia	100	0.00	50	0.00	100	0.00	50	0.00
Latin America	0	0.00	0	0.00	0	0.00	0	0.00
Africa	0	0.00	0	0.00	0	0.00	0	0.00
Oceania	0	0.00	0	0.00	0	0.00	0	0.00
Middle East	0	0.00	0	0.00	0	0.00	0	0.00

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, Isle of Man, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Ukraine, Switzerland, UK
Asia: Bangladesh, Bhutan, Cambodia, 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.

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 (HCP) to record the name and batch number of the administered vaccine to improve traceability.

The vaccine carton labelling also contains a scannable 2D barcode that provides the batch/lot number and expiry date. In addition, ModernaTx, Inc. also provides stickers (2 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-authorisation use in Special Populations

5.2.2.1 Use in Elderly

Evaluation of information received during this PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in the elderly population has not identified any clinically relevant new safety information for this subpopulation.

This reporting interval is 12 months, which has changed from the last PBRER reporting period of 6 months. The number of cases received during this 12-month reporting period and the MAH medical review of cases are presented by product in Table 5-8. There was a total of 45 cases with a reported fatal outcome. Most of these cases, irrespective of the variant formulation used, were assessed as unlikely related to the Company product due to concurrent polymorbidities that provided alternative aetiologies.

Refer to Appendix 12.2 for more information on individual case assessment.

Table 5-8 Case Reports and MAH Comment by Product

Source of New Information	• Moderna Global Safety Database (GSDB) • Literature Sources- See Appendix 13.4 • Retrieved: 555 (1 relevant article reviewed) • New and Significant Safety Information: There was no new and significant safety information identified.		
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	994	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/ Imelasomeran	>65 years of age	76	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/ Davesomeran	>65 years of age	127	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Andusomeran	>65 years of age	2,223	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
SARS-CoV-2 JN.1 mRNA	>65 years of age	225	The observed safety data were generally consistent with the known safety profile of elasomeran. The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation was positive.
SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula	>65 years of age	185	The observed safety data were generally consistent with the known safety profile of elasomeran. The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation was positive.
SPIKEVAX (NOS)	>65 years of age	139	There have been no new safety findings. The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.

Andusomeran

During this 12-month reporting period, the MAH received 2,223 cases (979 serious, 1,241 medically confirmed, 35 fatal) with 6,981 events (2,477 serious) in the elderly population (>65+ years of age) who received andusomeran. When gender was known, cases were disproportionately reported in females (1,174, 52.8%) compared to males (854, 38.4%), with small proportion of cases (195, 8.8%) having no gender reported. The mean patient age was 76.9 years (SD: 7.2) and median age of 76.0 years (range: 65.0 to 116.0 years). During the reporting period, there has been >2-fold increase in the number of case reports with andusomeran use compared to the previous reporting period which was likely reflective of the corresponding increase in the market uptake of andusomeran. This included, a four-fold increase of cases reported in the UK (1,401; 63.0%) and a decline in the US (374, 16.8%) and similar reporting rates in Canada (259, 11.7%) compared to the previous reporting period. No clustering or trends of any safety concerns were identified following the data review. The most commonly reported events (PTs) were consistent with the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2.

During the reporting period, when dose number and time to onset could be determined, events were most often reported after Dose 2 (1,280, 18.3%) followed by Dose 1 (314, 4.5%) and Dose 6 (186, 2.7%), typically within the first 5 days of vaccination. When outcome was recorded, 20.1% of events had resolved (1,404 events), 14.4% were resolving (1,006 events) and 16.8% of events had not resolved (1,172 events), at the time of report. Of the 35 cases reported with fatal outcomes, the majority of the cases with fatal outcome were evaluated as unlikely related to the use of the product. These cases often involved patients of advanced age and with concurrent polymorbid conditions, the likely progression/ worsening of which or their potential associated complications provided a more likely explanation of the reported fatal event(s). No new safety concerns were identified with the use of Company product in this population subgroup (Appendix 12.2).

SARS-CoV-2 JN.1 mRNA

Cumulatively, the MAH received 225 cases (61 serious, 156 medically confirmed, 5 fatal) with 605 events (123 serious) in the elderly population (>65+ years of age) who received mRNA-1273.167 formula. When gender was known, the majority of cases were reported in females (132, 58.7%) compared to males (86, 38.2%), with few cases (7, 3.1%) not reporting gender information. The mean patient age was 77.1 years (SD: 8.3) and median age of 76.0 years (range: 65.0 to 99.0 years), representing the population that is mainly getting vaccinated worldwide. Majority of cases were reported from the UK (209, 92.9%) followed by Denmark (6; 2.7%), and Switzerland (5; 2.2%).

The most frequently reported events (PTs) were generally consistent with reactogenicity events consistent with the marketed Moderna vaccines targeting SARS-CoV-2 safety profile.

Cumulatively, when dose number and time to onset could be determined, events were most often reported after Dose 2 (62; 10.2%) followed by Dose 1 (15, 2.5%) and Dose 6 (9, 1.5%), typically within the first 3 days of vaccination. When outcome was recorded, 16.5% of events had not resolved (100 events), 11.2% were resolved (68 events) and 10.1% of events were resolving (61 events), at the time of report. There were 5 cases with reported fatal outcomes (UK 4 cases; Denmark 1 case). A review of these cases yielded no safety issues of concern (Appendix 12.2).

SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

Cumulatively, the MAH received 185 cases (18 serious, 144 medically confirmed, no fatal cases) with 695 events (49 serious) in the elderly population (>65+ years of age) who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. When gender was known, more cases were reported in females (115, 62.2%) compared to males (62, 33.5%), with small proportion of cases (8, 4.3%) having no gender reported. The mean patient age was 75.1 years (SD: 6.9) and median age of 74.0 years (range: 65.0 to 107.0 years). All cases were from the United States.

The most frequently reported events (PTs) were consistent with reactogenicity events consistent with the known safety profile for marketed Moderna vaccines targeting SARS-CoV-2.

Cumulatively, when dose number and time to onset could be determined, events were most often reported after Dose 4 (37; 5.3%) followed by Dose 6 (33, 4.7%) and Dose 5 and Dose 8 (32, 4.6%), typically within the first 2 days of vaccination. When the outcome was recorded, 29.4% of events had not resolved (204 events), 15.7% were resolving (109 events) and 14.7% of events were resolved (102 events), at the time of report. There were no cases with a reported fatal outcome.

SPIKEVAX (NOS)

During this reporting period, the MAH received 139 cases (54 serious, 84 medically confirmed) with 362 events (92 serious) in the elderly population (>65+ years of age) who received SPIKEVAX (NOS). When gender was known, more cases were reported in females (79, 56.8%) compared to males (56, 40.3%), with 4 cases (2.9%) having no gender reported. The mean patient age was 74.0 years (SD: 6.6) and median age of 73.0 years (range: 65.0 to 92.0 years). The majority of the cases were reported in United States (83, 59.7%) followed by Asia (20, 14.4%) and the UK (17, 12.2%).

There were 5 cases with a reported fatal outcome. A review of these cases yielded no new safety issues (Appendix 12.2).

Overall, adverse events (AEs) reported during the review period of this PBRER for this special population reflected reactogenicity or those known to occur following vaccination with marketed Moderna vaccines targeting SARS-CoV-2. The reported events did not show any clustering or trends of safety concerns in this patient population.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the special population of elderly individuals 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 reported for this special population using routine surveillance. The benefit-risk evaluation remains positive.

5.2.2.2 Use in Children

The evaluation of information received during this PBRER reporting interval relating to use of marketed Moderna vaccines targeting SARS-CoV-2 in children has not identified any additional clinically relevant 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 5-9. Refer to Appendix 12.3 for additional information.

During the reporting period of this PBRER, the MAH received 636 cases (48 serious, 617 medically confirmed, and 3 fatal) with 1,573 events (100 serious) reported for children under 18 years of age who received marketed Moderna vaccines targeting SARS-CoV-2. When gender was known, more cases were reported in females (284; 44.7%) compared to males (241; 37.9%), with 111 cases (17.5%) lacking gender information. The mean patient age was 7.9 years (standard deviation [SD]: 5.3) and median age of 8.0 (range: 0.0 to 17.0 years). The Majority were spontaneous reports (635; 99.8%), with one (0.2%) literature-non-study report. Most cases were reported in The United States (507; 79.7%), followed by Asia (40; 6.3%) and Latin America (37; 5.8%).

The most frequently reported events in children, by Preferred Term (PT) were "No adverse event" (458; 29.1%), "Expired product administered" (180; 11.4%), "Wrong product administered (137; 8.7%)", "Poor quality product administered" (91; 5.8%) and "Overdose" (85; 5.4%).

Table 5-9 Case Reports and MAH comment by Age group

Source of New Information	• Moderna Global Safety Database (GSDB). • Literature Sources- 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 (Serious, fatal) • Elasomeran: 7 cases (6 serious, 1 fatal). • Elasomeran/imelasomeran: No cases were reported during this review period. • Elasomeran/davesomeran: No cases were reported during this review period. • Andusomeran:3 serious cases (0 fatal). • SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula: 3 non-serious cases. • SARS-CoV-2 JN.1 mRNA: 1 serious case, 0 fatal. • SPIKEVAX NOS: 1 non-serious case.	Cases ([redacted] (fatal case); [redacted] involved foetal or neonatal outcomes associated with elasomeran vaccine exposure. These cases included serious events such as hydrops fetalis, congenital anomalies (e.g., pulmonary valve stenosis, atrial septal defect, patent ductus arteriosus, and kidney duplex), premature birth, and growth restriction, For detailed information on these cases. Please refer to Section 16.3.5.1 for further details. A review of 4 serious cases [[redacted] (involved andusomeran) and case [redacted] (involved SARS-CoV-2 JN.1 mRNA)] received via UK MHRA suggested that the reported ages of the patients ([redacted]-day-old, [redacted]-day-old, and [redacted]-day old) may have been incorrectly reported. The reported ages suggest a potential inconsistency with the use of andusomeran in individuals under 6 months of age. Additional clarification regarding the correct ages of the patients would be beneficial for the accurate case assessments. At the time of this report, no follow-up information has been received to address these discrepancies. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children (6 months to 5 years)	• Elasomeran: 14 cases (4 serious, 0 fatal), • Elasomeran/imelasomeran: No cases were reported during this review period,	Case ([redacted] elasomeran) described occurrence of foetal growth restriction in 2-year-old male. Please refer to Section 16.3.5.1 for further details. Note: Case [redacted] was presented in

Exposed Population by Age groups	Number of Case Reports Received	MAH Comment on Benefit and/or Risk (any observed differences from overall population)
	• Elasomeran/davesomeran: 9 non-serious cases, • Andusomeran: 160 cases (3 serious, 0 fatal), • SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula: 43 non-serious cases, • SARS-CoV-2 JN.1 mRNA: No cases were reported during this review period, • SPIKEVAX NOS: 4 cases (1 serious fatal case).	both age groups (< 6 months and 6 months to 5 years of age) as the onset date was used for 2 values of PTs foetal growth restriction (Age: 2) and Premature baby (Age: 0). Five cases [redacted] (involved elasomeran), cases [redacted] (involved andusomeran), [redacted] (involved SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula)] reported seizures or febrile convulsions in children aged 2–4 years. In one case, a reported medical history was identified as a confounder ([redacted]. Another case described febrile convulsion potentially triggered by fever by a concurrent mycoplasma infection ([redacted]). Limited information was reported for the other cases. Case [redacted] concerns a 12-month-old patient of unknown gender who died after receiving a dose of SPIKEVAX NOS. Key details, including the vaccination date, onset date of event, cause of death, autopsy findings, medical history, concomitant medications and treatment details, were not reported. The case contained limited information for a meaningful assessment. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children 6-11 years	• Elasomeran: 2 non-serious cases, • Elasomeran/imelasomeran: No cases were reported during this review period, • Elasomeran/davesomeran: 14 cases (1 serious, 0 fatal), • Andusomeran: 122 cases (8 serious, 0 fatal), • SARS-Co-V-2 KP.2 mRNA	The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

Exposed Population by Age groups	Number of Case Reports Received	MAH Comment on Benefit and/or Risk (any observed differences from overall population)
	(COVID-19 Vaccine, mRNA) 2024-2025 Formula: 49 cases (1 serious, 0 fatal), • SARS-CoV-2 JN.1 mRNA: No cases were reported during this review period, • SPIKEVAX NOS: 5 non-serious cases.	
Adolescents (12 to 17 years)	• Elasomeran: 16 cases (4 serious, 0 fatal), • Elasomeran/imelasomeran: No cases were reported during this review period, • Elasomeran/davesomeran: 5 non-serious cases, • Andusomeran: 125 cases (14 serious cases, 0 fatal), • SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula: 51 cases (1 serious, 0 fatal), • SARS-CoV-2 JN.1 mRNA: 1 non-serious case, • SPIKEVAX NOS: 2 serious cases (1 fatal).	5 cases concerning myocarditis /pericarditis/ myopericarditis were reported in this age group: 1 case ([redacted]) involved elasomeran. 3 cases ([redacted]) involved andusomeran. 1 case [redacted] involved SPIKEVAX NOS. Please refer to Section 16.3.1.2 for further details. Case [redacted] reported occurrence of anaphylactic reaction in a 15-year-old male, after receiving elasomeran. Please refer to Section 16.3.1.1 for further details. One fatal case ([redacted]) was reported for a 14-year-old male patient who died after receiving a dose of SPIKEVAX NOS. Key details, including vaccination date, onset of event, cause of death, autopsy findings, medical history, concomitant or treatment details were not reported. The case had limited information for a meaningful assessment. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

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.

5.2.3 Other clinical topics

5.2.3.1 Overdose

Table 5-10 Overdose

Source of New Information	• Moderna GSDB • Literature Sources-See Appendix 13.4 • Retrieved: 0 • 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 of overdose-related terms where an AE was included, most of the reported events included reactogenicity events such as pyrexia, injection site erythema, pain, and headache.
Methods	The MAH queried the GSDB for valid case reports received from HCP, health authority (HA), consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 JN.1 mRNA, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The search criteria applied for identification of overdose cases included the following MedDRA terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.
Results	***Overdose Cases Involving use of Elasomeran*** During the review period, the MAH received 12 cases (5 serious) of overdose with 12 events (1 serious), and no cases with a fatal outcome. A total of 10 (10) cases (83.3%) were medically confirmed. The reported events were "Overdose" (12; 100.0%). Of the 12 cases, 6 cases involved paediatric patients (6 months to 3 years of age) who received an overdose of vaccine for one of the doses. All these cases came from the same medical practice, and vaccination occurred between October and November of 2022. None of the reports had any other associated AE. One of the serious cases [redacted] is a literature report of a 25-year-old male who 4 days after receiving second dose of mRNA-1273 experienced chest pain and myocarditis was suspected. No additional details (such as diagnostic tests, medical history, concomitant medications etc) were provided. According to the reporter the patient received double dose of mRNA-1273. No other information is available. ***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 2 medically confirmed cases (2 events) of overdose with no serious cases and no cases with a fatal outcome. The reported events were "Accidental Overdose" (2 events; 100.0%). Both events are from the same

	practice, in which expired product was administered as well as administering the entire amount of the multi-dose vial (a full syringe (2.5 ml)). No AEs were reported due to the accidental overdose and expired product administered. ***Overdose Cases Involving use of Andusomeran*** In 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. The paediatric SDV contained notably more than 0.25 ml of vaccine, which led to provider confusion or administration errors, including overdose. During the current review period, the MAH received 191 cases (191 events) with no serious cases, and no cases with a fatal outcome. A total of 188 cases (98.4%) were medically confirmed. The reported events were "Overdose" (156; 81.7%) and "Accidental overdose" (35; 18.3%). Of the 191 cases, 72 cases involved paediatric patients (6 months to 11 years of age) who received an overdose of vaccine due to the overfilling of the SDV. Majority of the paediatric overdose cases showed no AEs, and reactogenicity events such as headache, pyrexia, and vaccination site pain were reported. There were 112 cases that did not provided age information. ***Overdose Cases Involving use of SARS-CoV-2 JN.1 mRNA*** No cases involving SARS-CoV-2 JN.1 mRNA were received during the reporting period. ***Overdose Cases Involving use of* SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** During the review period, the MAH received 47 cases (47 events) with no serious cases, and no cases with a fatal outcome. All 47 cases (100.0%) were medically confirmed. The reported events were "Overdose" (40; 85.1%) and "Accidental overdose" (7; 14.9%). There were 43 cases which involved < 11 years old who received 0.5 ml of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula rather than the indicated 0.25 ml dose for the age group. The majority of the cases (41; 95.3%) had no AEs reported. ***Overdose Cases Involving use SPIKEVAX (NOS)*** During the review period, the MAH received 4 medically confirmed, non-serious cases (4 non-serious events). No cases with a fatal outcome were reported. The reported events were "Accidental overdose" (3; 75.0%) and "Overdose" (1 event; 25.0%).
Discussion	The MAH received 12 cases (5 serious cases) of overdose for the elasomeran original, no cases of overdose reported involving elasomeran/imelasomeran, 2 cases (no serious cases) of overdose involving elasomeran/davesomeran, 191 cases of overdose involving andusomeran, no cases of overdose reported involving SARS-CoV-2 JN.1 mRNA of overdose involving unspecified SPIKEVAX (NOS). 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 by any vaccine, with most of the events reported being reactogenicity events along with product administration and product quality issues. All of the overdose reports were due

	to human errors made during administration. The reports concerning medication error, where the entire volume of 0.5 ml of vaccine was administered to children 6 months through 11 years of age rather than 0.25ml dose for the age group, resulted in mostly reactogenicity events in the vaccinees. Please refer to Section 5.2.2.2 for further details. Based on the analysis of all the safety data available as well as review of the literature for the reporting period, the MAH considers cases of overdose do not impact the benefits and possible vaccine-associated risks.
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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV-2 JN.1 mRNA and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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 12.4 for more detailed information.

5.2.3.2 Off-Label use

Table 5-11 Off-Label use

Source of New Information	• Moderna GSDB • Literature Sources-See Appendix 13.4 • Retrieved: 0 • 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 authorisation. Examples include the intentional use of a product in situations other than the ones described in the authorised 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 authorisation 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 utilising the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) standardised 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 31 cases (32 events) of Off-label use with 19 serious cases (12 serious events), and no cases with a fatal outcome. There were 27 medically confirmed cases involving elasomeran. These cases were reported mostly in females (13 cases, 41.9%) and in males (10 cases, 32.3%). The mean age was 57.4 years (SD: 14.9) and median age was 61.5 years (range: 28.0 to 80.0 years). The country with the most frequent cases of Off-label use was Germany (17; 54.8%) followed by Canada (5; 16.1%). The events reported were "Off-label use" (29; 90.6%), "Intentional product use issue" (2; 6.3%) and "Intentional product misuse" (1; 3.1%). Review of cases did not identify any safety issues of concerns. ***Off-label Cases Involving use of Elasomeran/Imelasomeran*** During this review period, there was only 1 serious medically confirmed case (1 serious event) of Off-label use reported involving Elasomeran/Imelasomeran. This case involved a 49-year-old female from [redacted]. The event reported was "Off-label use" (1; 100.0%). This case was identified as part of a retrospective clean-up activity where certain reports downloaded from EVWeb were missed to be booked-in. ***Off-label Cases Involving use of Elasomeran/Davesomeran*** During the review period, there were no cases of Off-label use reported involving Elasomeran/Davesomeran. ***Off-label Cases Involving use of Andusomeran*** During the review period, the MAH received 137 medically confirmed cases (137 events) of Off-label use and no cases with a fatal outcome involving andusomeran. All 137 cases were non-serious. All the cases were missing gender and age information (137; 100.0%). All the cases were received from Israel (137; 100.0%). The events reported were "Off-label use" (137; 100.0%). No associated AEs were reported. ***Off-label Cases Involving use of SARS-CoV-2 JN.1 mRNA*** During the review period, there were no cases of Off-label use reported involving SARS-CoV-2 JN.1 mRNA. ***Off-label Cases Involving use of* SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** During the review period, there were no cases of Off-label use reported with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. ***Off-label Cases Involving Use of SPIKEVAX (NOS)*** During this review period, there was 1 medically confirmed case of Off-label use (1 event) in a female with an unknown age reported involving SPIKEVAX (NOS). The event reported was Off-label use (1; 100.0%).
Discussion	Consistent with the prior reporting period, "Off-label use" was the most frequently reported PT during the current reporting period. Off-label use observed during the review period did not change the safety profile of marketed 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 marketed Moderna vaccines targeting SARS-CoV-2 did not raise any safety issue of concern. The information provided does not support evidence of causality between off-label use and marketed 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 12.5 for more detailed information.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 was used for the coding of AEs/adverse drug reactions (ADRs) presented in this report. The line listings and summary tabulations are 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 2024) 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 following active treatment, the SAE originated from a clinical study with mRNA-1273, mRNA-1273.214, mRNA-1273.222, mRNA-1273.815, mRNA-1273.231, mRNA-1273.167, and mRNA-1273.712, 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 2024) and interval (18 Dec 2023 to 17 Dec 2024) 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, 11 ModernaTx, Inc sponsored CTs were completed and presented below:

mRNA-1073-P101: A Phase I/II, randomised, stratified, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1073 (SARS-CoV-2 and influenza vaccine) compared to co-administered mRNA-1010 (influenza) and mRNA-1273 (SARS-CoV-2) vaccines and to mRNA-1010 vaccine and mRNA-1273 vaccine alone in healthy adults 18-75 years of age.

mRNA-1083-P301: A Phase III, Randomised, Observer-blind, Active control Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA 1083 (SARS-CoV-2 and Influenza) Vaccine in Healthy Adult Participants, ≥50 Years of Age.

mRNA-1230-P101: A Phase I, randomised, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of multi-component vaccines mRNA-1045 (Influenza and RSV) or mRNA-1230 (Influenza, RSV, and SARS-CoV-2) compared with mRNA-1010 (Influenza), mRNA-1345 (RSV), and mRNA-1273.214 (SARS-CoV-2) vaccines in healthy adults 50-75 years of age.

mRNA-1273-P203: A Phase II/III, Randomised, Observer-Blind, Placebo-Controlled, Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to <18 years of age.

mRNA-1273-P204: A Phase II/III, Three-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomised, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA 1273 SARS-CoV 2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age.

mRNA-1273-P205: A Phase II/III Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants.

mRNA-1273-P304: A Phase IIIb, Open-Label, Safety and Immunogenicity Study of SARSCoV2 mRNA-1273 Vaccine in Adult Solid Organ Transplant (SOT) Recipients and Healthy Controls.

mRNA-1273-P305: A Phase II/III, Randomised, Observer-blind, Active-controlled, Multicentre Study to Evaluate the Immunogenicity and Safety of Omicron Variant Vaccines in Comparison with mRNA-1273 (Prototype) Booster Vaccine.

mRNA-1273-P401: A Randomised, Observer-Blind, Active-Controlled, Clinical Trial to Assess the Immunogenicity of an Investigational mRNA-1273.815 COVID-19 Vaccine in Previously Vaccinated Adults.

mRNA-1283-P101: A Phase I, Randomised, Observer-Blind, Dose-Ranging Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1283 and mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18-55 Years.

mRNA-1283-P201: A Phase IIa, randomised, stratified, observer-blind study to evaluate the immunogenicity and safety of mRNA-1283 vaccine boosters for SARS-CoV-2.

There were no significant safety findings from the 11 CTs that completed during the reporting interval.

7.2. Ongoing Clinical Trials

During the reporting period, there were 4 ongoing ModernaTx, Inc. sponsored CTs with mRNA-1273 (mRNA-1273-P206, mRNA-1273-P306, mRNA-1273-P403, and mRNA-1273-P404), and there were 4 ongoing CTs that included a mRNA-1273 treatment arm as active control (mRNA-1283-P301, mRNA-1083-P101, mRNA-1345-P302, and mRNA-CRID-001). Cumulative exposure by study is presented in Table 7-1.

There were no significant safety findings 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-1083-P101	148[a, b]
mRNA-1273-P206	68
mRNA-1273-P306	1,777[a]
mRNA-1283-P301	7,106[a, b]
mRNA-1345-P302	1,710[a]
mRNA-1273-P403	100[a]

Study ID	Total subjects exposed
mRNA-1273-P404	997[a]
mRNA-CRID-001	60[a]

[a]=Data from ongoing trials till 17 Dec 2024.
[b]=Estimated numbers per randomisation 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 included a total of 24 months follow-up; no long-term safety concerns were identified for the 2 dose mRNA-1273 100 mcg primary series based on the final analysis that included 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 completed 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 completed 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 ongoing paediatric Phase 3 Study mRNA-1273-P306, participants 6 months through 5 years have a median follow-up of 187 (1,386) days from Dose 1 and 168.5 (9,355) days from Dose 2. 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 marketed Moderna vaccines Targeting SARS-CoV-2 there were 2 CTs (mRNA-1073-P101, and mRNA-1230-P101) for combination therapies in which marketed Moderna vaccines Targeting SARS-CoV-2 were part of the fixed combinations. There are separate Development Safety Update Reports (DSURs) for each of these fixed combination therapies. No new safety information was

identified from the fixed combination therapy CTs which were completed during this reporting period.

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-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 Post-Market Surveillance (PMS) programme was to identify hypotheses for the safety evaluation of this product by confirming the occurrence status of non-acute hospitalisation associated serious events observed after vaccination in persons with underlying diseases considered to be at high-risk of exacerbation of COVID-19 in Japan. There were no major differences in the overall incidence of SAEs associated with hospitalisation in the non-acute phase compared with SAEs associated with all-cause hospitalisation in the year prior to vaccination. In addition, there were no major differences in events observed and their incidences, and no particular trend was observed in the time to onset. Based on the above, the survey did not suggest any new safety concerns of this vaccine.
mRNA-1273-P918	Japan	General use-result 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 programme was 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 immunisation (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 immunisation, 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. No safety or efficacy problems were observed in this programme, and it was judged unnecessary to take any particular measures at this point in time.
mRNA-1273-P919	United States	An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to SPIKEVAX During Pregnancy	mRNA-1273-P919 was an observational post-marketing safety study evaluating the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to SPIKEVAX during pregnancy. A final study report was completed in Mar 2024 and amended in Aug 2024

			Study Design: This claims-based retrospective cohort study compared adverse neonatal, pregnancy, or birth outcomes among pregnant women exposed to SPIKEVAX with 3 reference populations. Exposure windows were defined based on etiologically relevant timing for each specific study outcome (e.g., the first trimester for major congenital malformations [MCM]). Generalised linear regression models and inverse probability of exposure (propensity score [7]) weighting were employed to adjust for confounding factors when comparing event rates in exposed vs reference populations. **Results:** The study population included 277,287 women who met study entry criteria. Of these, 22,622 women were exposed to SPIKEVAX at any time during pregnancy, 8,282 were distantly exposed to SPIKEVAX, and 246,383 were unexposed to any COVID-19 vaccine during pregnancy. Additionally, 23,584 unvaccinated women were diagnosed with COVID-19 during pregnancy. Primary analyses found no evidence of increased risk for any infant outcomes. Among livebirths, the proportion of infants with MCMs was similar among women exposed to SPIKEVAX and distantly exposed women (adjusted RR [8]: 0.96; 95% confidence interval [CI]: 0.75-1.22), unexposed women (aRR: 1.10; 95% CI: 0.91 - 1.36), and less than that among women who had COVID-19 during pregnancy (aRR: 0.74; 95% CI: 0.55-0.99). Similarly, other infant outcomes were not associated with and increased risk after SPIKEVAX exposure during pregnancy. Among the pregnancy complications assessed, no increased risk was observed for post-partum haemorrhage and eclampsia. However, a marginal increase in the risk of pre-eclampsia was noted for both pre-specified exposure windows from last menstrual period (LMP) to 20 gestational weeks (aRR: 1.11; 95% CI 1.00-1.24), and from greater than LMP + 20 weeks to the end of pregnancy (aRR: 1.18; 95% CI 1.03-1.35) compared to women distantly exposed to SPIKEVAX. Gestational hypertension presented a slightly increased risk for the risk window extending from greater than LMP+ 20 weeks to end of pregnancy (aRR: 1.25; 95% CI 1.12-1.39) compared to women distantly exposed to SPIKEVAX. Additionally, a small increased risk for gestational diabetes (GD) was observed for the pre-specified primary exposure window from LMP to 28 gestational weeks (aRR: 1.10; 95% CI 1.00-1.20) when compared to women who were distantly exposed to SPIKEVAX. These results were largely consistent when compared to women unexposed to any

Study ID	Country	Study Title	Study results
			COVID-19 vaccine during pregnancy and across most sensitivity analyses. Among the birth outcomes assessed following exposure to SPIKEVAX during pregnancy, aRRs were <1 when compared to pregnant women who were distantly exposed to SPIKEVAX or unexposed to any vaccines targeting SARS-CoV-2 during pregnancy. **Discussion** Consistent with the known safety profile of SPIKEVAX, this study showed no increased risks for infant outcomes (including MCM, neonatal encephalopathy, SGA, hospitalisation due to infections (including COVID-19) in the first year of life), stillbirth, or eclampsia. Lower rates among vaccinated women were observed for respiratory distress in the newborn, preterm birth, spontaneous abortions, and post-partum haemorrhage. Small increases were observed in rates of pre-eclampsia, gestational hypertension, and GD. Safety of Moderna COVID-19 will be further investigated in ongoing studies mRNA-1273-P905 and mRNA-1273-P951.
mRNA-1273-P920	United States	Post-marketing safety of elasomeran/ davesomeran and andusomeran vaccines in the United States	mRNA-1273-P920 was an observational post-marketing study that evaluated the safety of the elasomeran/davesomeran and andusomeran vaccines as used in routine clinical practice. A final study report was completed in Sep 2024. **Study Design** This retrospective observational cohort study used administrative healthcare data from HealthVerity (01 Sep 2022 through 15 Jan 2024) to compare the observed rates of AESI among patients who received at least one dose of elasomeran/davesomeran or andusomeran to 2 concurrent comparator groups (influenza vaccine and medically-attended COVID-19, analysed separately). When a potential increase in the rate of an AESI following elasomeran/davesomeran or andusomeran was identified, self-controlled risk interval (SCRI) analyses for signal refinement were planned. **Results** In analyses comparing elasomeran/davesomeran or andusomeran vs influenza vaccinated persons, 1,146,808 vaccinations of elasomeran/davesomeran or andusomeran and 13,082,338 episodes of influenza vaccination among adults (≥18 years of age) met inclusion criteria (without excluding any prevalent AESI as required for each AESI-specific analysis). Among children (<18 years of

Study ID	Country	Study Title	Study results
			age), 47,186 episodes of elasomeran/davesomeran or andusomeran and 5,827,873 influenza vaccinations were included. In analyses where elasomeran/davesomeran or andusomeran recipients and individuals diagnosed with COVID-19 were described, 3,059,540 vaccinations of elasomeran/davesomeran or andusomeran and 2,573,696 medically-attended COVID-19 disease episodes among adults met inclusion criteria (without excluding any prevalent AESI). Among children, 140,154 vaccinations of elasomeran/davesomeran or andusomeran and 521,570 medically-attended COVID-19 disease episodes were eligible. ***Myocarditis*** In primary analyses comparing elasomeran/davesomeran or andusomeran (without co-administration with influenza vaccine) vs influenza vaccinated adults, there were 6 myocarditis cases observed on days 1 to 7 following elasomeran/davesomeran or andusomeran (weighted IR 32.49, 95% CI: 24.92 - 42.38 per 100,000 PY) and 33 cases following influenza vaccination (weighted IR 15.74, 95% CI: 11.27 – 21.56). The proportional hazards assumption was not met in this model, and Restricted Mean Survival Time (RMST) did not show an increased risk (RMST = 0.999999, 95% CI: 0.999997 - 1.000001). Analyses restricted to 01 Sep 2023 – 15 Jan 2024 showed a weighted HR of 5.51 (95% CI: 1.14 - 26.61), however there were only 2 and 8 cases of myocarditis identified following elasomeran/davesomeran or andusomeran and influenza vaccination, respectively, and should thus be interpreted with caution. Case counts were not sufficient to support subgroups examining young adults in the primary analyses. In secondary analyses including individuals receiving concomitant influenza vaccine with elasomeran/davesomeran or andusomeran, an increased risk was observed individuals ages 25-39 years (weighted HR = 4.40, 95% CI: 1.29 – 15.02). Self-controlled risk interval analyses were largely consistent with the primary analysis. No cases were observed in children following elasomeran/davesomeran or andusomeran in primary analyses, and one case was observed in secondary analyses. In analyses describing elasomeran/davesomeran or andusomeran and medically-attended COVID-19 episodes among adults, 13 and 106 myocarditis cases were observed, respectively, in the 1-7 days following vaccination (weighted IR 30.11, 95% CI: 20.75 - 43.80) and COVID-19 diagnosis (weighted IR of 251.70, 95% CI: 221.20 – 285.88). Across all subgroups of interest, the weighted IRs of myocarditis were substantially lower following

Study ID	Country	Study Title	Study results
			elasomeran/davesomeran or andusomeran compared to medically-attended COVID-19, which persisted with sensitivity analyses that restricted to 1-21- and 1-28-day risk windows. ***Pericarditis*** Pericarditis was observed in 2 cases observed on days 1 to 7 following elasomeran/davesomeran andusomeran (weighted IR 12.04, 95% CI: 7.36 – 18.60 per 100,000 PY) and 80 cases on days 1 to 7 following influenza vaccination (weighted IR 37.35, 95% CI: 30.19 – 46.02) in the primary analysis. Among adults, the estimated HR from the weighted Cox model indicated no increased risk of pericarditis in the 1-7 days following elasomeran/davesomeran or andusomeran compared to influenza vaccination overall (weighted HR= 0.35, 95% CI: 0.08 – 1.55) or in subgroups of interest. Sensitivity analyses extending the risk window to 1-21 and 1-28 days led to similar conclusions. Results from SCRI analyses were generally consistent with the primary analysis across risk windows. No increased risk of pericarditis was observed; however, a numerical elevation was present in females aged 40-54 in the 1–28-day risk window. An increased risk of pericarditis was suggested in the 1-28 days following vaccination in a secondary analysis comparing elasomeran/davesomeran or andusomeran administrations with or without influenza vaccinations to influenza vaccination alone, wherein an ERR of 3.58 (95% CI: 1.12 – 11.45) was observed in SCRI analyses. This was again based on small numbers (10 and 4 cases in the 1-28- and 1-42-day risk and control windows, respectively). Among children, there were no cases of pericarditis observed in the 1-28 days following elasomeran/davesomeran or andusomeran administration. In analyses describing elasomeran/davesomeran or andusomeran and medically-attended COVID-19 episodes among adults, the weighted IR in the 1-7 days following elasomeran/davesomeran or andusomeran administration was 30.15 (95% CI: 19.87 – 42.54) per 100,000 PY compared to a weighted IR of 196.94 (95% CI: 170.13 – 227.41) per 100,000 PY following medically-attended COVID-19. Similar to myocarditis, rates of pericarditis were consistently lower following elasomeran/davesomeran or andusomeran than medically-attended COVID-19 across subgroups of interest and in sensitivity analyses using 1-21- and 1-28-day risk windows. ***Other AESI*** Across all other AESI, observed incidence was similar following elasomeran/davesomeran or andusomeran compared to influenza.

Study ID	Country	Study Title	Study results
			Event rates were often elevated following a diagnosis of medically-attended COVID-19. Variation in increased rates of other AESI was observed across age and sex strata for both comparator 1 and 2 analyses among adults and children, however in many instances low event counts following elasomeran/davesomeran or andusomeran administration led to imprecise effect estimates that indicated no differential risk with either influenza or medically-attended COVID-19 episodes. No AESI met the threshold for conduct of SCRI analyses, and as such no SCRI analyses were performed for outcomes other than myocarditis and pericarditis. **Discussion** This post-authorisation safety surveillance study, which analysed 41 AESI (including myocarditis and pericarditis) among adults and children following vaccination with elasomeran/davesomeran or andusomeran, confirmed the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2 consistent with published literature. No clear, new safety findings emerged in primary analyses, and elevated incidence rates of several AESI following medically-attended COVID-19 supports a favourable benefit-risk profile.
mRNA-1273-P935	Australia	Vaccine effectiveness against COVID-19 variants in Victoria, Australia	**Summary:** **Aims:** To assess the relative vaccine effectiveness (VE) of 3 vs. 2 doses and 4 vs. 3 doses of monovalent COVID-19 vaccines in preventing hospitalisations and deaths in Victoria during Omicron variant-dominant periods. **Design:** Retrospective analysis of linked national and state-wide administrative health data (Dec 2021–Feb 2023) using a modified Cox model for time-varying VE stratified by age and vaccination status. Outcomes included hospitalisations and deaths. The study included individuals aged 5 years and older who had received at least 2 vaccine doses. **Vaccines included/excluded:** The study focused on monovalent vaccines for the analyses. The following vaccines were included: Comirnaty (Pfizer/BioNTech), Spikevax (Moderna), Vaxzevria (AstraZeneca), Covishield (AstraZeneca/Serum Institute of India), Nuvaxovid (Novavax), Covaxin (Bharat Biotech), Sputnik V (Gamaleya Research Institute), Janssen COVID-19 Vaccine (Johnson & Johnson), Sinopharm BBIBP-CorV, and Sinovac Coronavac. Bivalent vaccines were excluded from the analysis (e.g.,

Study ID	Country	Study Title	Study results
			Moderna Biv BA.1, Moderna Biv BA.4-5, Pfizer Comirnaty Biv BA.1, Pfizer Comirnaty Biv BA.4-5). **Results**: • Older Adults (≥65 years): VE against hospitalisation and death was highest after booster doses. For example, VE against death was 80.9% after 3 doses (BA.1/BA.2 period) and 64.7% after 4 doses (BA.4/BA.5 period). • Younger Adults (<65 years): VE was lower and less precise due to fewer hospitalisations and deaths in these groups. **Discussion** Booster doses significantly reduced severe COVID-19 outcomes, particularly in older adults.
mRNA-1273-P942	United States	Evaluating the effectiveness of mRNA-1273.815 against COVID-19 in the United States	This non-interventional, retrospective cohort study using administrative claims data was conducted to evaluate the effectiveness of mRNA-1273.815 in preventing COVID-19 associated hospitalisation and medically-attended COVID-19. **Study Design** This study compared individuals vaccinated with mRNA-1273.815 versus matched individuals ("referent") who had not received mRNA-1273.815 at the time of the corresponding matched individual's vaccination date. Data accrual occurred from 01 Sep 2022 to 21 Feb 2024 (latest available data), and individuals were eligible for cohort entry between 12 Sep 2023 (approval date for monovalent XBB.1.5) to 20 Feb 2024 (one day prior to end of last available data at time of analysis). Individuals were matched on age, sex, geographic region within the US, and race. The eligible follow-up period was from 20 Sep 2023 through 21 Feb 2024. Individuals were censored on occurrence of the outcome (for each outcome separately), receipt of a dose of any 2023-2024 COVID-19 vaccine (mRNA-1278.815 or other), death, end of follow-up, or disenrollment. Inverse probability of treatment weighting (IPTW) was used to adjust for potential confounding. Hazard ratios (HRs) were used to estimate VE in the weighted study population. The estimated VE and 95% CIs were reported as (1-HR) * 100%. **Results** The final study population included 903,349 vaccinated and 903,349 matched referent patients. The median follow-up was 111 days in the vaccinated group and 99 days in the referent group for the primary outcome. For the primary outcome of COVID-19 associated hospitalisation (coded in the primary position), the weighted

Study ID	Country	Study Title	Study results
			incidence rate per 1,000 person-years was 4.10 in the vaccinated group, and 9.34 in the referent group. The estimated VE was 56% (95% CI: 52%, 60%). A similar VE was observed across all subpopulations, ranging from 52% in immunocompromised patients, to 62% in patients aged 50-64 years. For the secondary outcome of medically-attended COVID-19, the estimated VE was 24% (95% CI: 22%, 25%). **Discussion** In this large-scale, real-world study involving over 900,000 vaccinated patients, the mRNA-1273.815 vaccine demonstrated protection against COVID-19-related hospitalisations and medically-attended COVID-19 relative to those not having received mRNA-1273.815. The current study included a substantial proportion of participants who had previously received COVID-19 vaccine doses, highlighting the incremental protection provided by the additional dose regardless of prior vaccination history.
mRNA-1273-P943	United States	Evaluating the effectiveness of mRNA-1273.815 against COVID-19 hospitalisation among adults aged ≥ 18 years in the United States	In this real-world study, we estimated the VE of mRNA-1273.815 (XBB.1.5-containing mRNA COVID-19 vaccine) administered between 12 Sep 2023 and 31 Dec 2023 at preventing COVID-19 illness requiring hospitalisation, as well as medically-attended COVID-19, in adults ≥ 18 years. **Study Design** This observational, matched cohort study used aggregated medical and pharmacy claims data from HealthVerity. Adults vaccinated with mRNA-1273.815 between 12 Sep 2023, and 31 Dec 2023, were followed through 26 Jan 2024. Vaccinated individuals were matched 1:1 with individuals unvaccinated with any 2023-2024 COVID-19 vaccine on demographic and clinical characteristics. The primary outcome was COVID-19 hospitalisation, and the secondary outcome was medically-attended COVID-19. IPTW and Cox-proportional hazards regression were utilised to estimate VE. **Results** The study included 1,272,161 vaccinated individuals matched 1:1 with unvaccinated, with a maximum follow-up of 128 days (median 84 days). The VE against COVID-19 hospitalisation was 51% (95% CI: 48%-54%). Subgroup analyses showed a VE of 56% (95% CI: 51%-61%) among adults 65 and older and 46% (95% CI: 39%-52%) in immunocompromised adults. For medically-attended COVID-19, the VE was 25% (95% CI: 24%-27%). Time-varying analyses

Study ID	Country	Study Title	Study results
			showed that while VE declined over time, the effect remained significant. **Discussion** During the 2023-2024 respiratory season, which included the emergence of JN.1, the mRNA-1273.815 vaccine significantly protected against COVID-19-related hospitalisations and medically-attended COVID-19 across diverse adult populations. These results support the continued use of updated COVID-19 vaccines to mitigate severe outcomes and maintain public health safety. The consistent effectiveness across subpopulations underscores the vaccine's role in protecting high-risk groups and the general adult population. The durability of effectiveness over time further emphasises the vaccine's importance in ongoing COVID-19 management.
mRNA-1273-P946	United States	Effectiveness of the 2023–2024 Omicron XBB.1.5-containing mRNA COVID-19 Vaccine (mRNA-1273.815) in Preventing COVID-19–related Hospitalisations and Medical Encounters Among Adults in the United States	This study aimed to evaluate the VE of mRNA-1273.815, a 2023–2024 Omicron XBB.1.5-containing mRNA COVID-19 vaccine, at preventing COVID-19–related hospitalisations and any medically-attended COVID-19 in adults. **Design** In a linked electronic health record–claims dataset, we identified US adults (≥18 years) who received the mRNA-1273.815 vaccine (exposed cohort) between 12 Sep and 15 Dec 2023, matched 1:1 to individuals who did not receive a 2023–2024 updated COVID-19 vaccine (unexposed cohort). Cohorts were balanced using IPTW on demographics, vaccination and infection history, and underlying medical conditions. Study cohorts were followed until 31 Dec 2023 for COVID-19–related hospitalisations and medically-attended COVID-19. Cox regression was used to estimate HRs and VE. Subgroup analyses were performed for adults ≥50 years, adults ≥65 years, and individuals with underlying medical conditions. **Results** Overall, 859 335 matched pairs of mRNA-1273.815 recipients and unexposed adults were identified. The mean (standard deviation) age was 63 (16) years. More than 60% of individuals in both cohorts had an underlying medical condition. Among the overall adult population, VE was 60.2% (95% CI, 53.4–66.0) against COVID-19–related hospitalisation and 33.1% (30.2–35.9) against medically-attended COVID-19 over a median follow-up of 63 (interquartile range: 44–78) days. VE estimates by age and underlying medical conditions were similar.

Study ID	Country	Study Title	Study results
			Discussion These results demonstrate the significant protection provided by mRNA-1273.815 against COVID-19–related hospitalisations and any medically-attended COVID-19 in adults, regardless of vaccination history, and support CDC and Prevention recommendations to stay up to date with COVID-19 vaccination to prevent COVID-19–related outcomes, including hospitalisations.

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

Study ID	Country	Study Title	Status
mRNA-1273-P901	United States	Real-world study of the effectiveness of the Moderna COVID-19 Vaccine	For this observational cohort study carried using data from Kaiser Permanente Southern California, the most recent interim study analyses. The final study report is expected in Apr 2025.
mRNA-1273-P904	Denmark, Norway, Spain, United Kingdom	Post-Authorisation Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU	For this observational cohort study carried using large administrative databases in Denmark, Norway, Spain, and the UK, interim analyses described in the Mar 2023 interim study update. The final study report is expected in Mar 2025.
mRNA-1273-P905	Denmark, Norway, Spain, United Kingdom	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in 4 European countries	For this observational cohort study carried using large administrative databases in Denmark, Norway, Spain, and the UK, with feasibility counts were described in the Mar 2023 interim study update. The final study report is expected in Mar 2025.
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 SARS-CoV-2	The overarching goal of this study is to characterise the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and elasomeran bivalent vaccination. Analyses are ongoing, and the final study report is expected in Jun 2025.
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 characterise presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (elasomeran). An interim report was completed 31 Oct 2024. Cases of myocarditis identified

Study ID	Country	Study Title	Status
			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, however no relevant safety information was identified at this time. The final study report is expected in Oct 2028.
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 (XBB.1.5)	The study was amended to remove the optional long-term follow-up for Part A on 08 Jan 2024, and amended to remove the optional long-term follow-up for Part B on 07 May 2024. The study includes 2 parts: Part A: 2022-2023 mRNA COVID-19 Bivalent Vaccine (Original and Omicron BA.4/BA.5) A six-month observational prospective study, to investigate antibody levels with respect to time since receiving a bivalent COVID-19 booster dose. The original protocol was dated 04 Jan 2023. At this time, no safety findings have been identified. The protocol was amended on 25 Jul 2023 to add Part B: 2023 mRNA COVID-19 Updated Vaccine (XBB.1.5). A six-month observational prospective study, to investigate antibody levels with respect to time since receiving an updated monovalent COVID-19 vaccine (XBB.1.5).
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. Enrolment for this study is ongoing. No safety findings have been identified that differ from the known safety profile.
mRNA-1273-P929	Japan	Special Use Results Survey: Assess the safety of Moderna vaccines targeting SARS-CoV-2 in the Japanese paediatric population	The overarching aim of the study is to characterise the safety of Moderna vaccines targeting SARS-CoV-2 in the paediatric population in Japan. No safety findings have been identified to date.
mRNA-1273-P934	United States	Effectiveness Comparison Between the 2 mRNA Monovalent COVID-19	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.

Study ID	Country	Study Title	Status
		Vaccine Boosters in Medicare Fee-For-Service	**Study Design** This retrospective cohort study used Medicare Fee-For-Service (FFS) claims data from Oct 2020 through Aug 2022. Individuals who received a BD of mRNA-1273 (2.4 million) or BNT162b2 (1.6 million) after ≥1 dose of mRNA-based primary vaccine series were followed from 14 days after index until receipt of an additional BD, outcome occurrence, end of continuous enrolment, or end of study period. IPTW was applied to adjust for baseline confounding. Comparative VE against COVID-19 hospitalisation (principal or secondary diagnosis) and differences in total expenditures during hospitalisation and up to 90 days post-discharge were estimated. **Results** After IPTW, individuals who received mRNA-1273 as a booster had a reduced risk of hospitalisation (HR 0.789; 95% CI: 0.766, 0.813) compared to BNT162b2. Differences in total expenditures during hospitalisation and up to 60 days post-discharge between mRNA-1273 versus BNT162b2 recipients were -$723 (USD) or -1.8% (p=0.08), showing savings compared with BNT162b2. In sensitivity analysis, differences in total expenditures during stay up to 30 days post-discharge were -$678 (-2.4%, p=0.02); up to 90 days post-discharge were $10 (0.0%, p=0.99); and for hospitalisations with COVID-19 as principal diagnosis (up to 60 days post-discharge) were -$2,224 (-6.3%, p<0.001), respectively. **Discussion** mRNA-1273 administered as a first booster was more effective than BNT162b2 in preventing COVID-19 hospitalisations and associated with lower medium-term Medicare expenditures for those hospitalised.
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 completed the primary series of mRNA-based COVID-19 vaccines. A study report is expected to be complete in 2025 Q1.

Study ID	Country	Study Title	Status
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 2025 Q1.
mRNA-1273-P941	United States	mRNA1273 Bivalent BA4/5 US Nursing Home comparative effectiveness study	The aim of this study is to assess effectiveness of mRNA-1273.222 booster vaccination among nursing home residents. A study report is expected to be complete in 2025 Q1.
mRNA-1273-P949	United States	Observational Study to Assess Maternal and Infant Outcomes Following Exposure to Updated Moderna Vaccines Targeting SARS-CoV-2 During Pregnancy	Retrospective cohort study assessing whether receipt of updated Spikevax formulations (mRNA-1273.222 or mRNA-1273.815) during pregnancy is associated with an increased rate of pregnancy complications, adverse pregnancy outcomes, or adverse infant outcomes. Analyses are currently ongoing.

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 SPIKEVAX (elasomeran) in the Kingdom of Saudi Arabia (KSA)	The overarching aim of this study is to characterise 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 characterise 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-P951	United States	Post-marketing safety of the Moderna COVID-19 vaccine following the 2024/2025 strain change in the United States	Retrospective cohort study assessing whether the risk of myocarditis, pericarditis and other safety topics of interest for active surveillance among persons vaccinated with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is higher than the expected risk in a similar population in absence of this vaccine. A SAP is currently 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: Fukushima Community Vaccine Study.

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

Summary: For this study enrolment is complete, the first patient first visit was on 31 Aug 2023, and study ended 31 Mar 2024. The total number of subjects enrolled was 1,353. The study assessed a range of systemic and localised AEs following the second, third, and fourth doses of COVID-19 vaccines. Fever, fatigue, and local pain were among the most frequently reported AEs. The study reported a consistent pattern where younger individuals, females, and those with a history of allergies were more likely to experience AEs from both Moderna and Pfizer vaccines. The analysis does not specify separate adverse event details or immune responses (IgG and T-spot values) for Pfizer and Moderna within each group but combines them under overall group results. Additionally, this study aimed to understand the longitudinal AEs patterns after a fourth dose of the COVID-19 vaccine of 1,175 participants (of which 903 participants received Moderna vaccines) using a latent class analysis. The CSR was published on 18 Mar 2024. While this study explored various factors associated with the occurrence of adverse events, it did not evaluate Adverse Events of Special Interest (AESI). No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: A survey of COVID-19 vaccine acceptance across 23 countries in 2023.

Title: A survey of COVID-19 vaccine acceptance across 23 countries in 2023.

Summary: For this survey enrolment is complete, the first patient first visit was on 30 Sep 2023, and study ended 01 May 2024. The total number of subjects surveyed were 23,000. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Title: Predictors of Hospitalisation.

Title: Predictors of Hospitalisation and Severe Disease due to Breakthrough COVID-19 Infection in Fully Vaccinated Individuals.

Summary: For this study enrolment is complete, the first patient first visit was on 01 Jun 2023, and study ended 15 Dec 2023. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER. Data from 20,584 emergency department visits between 15 Dec 2020 and 19 Dec 2021 were analysed.

Short Title: Vaccine uptake.

Title: Enhancing COVID-19 immunisation uptake amongst culturally and linguistically diverse populations.

Summary: For this study enrolment is complete, the first patient first visit was on 01 Nov 2023, and the final report date was 11 Nov 2024. The total number of subjects enrolled was 24 (qualitative interviews). No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

Short Title: VI

Title: Update of HS-CoVulnerability Index (VI) d score to assess eligibility and prioritisation for anti-COVID first ever vaccination or booster.

Summary: The first patient first visit was on 01 Feb 2023 and study ended on 01 Aug 2024. A total of 2,192 patients were included in secondary analysis. No AEs were reported. 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 on 26 Oct 2022 and study ended 31 Aug 2024. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

Short Title: ARNCOMBI

Title: Multicentre, Randomised, Open-label Trial Comparing the Immunological Efficacy of a Vaccine Regimen Combining 2 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 on 22 Nov 2022 and study ended 30 Aug 2024. The total number of subjects enrolled was 414. No AEs were reported. No significant safety findings were 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 on 01 Aug 2022 and study ended 01 Aug 2024. The total number of subjects enrolled was 917. No AEs were reported. No significant safety findings were 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 on 01 Dec 2022 and study ended 01 Nov 2024. The total number of subjects enrolled was 320. 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: PARACOV Study in Japan.

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

Summary: The study enrolment commenced on 06 Nov 2023 and completed 31 Mar 2024. The total number of subjects enrolled were 109. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER. The expected study end date in 31 May 2025.

Short Title: BE-Direct

Title: Determining the Immune Response in Ethnic minority healthcare workers to COVID-19 infection and Vaccination –Autumn 2022 COV-19 boosters (a sub-study of UK-REACH).

Summary: Planned enrolment for this study is not reported, first patient first visit was on 12 Sep 2023 and expected study end date is 31 Oct 2025. The total number of subjects enrolled was 384. No AEs were reported. No significant safety findings were identified for this study during the reporting period of this PBRER.

9.1.2 License partner studies

9.1.2.1 Completed 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, randomised study to access the safety and immunogenicity of a SARS-CoV-2 variant vaccine (mRNA-1273.351) in naïve and previously vaccinated adults.

Country: US

Dosing details: In this study, dosing was conducted in 2 different arms and further 2nd arm was divided into 8 arms according to the doses as follows:

1. ARM 1A: 50 µg 1273.351,
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 CSR has been finalised for cohort 1 on 12 Jan 2024 and for cohort 2 on 13 Feb 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.

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 BD 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. 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 has been completed. The CSR was completed for cohort 1 on 21 Oct 2022 and for the addendum on 18 Oct 2023.

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 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 Merck, Sharp and Dohme (MSD):

Study or Protocol Number: V110-911-00:

A Phase 3, Randomised, 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 BD 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 received 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 received placebo (blinded) in the left arm 30 days later at Visit 3 (Day 30). Participants enrolled in the non-concomitant groups received placebo (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then received 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. The CSR was finalised on 01 Feb 2024 and the CSR synopsis was submitted to FDA with Investigational New Drug (IND) annual report on Aug-2024.

Study conclusions:

Immunogenicity for V110:

- Serotype-specific OPA GMTs at 30 days postvaccination with V110 were generally comparable when V110 was administered concomitantly or nonconcomitantly with mRNA-1273.
- SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V110 compared with mRNA-1273 administered with placebo.

Immunogenicity for V114:

- Serotype-specific OPA GMTs at 30 days postvaccination with V114 were generally comparable when V114 was administered concomitantly or nonconcomitantly with mRNA-1273.
- SARS-CoV-2-specific bAb GMTs at 30 days postvaccination with mRNA-1273 were lower when mRNA-1273 was administered concomitantly with V114 compared with mRNA-1273 administered with placebo.

Concomitant administration of either V110 or V114 with mRNA-1273 is generally well-tolerated, with a safety profile comparable to V110 or V114 alone.

9.1.2.2 Ongoing trials

Sponsored by DMID of National Institute of Allergy and Infectious Diseases (NIAID):

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 (154); mRNA-1273-50 µg (143), 1273-211-100 µg (93), 1273.222-50 µg (23).

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 cohort 2 CSR is estimated early 2025.

Protocol or Study Number: mRNA-1273-P511/22-0004:

Phase 2 Clinical Trial to Optimise 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 Haematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumours 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 2024, 19 subjects were exposed to mRNA-1273. Start date for this study was 30 Apr 2021 and estimated study completion date is 31 Dec 2025. No significant safety findings in this ongoing CT have been identified during the reporting period.

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 2 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 12,342 subjects. Actual recruitment end date was 12 Nov 2022 and last subject visit was on 09 May 2023. One hundred and 15 AEs have been reported, of which 18 were Grade 1 related AEs and 4 were Grade 2 related AEs. Seventeen SAEs were reported, all of which were assessed as not related to the study product. Seven AEs of special interest have been reported, 4 of which were related to study product (Grade 1 and 2). Three unrelated events met seriousness criteria. 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 met criteria for severe disease. 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 MSD:

Study or Protocol Number: V503-076-00:

A Phase 3, Multicentre, 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 160[1] 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 2nd quarter of 2025. No new safety concerns, and no regulatory actions taken for safety reasons during the reporting period. There is no information that would affect the safety profile of the product with no AESIs identified in trial participants through the reporting period. There is no new efficacy, effectiveness, or immunogenicity information.

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 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.

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

[1]As per partner response, planned enrollment has been modified to 160 on 15 Feb 2023 from 400.

	information on medication errors to be collected and reported through national pharmacovigilance systems. In the UK, the SARS-CoV-2 JN.1 mRNA (mRNA-1273.167; JN.1) variant formulation was approved on 02 Sep 2024. However, it was noted that after the JN.1 approval, Moderna continued to receive spontaneous cases from the UK (MHRA) which were coded to the SPIKEVAX 2023-24 (XBB.1.5) variant formulation. Upon further investigation, it became evident that the MHRA Yellow card reporting site was not updated to include the JN.1 product as an option for selection for reporters. The issue was raised with the MHRA and subsequently their website was updated to include JN.1 at the top of their drop-down list for selection. Internally, the Moderna case processing added the event of "discontinued product administered" to identify these cases.
Methods	The ModernaTx, Inc. GSDB was searched using the standard MedDRA query (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	**Medication Errors Involving Use of Elasomeran** During this review period, the MAH received 805 cases (4,074 events) of Medication errors with 373 serious cases (1,286 serious events), and 11 cases with a fatal outcome. There were 601 medically confirmed cases involving elasomeran. The most frequently reported PTs were "No adverse event" (347; 8.5%), followed by "Expired product administered" (332; 8.1%) and Interchange of vaccine products (236; 5.8%). During the review period, there were 407 cases (2,672 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (127; 4.8%), followed by "Drug ineffective" (89; 3.3%) and "Fatigue" (68; 2.5%). **Medication Errors Involving Use of Elasomeran/Imelasomeran** During the review period, the MAH received 60 cases (182 events) of Medication errors with 19 serious cases (48 serious events), and 1 case with a fatal outcome. There were 59 medically confirmed cases involving elasomeran/imelasomeran. The most frequently reported PTs were Expired product administered", "No adverse event'' and "Product expiration date issue" (38 events; 20.9% each). During the review period, there were 58 cases (83 events) of medication error reported with an associated AE. The most frequent AE reported were "Product expiration date issue" (38; 45.8%) and "Myocardial injury" (12; 14.5%). The 12 cases were described in an abstract with limited information. All were women with mild symptoms with good outcome. There was insufficient information presented to make any conclusions from the report. **Medication Errors Involving Use of Elasomeran/Davesomeran** During the review period, the MAH received 151cases (207 events) of Medication errors with 9 serious cases (24 serious events), and no cases with a fatal outcome. There were 143 medically confirmed cases involving elasomeran/davesomeran. The most frequently reported PTs were "Medication error" (115; 55.6%) followed by "Expired product administered" (25; 12.1%) and "No adverse event" (17, 8.2%). During the review period, there were 19 cases (30 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-

	19" and "Drug ineffective" (7 events; 23.3% each), followed by "Irritability" (6; 20.0%). **Medication Errors Involving Use of Andusomeran** During the review period, the MAH received 3,607 cases (8,918 events) of Medication errors with 284 serious cases (697 serious events), and 3 cases with a fatal outcome. There were 3,237 medically confirmed cases involving andusomeran. The most frequently reported PTs were "No adverse event" (3,002; 33.7%) followed by "Expired product administered" (2,478; 27.8%), and "Discontinued product administered" (392; 4.4%). During the review period, there were 609 cases (1,672 events) of medication error reported with an associated AE. The most frequent AE reported were "Pain in extremity" (141; 8.4%) followed by "Headache" (95; 5.7%), and "Pyrexia" (85; 5.1%). **Medication Errors Involving Use of SARS-CoV-2 JN.1 mRNA** During the review period, the MAH received 1,199 cases (2,427 events) of Medication errors with 3 serious cases (8 serious events), and 1 case with a fatal outcome. There were 1,186 medically confirmed cases involving SARS-CoV-2 JN.1 mRNA. The most frequently reported PTs were "No adverse event" (1,190; 49.0%) followed by "Expired product administered" (1,162; 47.9%). During the review period, there were 9 cases (13 events) of medication error reported with an associated AE. The AE reported were Arthralgia, Back pain, Cerebral infarction, Headache, Increased tendency to bruise, Inflammation, Pain, Pain in extremity, Product expiration date issue, Pyrexia, Rash Macular, Seizure, and Swelling (1 event each; 7.7%). **Medication Errors Involving Use of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** During the review period, the MAH received 380 cases (1,106 events) of Medication errors with 2 serious cases (3 serious events), and no cases with a fatal outcome. There were 372 medically confirmed cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The most frequently reported PTs were "No adverse event" (369; 33.4%) followed by "Wrong product administered" (213; 19.3%), and "Underdose" (121; 10.9%). During the review period, there were 12 cases (40 events) of medication error reported with an associated AE. The most frequently reported AE was "Malaise" (3; 7.5%). **Medication Errors Involving Use of Unspecified SPIKEVAX COVID-19 Vaccine-SPIKEVAX (NOS)** During the review period, the MAH received 64 cases (196 events) of Medication errors with 14 serious cases (45 serious events), and no cases with a fatal outcome. There were 52 medically confirmed cases involving SPIKEVAX (NOS). The most frequently reported PTs were "No adverse event" (37; 18.9%) followed by "Interchange of vaccine products" (18; 9.2%) and COVID-19 immunisation (14; 7.1%). During the review period, there were 27 cases (65 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (8; 12.3%) and "Drug ineffective" (5; 7.7%).
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 beyond the primary series or any interchange of other COVID-19 vaccine products. There appeared to be no difference for the nature of reported medication errors and importantly associated AEs among marketed Moderna vaccines targeting SARS-CoV-2 in general. AEs associated with reported medication errors were usually known to the safety profile, and no events were associated with significant harm to the patient due to the medication error. A few cases involving medication errors described fatal events; however, based on a detailed review of the case narratives, no evidence was found to suggest that the medication errors directly contributed to the fatal outcomes. As stated in the background, during the review period, the MAH noticed that after SARS-CoV-2 JN.1 mRNA approval, the MAH continued to receive andusomeran formula cases from the MHRA. Upon further investigation it appeared that the MHRA Yellow card reporting site had not been updated to include the JN.1 product as an option for selection for reporters. The MHRA informed that their sites had been updated approximately 1 month after JN.1 approval to include JN.1 at the top of their drop-down list for selection. In total, 428 cases from the UK were mistakenly reported by the MHRA as related to andusomeran instead of SARS-CoV-2 JN.1 mRNA. In 367 of these cases, MAH added the event of "Discontinued product administered" for purposes of identification.
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 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 findings were 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 utilising Embase, Medline and PubMed databases for the reporting period 18 Dec 2023 to 17 Dec 2024. The literature search was performed for the publications related to Spikevax 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), Spikevax 2024-2025 Formula, SARS-CoV-2 JN.1 mRNA, Spikevax KP.2, SARS-CoV-2 JN.1 mRNA, mRNA COVID-19 vaccine and other elaborated key terms. 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 Dec 2023 to 17 Dec 2024. Please find the journal list under Appendix 13.3.

During the reporting period, there were a total of 33,726 abstracts retrieved and upon removal of duplicates, 17,071 abstracts reviewed from the global searches. There were 20,558 local journal searches performed, and 124 abstracts were reviewed. From all the searches performed, there were no articles that had new significant safety information but there were 4 articles identified with relevant safety information and these are summarised below:

Article Summary: This article describes a comparative retrospective observational cohort study, leveraging deidentified data of N3C (a large dataset managed by the National Institutes of Health (NIH) with over 20 million individuals) from 11 Dec 2020 (COVID-19 vaccine introduction) to 01 Aug 2023 [8]. The authors identified 2 cohorts defined as the vaccination group and the infection group based on patients' index events, either COVID-19 vaccination or infection. The primary follow-up period was 30 days after index event, with secondary analyses conducted using follow-up periods of 60 and 90 days.

For the vaccination group, the inclusion criteria included: (1) patients receiving the first dose of COVID-19 vaccines between 11 Dec 2020, and 01 Aug 2023. Only the first dose was considered for patients who received multiple doses. (2) patients having never been diagnosed with COVID-19 infection or tested positive for COVID-19 before the index date or during the follow-up period. For the infection group, the inclusion criteria included: (1) patients who were first diagnosed with COVID-19 infection or testing positive for COVID-19 between 11 Dec 2020, and 01 Aug 2023; (2) patients who had never received COVID-19 vaccines before the first infection or during the follow-up period. Patients were censored at death or the end of the follow-up period. Patients who were (1) ≤18 years old, (2) diagnosed with end-stage kidney disease, or (3) with diagnostic AKI codes within the 30 days before the index date were excluded.

There were 20,905,766 subjects reviewed and after inclusion and exclusion criteria were applied, the vaccinated cohort had 2,953,215 subjects while the infected group had 3,616,802. The absolute

risk of AKI was 0.66% in the vaccination group versus 4.88% in the infection group. There were significant differences between the baseline characteristics between the 2 cohorts, including age, race, gender, previous AKI, HBP, DM, heart failure, CVD, and obesity. After adjusting for various confounders, COVID-19 infection was associated with a significantly higher risk of AKI than COVID-19 vaccination (aHR = 10.31, $P < 0.001$). The authors conclude that the study demonstrated that COVID-19 vaccination is associated with a significant lower AKI risk compared to COVID-19 infection.

There were limitations to the study, such that the findings need to be interpreted with caution. Inherent weaknesses of Electronic Health Record (EHR) data posed challenges, such as potential inaccuracies, missing or incomplete records about COVID-19 vaccination and infection in N3C, and variations in data quality. Secondly, despite the extensive data available in N3C, it represents only a portion of the country rather than its entirety, limiting the generalizability of the authors findings. Third, the study design was retrospective and observational, introducing potential biases due to unmeasured confounders and lacking the ability to establish causal relationships between outcomes and exposures. However, the N3C dataset provides the largest ever EHR dataset related to COVID-19 and a unique opportunity to investigate the vaccine AEs and compare them with the occurrences of the diseases or symptoms following infections. It is critical that the COVID-19 vaccination campaigns significantly limited the impact of the COVID-19 pandemic. The comparison AKI rates provide a unique perspective examining the risk of a health outcome following vaccination or natural infection.

Company comment: In spite of its limitations, the article provides compelling data demonstrating that COVID-19 vaccination has a much lower risk of a temporal association with AKI than COVID-19 infection. However, it does not provide direct data on elasomeran.

Article Summary: This article describes a population-based retrospective cohort study and sibling matched analysis in Ontario, Canada's most populous province with about 15.1 million residents and 140,000 live births each year [9]. The authors primary objective was examining the association between maternal mRNA covid-19 vaccination during the first trimester of pregnancy and the prevalence of major congenital anomalies in offspring. The primary cohort included singleton live births after >20 weeks' gestation with an expected birth date between 16 Oct 2021 and 01 May 2023. The authors examined 174,296 singleton live births: 34,181 (20%) born to mothers who received one or 2 doses of an mRNA covid-19 vaccine in the first trimester and 34,951 (20%) born to mothers who did not receive a vaccine before or during pregnancy. The sibling matched analysis included 13,312 infants exposed to a Covid-19 vaccine in the first trimester and 15,089 matched older siblings with no reported in-utero exposure to a Covid-19 vaccine. The primary outcome was major congenital anomalies, overall and grouped by specific organ systems, diagnosed within 28 days of birth.

The authors found that the major congenital anomalies were present in 832 (24.3 per 1000 live births) infants exposed to an mRNA COVID-19 vaccine in the first trimester compared with 927 (26.5 per 1000 live births) infants not exposed to a vaccine, resulting in an adjusted prevalence ratio (vaccinated/not vaccinated) of 0.89 (95% CI 0.79 to 1.01). Major congenital anomalies were present in 283 (21.3 per 1000 livebirths) and 343 (22.7 per 1000 live births) infants exposed to an mRNA covid-19 vaccine in the first trimester and their older siblings not exposed to a vaccine, respectively (adjusted prevalence ratio 0.91, 95% CI 0.77 to 1.07). Results were similar across a range of subgroup and sensitivity analyses.

The authors concluded that mRNA Covid-19 vaccination during the first trimester of pregnancy was not associated with an increase in major congenital anomalies in offspring, overall or grouped by organ system, when compared to non-vaccinated mothers, as well as compared to matched older siblings. The strengths of the article were the large cohort size: however, there were limitations that included the inability to rule out residual confounders such as smoking or excessive alcohol intake. In addition, outcomes were assessed at 28 days rather than a longer period. Finally, the authors only looked at live births and did not include stillbirths or spontaneous abortions.

Company comment: This study supports the safety of mRNA COVID-19 vaccination during early pregnancy, demonstrating no increased risk of major congenital anomalies. Findings align with previous research on the topic and provide reassurance for public health recommendations encouraging vaccination during pregnancy.

For additional information, see topic of pregnancy in Appendix 12.10.

Article Summary: For detailed summary of the article [10], please see the topic of Myocarditis and Pericarditis in Section 16.3.1.2.

Company Comment: please see the topic of Myocarditis and Pericarditis in Section 16.3.1.2.

Article Summary: This article describes a retrospective study with a primary objective to analyse the clinical features and evolution of patients who develop Chronic Urticaria [11]. The authors asked a group of 16 allergists to identify eligible patients with chronic urticaria (CU) after receiving a dose of COVID-19 mRNA vaccine. Subjects were asked for consent, and when given, were sent a link to online questionnaire in 2022. All patients received a link to a second online questionnaire in 2023. Additional objectives included defining the contribution of COVID-19 infection to the onset of CU, and to compare the sensitisation rate against the vaccine in CU patient with a control population. To that end, blood tests were performed in subset of 50 patients, and their results were compared with individuals without a history of urticaria (N=135).

The authors found that among the 111 identified CU patients, they were able to contact 110, and 88 responded to our first survey. Of these 88 patients, 66% were middle-aged female (median age

41, IQR 35-48, Fig. 1b). In 89% of cases, CU started after the booster shot and not after primary vaccination. As of Jun 2022, CU remained active in 81% of these cases. The authors found that most-vaccination CU occurs after a median interval of 10 days and significantly more after the Spikevax booster, affecting middle-aged individuals (median age 41, and 66% females). In 2023, CU was still active in 53% of the cases. Inducible forms of CU, primarily dermographism, are reported in 54% (2022) and 61% (2023) of the cases.

Basophil Activation Test (BAT) positivity was not specific to CU, anti-nucleocapsid positivity, or atopy but is significantly associated with higher anti-spike neutralising activities and younger age. Importantly, 4 CU patients received a BD, and all tolerate the additional dose of mRNA vaccine with no disease exacerbation/recurrence.

The authors concluded that the Spikevax booster induces anti-vaccine Immunoglobulin E (IgE) independently of CU, the latter being not directly associated with COVID-19 infection nor atopy. The tolerance to a new booster in 4/4 patients suggests that the mRNA vaccines potentially indirectly trigger CU in predisposed individuals. Limitations of this study include a retrospective design in which subjects were identified by a non-random collection of allergists from their practices. Further bias could be introduced as only 88 of the 111 potential subjects participated in the first survey. The small sample size and nature of subject identification limit generalizability of the finding.

Company Comment: The study postulates a potential link between mRNA COVID-19 vaccination and CU in predisposed individuals but does not establish direct causality. The lack of a control group of non-vaccinated individual for the primary analysis limits the applicability of the finding. And the authors note the majority of the selected subject were exposed to Spikevax, it failed to provide a general background exposure to different background rates to contextualise this finding.

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, prioritisation, 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 analyses 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 recognised 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 analyses, which are performed as described in Appendix 12.1.

During the reporting period of this PBRER, 7 (7) new signals were validated; all of them were closed by the MAH as refuted signals following evaluation. The list of validated 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	Source	Status (Ongoing/ Closed)	Outcome (Refuted/ Substantiated)	Assessed in another regulatory procedure (Safety summary report or a variation)
Cerebral venous thrombosis	TGA request	Closed	Refuted	QSSR04
Dermatitis allergic	Saudi Food & Drug Authority (SFDA) signal	Closed	Refuted	QSSR04
Erectile dysfunction	Rwanda HA	Closed	Refuted	QSSR01
Hypotension	SFDA signal	Closed	Refuted	QSSR04
Ischaemic stroke	Advisory Committee on Immunisation Practices (ACIP)	Closed	Refuted	QSSR03
Pre-eclampsia, gestational hypertension and GD (P919)	Post-authorisation safety study mRNA-1273-P919	Closed	Refuted	QSSR02
Renal Failure	SFDA signal	Closed	Refuted	QSSR01

15.2. Requests from Health Authorities or regulatory bodies

No ongoing requests from health authority for this product.

15.3. Other Safety Topics

No other safety topic to present for this product.

16. SIGNAL AND RISK EVALUATION

16.1. Summaries of Safety Concerns

Table 16-1 provides the Summary of Safety Concerns as per RMP v8.1 approved on 23 Oct 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 v8.1 approved on 23 Oct 2023)

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

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

- SPIKEVAX RMP v8.1 was updated to v8.2 (approved on 11 Apr 2024) to update the Module SVII to provide myocarditis and pericarditis data from completed Study mRNA-1273-P301, and to update studies charactering long-term safety in Module SVII 3.
- SPIKEVAX RMP v8.2 was updated to v8.3 (approved on 11 Jul 2024) to remove the Myocarditis and Pericarditis follow-up questionnaire in Part v3 and from Annex 4.
- SPIKEVAX RMP v8.6 (approved on 03 Sep 2024) updated study milestones for studies mRNA-1273-P306, mRNA-1273-P904, and mRNA-1273-905 with no additional changes to the list of safety concerns.
- SPIKEVAX RMP v8.6 was updated to v9.1 (approved on 10 Sep 2024) which was a consolidation of RMP v8.3 (Procedure # PSUSA/00010897/202312) and RMP v9.0 (Procedure # EMEA/H/C/005791/II/0136) to include SARS-CoV-2 JN.1 mRNA and indication for SARS-CoV-2 JN.1 mRNA with no further updates on safety concerns.

Table 16-2 provides the Summary of Safety Concerns as per RMP v9.1 approved on 10 Sep 2024 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 v9.1 CHMP favourable opinion received on 10 Sep 2024)

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

16.2. Signal Evaluation

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

Seven signals were closed by the MAH during the reporting period. Based on scientific evaluation of the available information, all 7 closed signals were refuted (Cerebral venous thrombosis, Dermatitis allergic, Erectile dysfunction, Hypotension, Ischaemic stroke, Pre-eclampsia, gestational hypertension and GD (P919), and Renal Failure. Please refer Appendix 5.2 for the signal evaluation reports (SERs) of the respective signals.

** **Please note that the DLPs for signal evaluations reflect the dates of the data that were included in the respective assessments.**

16.2.1 Cerebral venous thrombosis

Table 16-4 Cerebral venous thrombosis

Signal evaluation criteria	Summary
Source	The MAH considered Cerebral venous thrombosis as validated signal, based on the request from the Therapeutics Goods Administration (TGA) Health authority Australia. On 17 Sep2024, The TGA requested Moderna to provide a signal analysis for all Spikevax vaccines and the risk of CVT. Exact request is stated below: As a guide, information to include (but is not limited to) in this safety analysis are as follows: • An observed versus expected analysis, using risk windows out to 7, 14 and 21 days. Justification for the background rates chosen should be provided. • An analysis of any global Company held data, case reports and literature regarding the risk of CVT and Spikevax. As well as the results and analysis of these searches, please include:

	○ The literature search strategy. ○ The MedDRA search terms used for the search of global case reports and rationale for selection of these. ○ The case series inclusion and exclusion criteria, with justification for these. • Details of any other regulatory actions undertaken by Moderna relevant to this issue. • A risk-benefit analysis for the approved indications of Spikevax. • An analysis if an update to include the risk of CVT to the Australian PI for Spikevax is warranted.
Background	On 12 Apr 2024, Singapore Health authority (HSA) notified Moderna that based on their Nationwide safety surveillance study on COVID-19 mRNA vaccines, they found an elevated risk for CVT with Spikevax Vaccination and proposed to update the local PI and PIL for Spikevax XBB.1.5. On 26 Apr 2024, MAH responded to HSA stating that: • Multiple evaluations were conducted for the safety topic "Cerebral venous thrombosis (CVT)", including Cerebral venous sinus thrombosis (CVST) in the context of requests from health authorities and as part of ongoing monitoring of adverse events of special interest (AESI) within signal detection activities. • Review of the data did not indicate any safety issue of concern with CVST/CVT. • In addition, the accumulating post-authorisation safety data over the last 3 years provide insufficient evidence of a potential causal association between CVST and the administration of Spikevax. • MAH considers that an update to Spikevax's RSI is not warranted at this point of time. • The MAH continues to monitor the reported events of CVST using routine surveillance activities. On 03 May 2024, SG HSA provided a response back and mandated to include CVT in Singapore PI for Spikevax XBB.1.5. under post-marketing experience indicating that these events have occurred without ascribing causality and for HCP to be aware. After this second request MAH agreed to SG HSA proposal to include CVT to the Singapore product label. Moderna indicated all the health authorities including TGA (on 29 May 2024) about the Singapore HSA decision to include CVT in the local product information (PI) for Spikevax XBB.1.5 (andusomeran).
Methodology	A cumulative search of the GSDB was performed as of 17 Sep 2024 with the following PTs using the MedDRA v27.1: • Cavernous sinus thrombosis, CVST, Cerebral venous thrombosis, Sigmoid sinus thrombosis, Superior sagittal sinus thrombosis, Transverse sinus thrombosis. The above specified MedDRA terms were chosen to provide a detailed and thorough approach to identify cases of CVT by including both general and anatomically specific forms of the condition. Use of these PTs will help to capture all possible variations of CVT cases in different parts of the brain's venous drainage system.

	The cases retrieved form the GSDB were classified using The Brighton Collaboration case definition for Thrombosis and Thromboembolism (V1, Sep 2022) Categories: • Level of Certainty 1 –Definitive case, • Level of Certainty 2 – Probable case, • Level of Certainty 3 – Possible case, • Level 4 – Insufficient information available to confirm a possible, probable or definitive case of venous thrombosis/ thromboembolism, • Level 5 – Sufficient information to determine that it is NOT a case of venous thrombosis/ thromboembolism. The WHO causality assessment was applied for the assessment of the cases. The CVST risk factors identified from UpToDate were used for the assessment of the cases.
Results	The cumulative search of the GSDB (Cumulative through 17 Sep 2024) retrieved 296 cases. 321 events were reported across the 296 cases. Several of the cases described more than one of the PTs: • 277 cases reported only one PT, • 13 cases reported 2 PTs, • 6 cases reported 3 PTs. The majority (n=264, 82.2%) described a preferred terms that did not specify a specific anatomical location other than cerebral (CVST and CVT. **Review of 296 Cases with 321 Events:** All 296 cases were carefully reviewed by a clinician. Each case was classified using the Brighton case definition for Thrombosis and Thromboembolism (V1, Sep.2022), detailed in Methodology. All cases were categorised carefully as Level 1 to Level 5 and WHO causality assessment was applied for all cases. • 120 cases were determined to be Level 1. In all of these Level 1 cases, this was due to the presence of imagining (venogram, MRI, CT) that led to the diagnosis. However, large number of these cases provided generally limited information other than the imaging study. • No cases were determined to be level 2. • 58 cases were determined to be level 3. Generally, these cases contained limited information. However, if the reports did describe symptoms generally associated with CVT in addition to the reported term, they were placed in this level. • 115 cases were Level 4. These cases contained very limited information regarding the event of CVT and described no symptoms or diagnostics suggestive of CVT other than the reported term. • 3 cases met Level 5 definition. On review, the verbatim reported term was purely speculative or described a different medical issue. The 296 cases were identified as at least a Level 4 of CVT were reviewed to determine if any pattern indicating a potential safety signal was discernible. Age and gender were generally consistent with epidemiology of CVT. A review of the dose number and time to onset after vaccination did not show

a clear pattern across these reports.

Review of the clinical course, presenting symptoms, and diagnostic findings also failed to identify any concerning pattern. The presenting symptoms were not consistent across cases, and reflected a range of underlying cerebral venous structures that would be expected in the general population experiencing CVT. Diagnostic findings (MRI, CT and venogram) did not show a consistent pattern in terms of the location or evolution of the CVT.

WHO-UMC causality assessment of the 296 cases:

- No cases described elements that would suggest either Probably/Likely or Certain causal association.
- One hundred forty-three (143) of the cases were deemed Unassessable. These cases did not include key clinical data elements to allow a causal assessment. These reports were all missing at least 3 critical data elements, including past medical history, concomitant medications, details of the clinical course of the events, information on the time to onset vis a vis vaccination, treatment details, diagnostic results, or age/gender.
- One hundred thirty-one (131) of the cases were deemed as Unlikely. These reports contained strong confounding factors that provide a plausible explanation for the event. These included factors such as a history of a coagulopathy (included Factor V Leiden disease), a concurrent cancer diagnosis, or use of medications strongly associated with CVT, especially oral contraceptives.
- Twenty-two (22) cases were determined to have a Possible causal association with vaccination.
    - Six (6) of these were only Level 3 in terms of Brighton classification. These cases generally provided limited information; the causal relationship was generally only based on a plausible temporal relationship. But these cases failed to provide a confirm diagnosis or enough detail to truly assess causality.
    - 16 cases met the Level 1 case definition and are further described below.

Sixteen Level 1 Reports with Possible Causal Association

Sixteen cases described case with evidence of being a true event of CVT and were deemed to have a Possible association with vaccination. These reports either contained at some risk factor(s) for CVT, or an ongoing disease entity that could explain the events. Many also failed to provide critical data elements that would allow a full causal analysis for the complex event of CVT.

Generally, these 16 cases were not meaningfully different from the overall cases in terms of age or dose number. They did tend to have a shorter time to onset, but this is reflective of their being cases with at least a potential association. They also reflected a higher proportion of male patients, but this is most likely a difference to the small numbers of cases in the subset. Review of these 16 Level 1/Possibly Related reports did not identify any sentinel case of concern for a potential association with vaccination. All reports described potential confounder for the events or provided limited information limiting a full medical assessment of causality. Review across the reports, including clinical course, presenting symptoms, and diagnostic findings failed to identify any concerning pattern. The presenting symptoms were not consistent across reports, and reflected a range of underlying cerebral venous structures that would be expected in the general population experiencing

	CVT. Diagnostic findings (MRI, CT and venogram) and clinical examination (when provided) did not show a consistent pattern in terms of the location or evolution of the CVT. **Review of Fatal reports** Of the 296 cases, only 10 cases reported a fatal outcome. Among these 10 cases, 6 were female and 4 were male. Seven cases were reported in the Elderly age group ≥65 years and 3 cases were reported in the adult age group (42-64Y). Time to onset ranged from 0-138 days. Based on the Brighton collaboration case definition: 2 cases met Level 1 definition, 3 cases met the Level 3 definition, and 5 cases met Level 4 definition. According to the WHO causality assessment, 6 cases were assessed as Unlikely; and 4 cases assessed Unassessable. **Summary:** In summary, the review of the 296 cases showed that the age and gender reported in these cases were consistent with the background rates in general population. Time to onset did not identify any pattern. Case assessment showed that 48.3% (143/296) were unassessable; 44.3% (131/296) were unlikely; and only 7.4% (22/296) were assessed as possible based on plausible temporal association and these possible cases contained potential risk factors and/or had limited information. No Sentinel cases were identified. The review did not identify any significant safety issue of concern or any pattern/trend.
Discussion	Cerebral venous sinus thrombosis is a rare form of venous thrombosis disorder affecting the cerebral veins and Dural sinuses. The annual incidence of CVT ranges from 1.16-2.202 per 100,00 in the general population, with an increased risk in patients with COVID-19 infection (42.8 per million ref: [12]). In COVID-19 patients, especially those in intensive care units, CVT and other thrombotic events occur between 3–30 days after infection onset [13]. Venous thromboembolic (VTE) complications have been consistently reported to be increased in SARS-CoV-2 infection, most probably as the results of a thrombophilic state secondary to inflammation and immune thrombosis [13]. Several cases of Unusual thrombotic events including CVT, have been reported with the recombinant adenoviral vector vaccines. The primary mechanism by which adenoviral vector vaccines such as ChAdOx1 (AstraZeneca) and Ad26 (Johnson & Johnson) cause thrombotic events is through Vaccine Induced Thrombotic Thrombocytopenia (VITT). VITT is caused by antibodies that recognise platelet factor 4 (PF4), leading to platelet activation and subsequent thromboembolism. However, no similar immunopathogenic mechanism has been described for mRNA vaccines. A cumulative review of clinical trial data did not identify any cases for the safety topic of interest and the cumulative review of the post-marketing data did not identify any sentinel case. Majority of the post-marketing data cases were assessed as either Unassessable (48.3%) or Unlikely (44.3%), and only 7.4% were assessed as possible based on temporal association. These possible cases described potential confounder(s) for the events or provided limited information precluding adequate medical assessment. In addition, the clinical review did not identify any safety concern/pattern/trend. Review of the external safety databases EVDAS and VAERS did not provide any significant disproportionality for the product event combination. Review of the published literature identified articles that showed the mechanism by which COVID infection causes CVT. There were many articles that showed an established mechanism (VITT) by

	which ChADOX1 CoV-19 Vaccine (AstraZeneca) and Ad 26. CoV2 (Jansen) would cause CVT. The literature review did not identify articles that would suggest an established mechanism by which mRNA vaccine could cause CVT. The Observed to expected analysis and the PASS studies (P920 and P903) did not identify any elevated risk for CVT with all Spikevax marketed products. In summary, CVT is a recognised complication of COVID-19 infection and a known ADR for adenoviral vector vaccines. However, there are no well-established mechanism of action by which the mRNA vaccine could cause CVT. The review of the available data from the different sources (Clinical trial, postmarketing, literature, external safety databases, O/E analysis and PASS study) does not support a clear causal association between mRNA vaccines and the development of CVT. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to be favourable.
Conclusion	The comprehensive evaluation of available data from CTs, pharmacovigilance databases, external databases, epidemiological studies, and published literature does not substantiate a relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the occurrence of CVST. The current CCDS (version 19.0) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified. The cumulative safety data evaluated do not provide a sufficient basis for new recommendations or product labelling changes and/or RMP, including relevant risk minimisation measures regarding CVT. The validated signal of CVT is refuted and closed at this point of time. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive. The MAH will continue to monitor through routine pharmacovigilance activities and as an AESI through additional pharmacovigilance activities (PASS study mRNA-1273-P951).

16.2.2 Renal Failure

Table 16-5 Renal Failure

Signal evaluation criteria	Summary
Source	On 25 Dec 2023, Moderna received a request from the SFDA via the local affiliate (Tabuk Pharmaceuticals), for the following information: o We would like from you to Submit a comprehensive signal evaluation report within 60 days regarding the potential risk of Renal Failure with the use of SPIKEVAX (mRNA-1273; elasomeran). o The evaluation should include, but not be limited to, background rate, results from CTs database, epidemiology, preclinical findings, PASS, global pharmacovigilance database medical literature, estimated reporting rate, integrated benefit-risk analysis, conclusion and recommendation.
Background	The MAH considered renal failure as a validated signal following receipt of a request from the

	SFDA requesting the MAH for Spikevax (Moderna Biotech Spain S.L.) to perform a cumulative review of all cases of renal failure. Acute Kidney Injury (AKI) has generally become the PT replacing Acute Renal Failure (ARF). It can be defined as an abrupt decrease in kidney function leading to azotaemia, may or may not involve decrease in urine output. The loss of kidney function may also involve structural damage/injury to the renal interstitial tissue, glomerular apparatus, vasculature. Aetiology can be multi-factorial and with early identification and adequate treatment of the underlying cause, it is generally reversable. If untreated, it can lead to accumulation of fluid overload and electrolyte disturbances (hyperkalaemia, hyperphosphatemia, hypocalcaemia), and may also have a cascading impact on the functioning of other organ systems.
Methodology	The MAH's clinical database and the GSDB were queried for valid case reports of Renal failure received from HCP, HA, consumers, and literature, worldwide, for elasomeran , elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran using the MedDRA SMQ Narrow 'ARF' which includes the following PTs: " AKI; Acute phosphate nephropathy; Anuria; Azotaemia; Continuous haemodiafiltration; Dialysis; Foetal renal impairment; Haemodialysis; Haemofiltration; Neonatal anuria; Nephropathy toxic; Oliguria; Peritoneal dialysis; Prerenal failure; Renal failure; Renal failure neonatal; Renal impairment; Renal impairment neonatal; Subacute kidney injury". Two different MedDRA versions were used. For the CTs MedDRA version 23.0 was used and for querying the GSDB, cumulative as of 17 December 2023, the MedDRA version 26.1 was used. Identified cases were classified into one of 5 categories, following the Company case definition that was developed using the above KDIGO guideline as a basis, as follows: Definite case: per KDIGO criteria contains all relevant diagnostic information available. Probable case: event reported as AKI/ARF with full supportive renal diagnostic information provided [however KDIGO criteria specifically was not met]. Possible case: event reported as AKI/ARF/or SMQ term with only partial supportive renal diagnostic information provided. Unassessable: event reported as AKI/ARF/or SMQ term with no supportive renal diagnostic information provided. Not a case – Not a case for Spikevax; containing alternative diagnosis. This search retrieved a total of 1185 cases (1260 events) of which 1153 were considered serious cases (1224 serious events). A list of key terms was developed for relevant (i) concomitant medication(s) which have well known association with ARF/AKI (or related terms) based on the approved labels; and (ii) Medical history/concurrent co-morbidities which likely constitute clear risk factors in the development of ARF/AKI (or related events). The medical history and concomitant medication fields for all identified cases were searched to determine if they had a match for the above terms. • All cases that had both a medical history match and a concomitant medication match to the above lists were assumed to be likely confounded for review. However, all of these cases were medically reviewed to confirm they had confounding factors that could

present a more plausible explanation the events of AKI.

- Cases reporting only medical history matches to the above list were medically reviewed carefully to confirm that the reported medical history could present a more plausible explanation for the reported events of AKI.
    - Critically, all cases confounded by a history of significant kidney disease were carefully reviewed to confirm there was no pattern of exacerbation of disease after vaccination with Spikevax.
- Cases reporting only concomitant medication matches to the above list were medically reviewed carefully to confirm that the reported concomitant medication(s) could present a more plausible explanation for the reported events of AKI.
- If these medical reviews determined that a case was not truly confounded, they were moved to the next step of screening.

All remaining cases (not medically confirmed to be confounded) were classified to determine if they provided medical history and concomitant medications information to determine if any cases had insufficient information to medically assess any relationship to vaccination or another source of AKI.

- If the case was missing both of these elements, the other available information (e.g., narrative) was medically reviewed to confirm the case did not contain sufficient medical information to allow an assessment.
- If the case was missing only one of these elements, the available information was medically reviewed to confirm whether the case had sufficient evidence to make a meaningful medical assessment.
- Only those reports with sufficient information to provide a medical assessment were further reviewed.

All remaining cases (not truly confounded or without sufficient information) were screened to determine if they medically confirmed, and if not, did they contain sufficient medical information to allow a thorough clinical assessment.

- Any of the remaining cases that was not medically confirmed were highlighted. These cases were medically reviewed to confirm whether they had sufficient clinically valid information to allow a full medical assessment. If not, they were not further reviewed.
    - Though most of these reports did not contain sufficient clinical detail to allow assessment, they were still reviewed to determine if they had any meaningful pattern suggesting an association with Spikevax vaccination.

Remaining cases (not confounded, with sufficient information, medically confirmed) were further reviewed.

A final screen of these reports was performed, focused on the time to onset between vaccination and the event of AKI. Given the potential mechanisms for a potential for a vaccination to be associated with AKI, any case with a TTO of greater than 30 days was deemed unlikely to be associated with vaccination. These cases were medically reviewed to confirm the sequence of clinical events and to determine if any pattern of potential association could be determined.

	The applicable cases that met the Company case definition criteria of 'definite', 'probable' or 'possible' were subsequently assessed for causality using the WHO-UMC standardised causality assessment criteria.

Results	**Nonclinical data:**
	The available non-clinical safety data for mRNA-1273 did not demonstrate the potential to induce AKI (or related events).
	Clinical Studies:
	mRNA-1273-P301 Study: There were 24 participants (15 in the placebo group and 8 in the mRNA-1273 treatment group) in the P301 study, in whom AKI (or a related event term) were reported. There was not an imbalanced noted in study P301 for any of the study arm participants.
	mRNA-1273-P205-Part H Study: No participants in P205-Part H reported the events from the MedDRA SMQ Narrow "ARF".
	mRNA-1273-P205-Part J Study: No participants in P205-Part J reported the events from the MedDRA SMQ Narrow "ARF".
	The **MAH GSDB** was queried cumulative as of 17 Dec 2023, for valid case reports of ARF received from HCP, HA, consumers, and literature, worldwide, for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran using the MedDRA narrow SMQ of AKI v.26.0. This search retrieved a total of 1185 cases (1260 events) of which 1153 were considered serious cases (1224 serious events). A total of 985 cases were medically confirmed, and there were 204 cases that reported a fatal outcome. There were no important differences between males (637; 53.8%) and females (537; 45.3%), with 11 cases (0.9%) not reporting sex information. The mean age of these reports was 65.9 years with a median of 69.0 (min:0.2/max:102.0).
	All cases in which medical review did not determine they belonged into one of the above 4 categories were determined to need additional medical review and assessment. A description of the reports in each of these categories, especially those receiving the most thorough medical review, is provided below. In summary, after screening and medical review of the 1185 case reports, they were classified as follow:
	• 428 reports were deemed to have confounding factors that provided a more plausible explanation for the reported events of AK.
	  • These case reports predominantly involved elderly patient population with 238 males (mean/median age 72 years; range 13 to 92 years), and 186 females (mean/median age 69; range 15 to 99 years) and 4 (4) did not have information on gender, often in poor/critical health status or received care in hospital setting and largely involved progression/complications of underlying or concurrent significant medical conditions. A number of these patients notedly received polypharmacy including medications having known associations with AKI (or related events). These included: various Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), furosemide, lisinopril, lithium, losartan, methotrexate, tacrolimus, enalapril ramipril, cyclosporine, acyclovir, omeprazole, acetaminophen; aspirin, etc.
	  • Majority of these reports were reported via RA (348 cases), followed by spontaneous

	(48 cases) and Literature-Non-Study (32 cases). • The more commonly reported relevant medical history and/or concurrent medical conditions which preceded and likely contributed towards the reported AKI (or related events) in these case reports included, but not limited to: chronic kidney disease, hypertension, hyperlipidaemia/ dyslipidaemia, diabetes mellitus, COVID-19 infection, benign prostatic hyperplasia, pneumonia, pulmonary hypertension, dialysis, respiratory failure/arrest, hypotension, hypovolemia, dehydration, cardiac failure/congestive, atrial flutter, myocardial infarction, sepsis/septic shock, end-stage renal disease, renal transplant, AKI, cardiomyopathy, renal failure, urinary tract infection, left ventricular failure/ejection fraction decreased, mechanical ventilation, nephrolithiasis, IgA nephropathy, urinary retention, diabetic nephropathy, gastrointestinal haemorrhage, dilated cardiomyopathy, hepatic cirrhosis, haemodialysis, hyperkalaemia, renal disorder, pulmonary embolism, respiratory failure, aortic stenosis, cardiac disorder, lung/ heart transplant, hydronephrosis, chemotherapy, cancer (breast, prostrate, etc.), malignant neoplasm, nephropathy, lactic acidosis, malnutrition/ feeding disorder, peripheral arterial occlusive disease, single functional kidney, vascular graft, acute respiratory distress syndrome, anaemia of chronic disease, bacteraemia, bradycardia, cerebrovascular accident, chronic lymphocytic leukaemia, lymphoma, hepatocellular carcinoma, proteinuria, renal cell carcinoma, renal impairment, hypothyroidism, myasthenia gravis, and major surgeries (cardiac bypass, cancer surgery, etc.). • No other specific patterns were identified following a review of these case reports. • 461 reports were deemed upon screening and medical review to contain insufficient information to allow a meaningful medical assessment of any relationship to Spikevax vaccination. • These cases were reported in 253 males (mean/median age 69 years; range 20 to 98 years), 202 females (mean/median age 72; range 1 to 98 years) and 6 were unknown gender. Majority of these reports were reported via RA (411 cases), followed by Spontaneous (40 cases) and Literature-Non-Study (10 Cases). • Vital information was deemed missing from these reports for a detailed causality assessment, including, but not limited to: • missing relevant medical history and/or concomitant medication details. • relevant details around the clinical course of the reported AKI event, including supportive renal diagnostic data were missing or unremarkable (no corresponding elevated blood creatinine and/or eGFR decrease or the laboratory data were inconclusive). • the precise information on time to onset (latency) of the reported renal event could not be ascertained with respect to Spikevax administration; In other cases, the timing of administration of Spikevax was not known/reported in relation to the reported AKI event. • consumer cases with insufficient details; non-medically confirmed information.

	• reports involving a related SMQ term e.g., anuria; lacking further details establishing an AKI. • In a number of these cases, where the information was available, significant comorbidities were often noted that may have been potentially contributory towards the reported renal event e.g., pulmonary embolism, heart failure, liver failure, CLL, sepsis, etc. • No other specific patterns were identified following a review of these cases. • 86 non-medically confirmed reports after review were determined to not contain medically valid information to allow for a thorough medical review for any potential association with vaccination. • These cases were reported in 44 males (mean/median age 61 years; range 15 to 88 years), 42 females (mean/median age 59 Years; range 27 to 87 years). Majority of these reports were reported from regulatory authorities (51) and spontaneous (35) source. • These cases were lacking information to observe any pattern suggesting an association given the lack of medically confirmed information. • 30 reports had a time to onset of greater than 30 days and upon medical review were determined to not demonstrate a potential relationship with vaccination. • These cases were reported in 17 males (mean/median age 69 years; range 18 to 91 years), 12 females (mean/median age 64; range 21 to 80 years) and One (1) patient did not report gender. Majority of these reports were reported via RA (26) and Spontaneous (4). • The median time to onset for the reported renal event in these cases was 67 days (range 32 to 259) following Spikevax administration. • In the majority of these cases, where the information was available, the reported renal event occurred in the setting of other severe comorbidities which provided a more likely explanation for the renal event e.g. a concurrent severe infection (including Covid-19), pneumonia, sepsis, septic shock, bacteraemia, chronic kidney disease, lupus, vasculitis, tubulointerstitial nephritis, acute respiratory failure, multiple organ dysfunction, cardiac failure, right ventricular failure, cardiac valve insufficiency, myocardial infarction, cardiac arrest, cardiogenic shock, atrial/ventricular fibrillation, hepatic failure, haemorrhage, End-Stage renal disease, renal aplasia, reduced fluid intake, etc. Also, these involved patients, mostly elderly, with significant medical history: heart failure, coronary artery disease, BPH, hypertension, diabetes (poorly controlled in some cases), hyperlipidaemia, atopic dermatitis, cancers, SLE, COPD, lupus, etc. • Given the long time to onset and reports involving significant comorbidities, often severe in nature and/or the underlying medical history of the patients which were likely contributory, no other specific patterns were identified following a review of these cases. • After this review, 180 Reports could not be confirmed as fitting in any of these categories and were deemed to require a more thorough medical review.
Discussion	Acute Kidney Injury (AKI) has generally become the PT replacing ARF. It can be defined as an abrupt decrease in kidney function, including both structural damage/injury and loss of function/impairment. In generally signifies a sudden, and often reversable reduction in kidney

	function, usually noted by a reduced glomerular filtration rate. The medical concept of AKI has been complex, and over the years multiple AKI definitions (up to 35) were developed, but this has also led to some variance when the AKI data and case reports have been described in medical literature. For the purpose of this safety review, a more recent and widely accepted definition from KDIGO were utilised to evaluate the AKI case reports, as these provide a framework for diagnosis, staging, and management of AKI case reports based on changes in serum creatinine levels, urine output, or the need for renal replacement therapy. A total of 1185 case reports (1260 events) of ARF retrieved from the MAH GSDB using narrow SMQ of AKI for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran were evaluated in detail using a stepwise approach. The majority of case reports for AKI (or related event including for flare-ups/recurrence), where the information was available, involved elderly patients often in poor/critical health status or received care in hospital setting and often a result of progression/complications of underlying or concurrent significant medical conditions (alternative aetiologies). Also, number of these patients notedly received polypharmacy including medications having known associations with AKI (or related events). No other clear trends or patterns were observed (time to onset, dose number, etc.) that would suggest an association of AKI (or a related event) with Spikevax administration. A review of the available published literature articles have highlighted the enormous benefits of mass vaccination for COVID-19 and postulated potential mechanisms of COVID-19 vaccination may potentially lead to AKI, including the effect of a COVID-19 infection leading to renal insult, however, there have been no high-quality studies which may provide sufficient evidence yet for a plausible direct mechanism towards a causal association between AKI/ARF and SPIKEVAX vaccination. A review of the available clinical trial data from a phase 3 study for mRNA-1273 (N=30,346), there was not an imbalanced noted in study P301 for any of the study arm participants as the incidence of the event of ARF (or related term) in the mRNA-1273 arm (<0.1%; 8 events) compared to the comparator (placebo) arm (<0.1%; 15 events) and none of the events in the mRNA-1273 arm were considered to be related to the mRNA-1273 by the investigators. Also, there has been no relevant non-clinical safety findings demonstrating a renal injury potential for mRNA-1273. Further, the available data from the 2 PASS studies involving Spikevax suggest instances of ARF post-vaccination were rare and not statistically linked to the vaccine. Data from these 2 studies has showed no evidence of increased risk of AKI following elasomeran vaccination. These findings are also in line with the observed to expected (O/E) analysis which has shown the observed reporting rate for AKI was 1.98 per 100,000 person-years (based on the 1185 case reports cumulatively). Overall incidence described by [14] (data from Netherlands) was 185.51 per 100,000 person-years, corresponding to an estimated 111,306 cases expected. The rate ratio was 0.01 (95% CI: 0.01, 0.01). Further, no disproportionality was observed for the PTs from the MeDDRA SMQ of 'Renal Failure' in the EVDAS and VAERS databases. Overall, a review of available safety data from various sources has not yielded any new significant safety findings or demonstrated a potential for AKI/ARF with Spikevax use.

Conclusion	Overall, based on the analysis of all safety data available as of 17 Dec 2023 including the data from all sources as discussed above, the MAH considers that there is insufficient information to establish a causal relationship between the administration of Spikevax and ARF (or related events). The current CCDS (version 18.0) is considered to adequately reflect the safety profile of Spikevax. No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor ARF 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 minimisation measures with regard to ARF. The signal of ARF is refuted and closed.

16.2.3 Erectile dysfunction

Table 16-6 Erectile dysfunction

Signal evaluation criteria	Summary
Source	The MAH considered Erectile Dysfunction as a validated signal for the marketed Moderna COVID19 vaccines (mRNA-1273-related vaccines), upon receipt of a request from the Rwanda HA to gather "more evidence and further investigation" on the safety signal.
Background	The MAH considered "Erectile dysfunction" as a validated signal with COVID-19 vaccine Moderna (mRNA vaccine) following a request from Rwanda FDA to gather "more evidence and further investigation" on the safety signal. Erectile dysfunction (ED), previously known as impotence, is defined as consistent or recurrent inability to achieve or maintain a rigid penile erection for satisfactory sexual intercourse. ED can be (i) Primary, when the man has never been able to attain or sustain erections; and (ii) Secondary, which is acquired later in life in a man who was previously able to attain erections. Secondary ED is more common than Primary. Erectile dysfunction is more common in men 40 years and older, and the prevalence increases with age and co-existing co-morbidities. ED is considered an important social problem, which significantly impacts the quality of life of a patient and his partner. Patient's suffering from ED often delays or avoid seeking treatment. ED can be the initial manifestation of underlying vascular disease that increases the risk of cardiovascular/cerebrovascular events, so addressing ED is important to improve the patient's quality of life and to identify and treat underlying aetiologies.
Methodology	The MAH GSDB was queried cumulative as of 17 Feb 2024, for valid case reports of ED received from HCP, HA, consumers and literature, worldwide for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran using the MedDRA high level term (HLT) Erection and ejaculation conditions and disorders v.26.1.
Results	A total of 252 reports were identified in the database. Eighteen (18) of the reports described a female patient. All these reports were from regulatory sources and could not be further queried. These 18 reports were reviewed separately, and none described a true case of ED. No pattern suggesting a safety issue was seen in these cases. Out of the 252 cases, 234 reports remained for analysis. There were 253 events meeting the search

	criteria associated with the 234 reports, as 15 reports contained 2 or more events. One hundred and fifty-five cases (155) were considered serious, and 156 of the events of interest were considered serious. The vast majority of the serious events were serious due to medical significance of the reported term only; 15 events were considered serious due to disability, and 5 events were considered serious due to hospitalisation, with one report describing both. Time to onset could be determined in 158 of the 234 reports. The average TTO was 9.5 days, with a median of 2.0 days, ranging from 0 to 262 days. No consistent pattern in terms of TTO was noted. Age was reported in 214 of the 234 reports. The average age of the patients' reporting age was 46.4 years, ranging from 18-78 years. 139 reports were from non-medically confirmed reports, while just 85 were from medically confirmed sources. 204 reports were from regulatory sources, and only 30 reports were spontaneous reports. 174 reports were from Europe, 54 from the United States, and 6 from the rest of the world. All 234 reports were medically reviewed and a WHO-UMC based causality assessment was conducted. • 184 reports were medically unassessable due to lack of key information such as a combination of missing medical history, concomitant medications, age, time to onset, or a clinical course of events and treatment. • 48 reports were deemed unlikely related to Spikevax vaccination. These cases were confounded due to reported medical history, concomitant medications, or had a clear alternative aetiology for the events of interest. These included medical conditions and medications commonly associated with ED, and/or another medical condition and a course of events which likely contributed to the event(s) of interest. • There were 2 reports assessed as possibly related to vaccination, but generally provided limited information. [redacted] (WW Identifier: [redacted]): This is a regulatory report (EMA) regarding a male patient of unknown age, with no reported medical history or concomitant medications reported events erection failure, rash, anxiety (worry due to erection failure), 2 days after the 3rd dose of mRNA-1273 vaccination. Outcome of ED was reported as not resolved. • MAH Comment: The case lacked information pertaining to age of the patient, medical history, sexual history, concomitant medications, event details, diagnostic/laboratory tests, physical/psychological examination etc limiting causality assessment. [redacted] (WW Identifier: [redacted]): This is a report from a regulatory source [redacted], regarding a 41-year-old male patient with medical history of Tourette's disorder experienced the events ED (had difficulty achieving and maintaining an erection) and libido decreased, 3 days after the first dose of mRNA-1273 vaccine. The events were reported as recovered 3 weeks after the first dose. Following the second dose administration, the patient reported the same events (erection difficulties and drop in libido) on an unknown date. Treatment details were not provided. The symptoms had not resolved at the time of last update. • MAH Comment: Though the case described a positive rechallenge, there was lack of

	information pertaining to treatment medications for Tourette's disorder, sexual history including information about previous history of adequate erections, laboratory tests/diagnostic tests, physical/psychosocial examination etc., limiting adequate medical assessment.
Discussion	ED is the inability to develop and maintain an erection for satisfactory sexual intercourse or activity. The Diagnostic and Statistical Manual of Mental disorder-5 specifies a duration of at least 6 months in its definition of ED. ED is increasingly prevalent with age: approximately 40% of men are affected at age 40 and nearly 70% of men are affected at age 70. Aetiologies of erectile dysfunction is classified by psychogenic and organic causes. Diagnosis of an ED requires a careful medical history, sexual history, medication history, psychological history, physical examination, and diagnostic/laboratory to rule out and/or for the treatment of underlying aetiologies. ED is not labelled as an Adverse drug reaction in current CCDS/IB. ED is not labelled as an ADR in other COVID vaccines label. Results from Clinical trial data showed the incidence of the event was very low and roughly equal in both the placebo and mRNA-1273 group. No specific pattern or trend was noted. Results from the GSDB: Cumulatively through 17Feb2024, 252 cases reporting PTs within the HLT Erection and ejaculation conditions and disorders were retrieved from the GSDB. Of the 252 cases, 18 reported female gender and review of these cases did not identify any safety concerns. Review of the remaining 234 cases showed that the average age in these cases was 46.4 years old, which is consistent with epidemiological data. The majority of cases (87%) were from RA. WHO-UMC causality assessment was applied for all 234 reports. Of these 234 reports, 184 were assessed as unassessable, 48 were assessed as unlikely, and 2 cases were assessed as possible which contained limited information pertaining to medical history, sexual history, concomitant medications, laboratory/diagnostic tests, psychological examination/physical examination, etc. thereby precluding a meaningful medical assessment. The observed to expected analysis did not identify an elevated risk of ED following marketed Moderna vaccines targeting SARS-CoV-2. Results from the external safety database VAERS, showed that the PTs within the HLT Erection and ejaculation conditions and disorders did not meet the disproportionality threshold. Results from the external safety database EVDAS showed the PTs within the HLT Erection and ejaculation conditions and disorders did not meet the disproportionality threshold except for one PT Ejaculation delayed for the product andusomeran, and it should be noted that disproportionality was not meaningful due to low counts (1case count) reported for this product event combination. The literature review identified articles indicating COVID infection could affect the endothelial cells impacting endothelial function and cardiovascular health in males and thereby leading to ED. The literature review did not identify articles that proposes a plausible biological mechanism of action of mRNA vaccine leading to ED and/or articles that would suggest/imply a causal association between mRNA vaccination and ED. Overall, the review of the data from all the available data sources (MAH safety database, external safety databases, O/E analysis, and literature review) showed that there is insufficient evidence to suggest a reasonably possible causal association between use of mRNA vaccination and ED.

Conclusion	Overall, based on the analysis of all safety data available as of 17 Feb 2024 including the data from all sources as discussed above, the MAH considers that there is insufficient information to establish a causal relationship between the administration of SPIKEVAX and ED. The current CCDS (version 17.0) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified. The MAH will continue to carefully monitor ED 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 minimisation measures with regard to ED. The validated signal of ED is refuted and closed.

16.2.4 Pre-eclampsia, gestational hypertension and GD (P919)

Table 16-7 Pre-eclampsia, gestational hypertension and GD (P919)

Signal evaluation criteria	Summary
Source	The MAH considered gestational hypertension, pre-eclampsia, and GD as a validated signal, based on the results from the post-authorisation safety study mRNA-1273-P919, which are as follows: • A small but statistically significant increase in the risk of pre-eclampsia, gestational hypertension, and GD was observed following exposure to SPIKEVAX during pregnancy when compared to distantly vaccinated and unexposed populations. • The relative risk was more pronounced when exposure to SPIKEVAX occurred during the second trimester of pregnancy. • Pre-eclampsia, gestational hypertension, and GD did not show any statistical increase when compared to individuals with COVID-19 diagnosis during pregnancy.
Background	The MAH considered gestational hypertension, pre-eclampsia, and GD as validated signals, based on the results from the post-authorisation pregnancy safety study mRNA1273-P919. Hypertensive disorders in pregnancy are the common medical complications of pregnancy, affecting approximately 10% of pregnancies globally. Hypertensive disorders in pregnancy accounts for at least 14% of maternal mortality and 10-25% of perinatal deaths and affects the mother and new-born to varying degrees. Hypertensive disorders in Pregnancy may be chronic (predating pregnancy or diagnosed before 20 weeks of pregnancy) or de novo (either gestational hypertension or pre-eclampsia).
Methodology	The MAH GSDB was queried cumulative as of 17 Feb 2024, for valid case reports of gestational hypertension/pre-eclampsia and GD received from HCP, HA, consumers and literature, worldwide for SPIKEVAX(Original), both bivalent vaccines [SPIKEVAX Bivalent .214 (Original/BA.1) and SPIKEVAX Bivalent.222 (Original/BA.4/5)] and SPIKEVAX 2023-2024 Formula. • For the topic of Gestational hypertension and Pre-eclampsia, the MedDRA HLT of Hypertension associated disorders of pregnancy was used. This HLT included the following PTs: Eclampsia; Gestational hypertension; Haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; Mirror syndrome; Preeclampsia and

	Superimposed pre-eclampsia. • For the topic of GD, the MedDRA SMQ (Narrow)- Hyperglycaemia/new onset diabetes mellitus was used. It was applied to all pregnancy reports identified in the GSDB. This SMQ included the following PTs: Acquired generalised lipodystrophy; Alpha hydroxybutyric acid increased; Blood 1,5anhydroglucitol decreased; Blood glucose increased; Diabetes complicating pregnancy; Diabetes mellitus; Diabetes mellitus inadequate control; Diabetes with hyperosmolarity; Diabetic arteritis; Diabetic coma; Diabetic coronary microangiopathy; Diabetic hepatopathy; Diabetic hyperglycaemic coma; Diabetic hyperosmolar coma; Diabetic ketoacidosis; Diabetic ketoacidotic hyperglycaemic coma; Diabetic ketosis; Diabetic metabolic decompensation; Diabetic wound; Euglycaemic diabetic ketoacidosis; Fructosamine increased; Fulminant type 1 diabetes mellitus; GD; Glucose tolerance impaired; Glucose tolerance impaired in pregnancy; Glucose urine present; Glycated albumin increased; Glycated serum protein increased; Glycosuria; Glycosuria during pregnancy; Glycosylated haemoglobin abnormal; Glycosylated haemoglobin increased; Hepatogenous diabetes; Hyperglycaemia; Hyperglycaemic crisis; Hyperglycaemic hyperosmolar nonketotic syndrome; Hyperglycaemic seizure; Hyperglycaemic unconsciousness; Impaired fasting glucose; Insulin resistance; Insulin resistant diabetes; Insulin-requiring type 2 diabetes mellitus; Ketoacidosis; Ketonuria; Ketosis; Ketosis-prone diabetes mellitus; Latent autoimmune diabetes in adults; Maternally inherited diabetes and deafness; Monogenic diabetes; Neonatal diabetes mellitus; Neonatal hyperglycaemia; New onset diabetes after transplantation; Pancreatogenous diabetes; Pseudodiabetes; Steroid diabetes; Type 1 diabetes mellitus; Type 2 diabetes mellitus; Type 3 diabetes mellitus; and Urine ketone body present. • Additionally, all reports of pregnancies (cumulatively) in the global safety data base (GSDB) were identified through 17 Feb 2024. There were 5469 reports of pregnancy with 18,173 associated events. All the PTs associated with these reports were manually reviewed by a safety physician. Any preferred terms suggestive of a potential report of Gestational Hypertension, Pre-eclampsia, or GD were identified. Pregnancy reports with any of the following PTs were reviewed as potential cases by a physician, and included for the current review if they met the criteria for the events of interest: • Hypertension (17), Seizure (12), Blood pressure increased (8), Thrombocytopenia (7), Epilepsy (5), AKI (3), Blood glucose (3), Immune thrombocytopenia (3), Acute hepatic failure (2), Cluster headache (2), Pulmonary oedema (2), Blood pressure fluctuation (1), Chronic kidney disease (1), Epileptic encephalopathy (1), Hepatic failure (1), Hypertensive crisis (1), Protein urine (1), Protein urine present (1), Urine albumin/creatinine ratio (1). Once all potential reports of Gestational hypertension, Pre-eclampsia, Eclampsia, HELLP and GD were identified based on the above-described methodology, cases were classified following the case definitions presented in the Brighton Collaboration website from the article by Appendix 13.4 for gestational hypertension and preeclampsia (with and without severe features); and for GD using the case definition included in the article by Appendix 13.4. The Company causality assessment is provided utilising the WHO-UMC standardised case

	causality assessment.
Results	Cumulatively as of 17 Feb 2024, a total of 81 cases (excluding 2 cases of Eclampsia & HELLP [1 each]) were identified by the search strategy across the 3 topics of interest. Of the 32 Reports that were associated with Gestational Hypertension: • 2 reports clearly did not meet the case definition as the events occurred during the first trimester. (Both reports had otherwise very limited information). • 26 reports did not provide enough information to allow an assessment. They did not provide diagnostic information to document blood pressure measurement meeting the definition, and other than the reported terms, did not provide information to contribute to analysis of this topic. • These reports were reviewed in detail, and no pattern with regards to age, TTO, vaccine timing, etc. of interest was noted. • There are 4 (4) reports did meet the definition for gestational hypertension but did not provide enough information to assign a diagnostic level (proteinuria information was not available). Of the 4 reports, 1 case had WHO-UMC Causality of "Possible" and 3 cases were assessed "Unassessable", but generally provided limited information. Of the 26 Reports that were associated with the term Pre-eclampsia (1 also described eclampsia): • 1 report clearly did not meet the case definition as the events occurred during the first trimester (otherwise very limited information was provided). • 23 reports did not provide enough information to allow an assessment. They did not provide diagnostic information to document blood pressure measurement or evidence of proteinuria to meet the case definition, and other than the reported terms, did not provide information to contribute to analysis of this topic. • In addition, one case of eclampsia and one case HELLP were identified. Neither met the case definition. • The 2 (2) reports met the definition for pre-eclampsia of which one provided enough information to be considered Diagnostic Level 1 per the definition and another one (1) report provided enough information to be considered Diagnostic Level 2 per the definition. Of the 23 Reports that were associated with the term GD: • 2 cases were not a true pregnancy case (did not report an exposure during pregnancy). • 4 cases were categorised as Level 5, as they did not meet the case definition for GD. • 12 cases reported the diagnosis of GD and were categorised as level 4. • 5 cases were classified as Level 3, of which 3 were assessed as unlikely, 1 was assessed as possible, and 1 was un-assessable.
Discussion	The Moderna post-authorisation safety studies, particularly mRNA-1273-P919 and mRNA-1273-P903 studies, provided valuable insights into the potential association between SPIKEVAX™ vaccination and pregnancy outcomes. The results from mRNA-1273-P919 study, showed a small but statistically significant increase in the adjusted relative risk for preeclampsia, gestational hypertension, and GD when compared to distantly vaccinated and unexposed populations,

	particularly when exposure occurred during the second trimester. However, the outcomes did not show any evidence of increased risk for these outcomes when compared to COVID-19 infection during pregnancy. Results from mRNA-1273P903 study showed similar observation as mRNA1273-P919 study. The crude risk ratio was increased for GD and pre-eclampsia in mRNA-1273-P919. The results from the study mRNA-1273-P919 triggered the signal evaluation of these 3 topics gestational hypertension, pre-eclampsia, and GD. Review of RSI showed that Gestational hypertension, pre-eclampsia, and GD are not labelled as ADR in the current Moderna mRNA-1273 CCDS. Gestational hypertension, pre-eclampsia and GD are not labelled as an ADR in other COVID-19 vaccines label. There were 175 reports of pregnancy identified in mRNA-1273-P301. Of these 175 reports, there were 13 cases of the events of interest: gestational hypertension (3), pre-eclampsia (7), and GD (3). None of the 13 reports were considered related by the investigator. The observed long time to onset between vaccination and the events (152 – 582 days) make an association with vaccination unlikely. Additionally, many cases included other risk factors that confound potential association with vaccination. Medical review of these cases did not reveal any significant safety concerns related to pregnancy and the use of marketed Moderna vaccines targeting SARS-CoV-2. Review of the 60 reports for gestational hypertensive disorder, and 23 cases for GD from the GSDB revealed that there were only few reports that met the case definition for gestational hypertension (4); pre-eclampsia (2), and GD (5). Review of cases did not identify any sentinel case and/or any significant safety concern and/or any reasonably possible association between use of marketed Moderna vaccines targeting SARS-CoV-2 administration and the events gestational hypertension, pre-eclampsia, and GD. Literature review identified articles that demonstrated a potential association between COVID-19 infection itself and the events gestational hypertension, pre-eclampsia, and GD, though the finding were not consistent in all studies. Review of the literature articles did not identify any articles that may provide sufficient evidence of an association between gestational hypertension, pre-eclampsia, and GD and marketed Moderna vaccines targeting SARS-CoV-2 vaccination. Identified articles demonstrated that COVID mRNA vaccination does not affect the syncytiotrophoblasts and placental development. Several articles showed there was no consistent or significant increased risk of GD, gestational hypertension and pre-eclampsia following receipt of COVID-19 vaccination. The results from the external safety databases (EVDAS, VAERS) showed that the events gestational hypertension, pre-eclampsia and GD, did not meet the disproportionality threshold. Overall, the review of the data from all the available data sources (MAH safety database, Clinical trial data, external safety databases, epidemiological studies, and literature review) showed that there is insufficient evidence to suggest a possible causal association between use of marketed Moderna vaccines targeting SARS-CoV-2 and the 3 pregnancy-related outcomes at this point of time. The findings are consistent with the known safety profile of the vaccine, and the benefits of vaccination in the prevention of COVID-19 during pregnancy are clear. Continued surveillance and research are essential to monitor the safety of COVID-19 vaccines and to further understand their impact on pregnancy outcomes.
Conclusion	The comprehensive evaluation of available data from CTs, pharmacovigilance databases, external

	databases, epidemiological studies, and published literature does not substantiate a relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the occurrence of gestational hypertension, pre-eclampsia, or GD. While 2 post-authorisation safety studies (PASS) indicated a marginal increase in risk, these findings have not been corroborated by other data sources. The validated signal of gestational hypertension, pre-eclampsia, or GD is considered refuted and closed at this point of time. The MAH will continue to monitor Use during pregnancy (missing information in RMP), and these safety topics (gestational hypertension, preeclampsia, and GD) through routine pharmacovigilance activities. COVID-19 vaccination during pregnancy significantly reduces the risks of maternal SARS-CoV2 infection, hospitalisation, and ICU admission without increasing the risk of adverse pregnancy outcomes such as miscarriage, GD, or hypertension. These findings are reassuring and suggest that vaccination with the COVID-19 vaccines is safe during pregnancy. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive.

16.2.5 Ischaemic stroke

Table 16-8 Ischaemic stroke

Signal evaluation criteria	Summary
Source	The signal of "ischaemic stroke" was considered validated based on a CDC presentation at ACIP on 27 Jun 2024, showing a Vaccine Safety Datalink (VSD) statistical signal for ischaemic stroke for mRNA COVID-19 vaccines during the 2023-2024 season, requiring further evaluation. Statistical signal of ischaemic stroke was noted for the following: • Pfizer-BioNTech vaccine in patients 50-65 years of age, in the 1–21-day window. • Moderna COVID-19 Vaccine in patients 65 plus years of age, in the 1–42-day window.
Background	The MAH considered ischaemic stroke as a validated signal, based on the presentation by CDC at the ACIP meeting on 27 Jun 2024.
Methodology	The AHA/ASA Expert Consensus paper [15] emerged as the most accepted definition for stroke and Ischaemic Stroke and being referred to in numerous other literature article. It provided a very helpful and important flow chart to guide clinicians in diagnosing specifically an Ischaemic Stroke, with the end goal of accurate diagnosis leading to best treatment choices. This diagram (and accompanying elements) was especially useful for developing a robust case definition to be applied to the identified by our search strategy to find true cases of Ischaemic Stroke. It was supplemented with additional data from the AHA/ASA consensus document, and other sources, to help define details of what represented positive imaging, or which symptoms would be considered with consistent with ischaemic stroke. As well, this document provided definition for both haemorrhagic stroke and Transient Ischaemic Attack (TIA), and any cases meeting those definition rather than ischaemic stroke were identified if they met those definitions.

	With this additional information identified, this flow chart was applied to each report in a systematic way by a clinician. Definitions of how well each case described a potential case of ischaemic stroke given the nature of post marketed data were developed for use in this report. A Definite report of Ischaemic Stroke: • A definite case needed all the key elements. It had to include clinical symptoms consistent with an ischaemic stroke, and there had to be evidence that the symptoms lasted at least 24 hours. And there could not be a more likely disease process that explained the symptoms (e.g., migraines, trauma). As per the guidelines from AHA/ASA, if these conditions were met, imaging could be positive, or it could be not done/not provided/inconclusive. Cases were tracked as definite with positive imaging and definite without positive imaging, but they are treated equally in this report. • A report could also be considered definite for a silent infarction if there as positive imaging performed, but no specific symptoms provided. However, these would only be considering silent infarctions if the presenting events were deemed to last at least 24 hours. • For presentation all definite cases will be described together. A Likely report of Ischaemic Stroke: • A likely report of ischaemic stroke is one in which the imaging is positive, but 1 of the elements of the confirmatory symptoms is not provided. If a report had positive imaging and providing a symptom consistent with ischaemic stroke but failed to provide a timeframe for the symptoms, it will be defined as a likely case of ischaemic stroke. (note: if the symptoms were reported as less than 24 hours, then the case would be considered a TIA). • Similarly, if imaging is positive for ischaemic stroke, and no specific symptoms was included, but it was clear the event lasted greater than 24 hours, then the case will also be considered likely. A Probable report of Ischaemic Stroke: • A probable case of is stroke is defined for this report as in which imaging is not provided/unknown/inconclusive but a symptom(s) consistent with an ischaemic stroke are demonstrated. However, it is considered only probably because there was no data provided showing that the symptoms lasted more than 24 hours (that is, length of symptoms is unknown). • If symptoms provided are known to have resolved in less than 24 hours, this case would be considered a TIA. A Potential report of Ischaemic Stroke: • A report is considered only to be a potential ischaemic stroke if imaging is not provided/unknown/inconclusive, and no specific symptoms c/w ischaemic stroke is provided. However, a term consistent with ischaemic stroke was provided, and it was noted that the event lasted more than 24 hours. A Term Only report of Ischaemic Stroke:

	• A report is term only for an ischaemic stroke if imaging is not provided/unknown/inconclusive, no specific symptoms consistent with ischaemic stroke are demonstrated, and the timing of the events is unknown (no proof they lasted more than 24 hours). Effectively, the only positive evidence of an ischaemic stroke is that a term consistent with ischaemic stroke was provided by the reporter. Finally, if upon review a case was determined to be a TIA (e.g. symptoms we noted to have resolved in less than 24 hours), or a Haemorrhagic Stroke (e.g., the presenting symptoms and/or imaging were consistent with a haemorrhagic stroke (without evidence it evolved from an ischaemic stroke), they were categorised as such.
Results	Cumulatively as of 09 Jul 2024, review of GSDB search retrieve, a total of 663 cases were identified by the search strategy. Overview of the Reports Age and gender were broadly consistent with the epidemiology of Ischaemic Stroke. In terms of gender, there were 360 males (54.3%), 298 females (44.9%), and gender was not provided in 5 reports. In terms of age, the average age of these patients was 64 years. The median age was also 64 years. Age ranged from 20 to 96 years. Age was provided in all but 13 reports. Six hundred and sixty-one (661) reports were serious (99.7%). Most reports, 658 (99.2%) were spontaneous, with only 5 literature-non-study reports. Reports came from a wide variety of countries, with the United States and France providing the largest number of reports. United States (n=180), France (n=144), Italy (n=67), Switzerland (n=58), Taiwan (n=36), Germany (n=34), Netherlands (n=30), UK (n=21), Spain (n=12), Slovakia (n=10), Sweden (n=8), Australia (n=7), Austria (n=6), Poland (n=6), Greece (n=5), Portugal (n=5), Brunei (n=4), Thailand (n=4), Belgium (n=3), Argentina (n=2), Canada (n=2), Croatia (n=2), Czech Republic (n=2), Denmark (n=2), Japan (n=2), Lithuania (n=2), Cyprus (n=1), Estonia (n=1), Israel (n=1), Latvia (n=1), Luxembourg (n=1), Norway (n=1), Philippines (n=1), Singapore (n=1), and Romania (n=1) Overview of Reports by Case Definition and WHO-UMC Causality All reports were reviewed by a clinician to see if they met case definition for Ischaemic Stroke, using the definitions outlined above. The results were: • 15 were determined to be reports with TIA as a more likely diagnosis. • 38 were determined to be reports with haemorrhagic stroke as a more likely diagnosis. • 265 had only a reported term consistent with ischaemic stroke, but no elements of an ischaemic stroke were provided. • 102 reports described a potential case of ischaemic stroke. • 61 reports were determined to be probable reports of ischaemic stroke, with only limited details supporting this diagnosis provided. • 70 reports described a likely case of ischaemic stroke. • 112 reports described definite reports of ischaemic stroke. Regardless of the whether the reports met the case definition, all reports were reviewed for potential causal association with mRNA-1273 by a clinician. As 345 reports were identified as at

	least a potential case of Ischaemic Stroke, they were further reviewed to determine if any pattern indicating a potential safety signal was discernible. As with the overall review, age and gender were consistent with epidemiology of ischaemic stroke. A review of the dose number and time to onset after vaccination did not show a clear pattern across these reports and was consistent with an event more closely related to the patient's underlying disease and risk factors rather than causally related to vaccination. Review of the clinical course, presenting symptoms, and diagnostic findings also failed to identify any concerning pattern. The presenting symptoms were not consistent across reports and reflected a range of underlying vascular structures and causes of ischaemic stroke that would be expected in the general population experiencing stroke. Diagnostic findings (MRI and CT) did not show a consistent pattern in terms of the location or evolution of the ischaemic injury. Clinical examination was similar. As part of the careful review of these reports at least providing minimum data consistent with the diagnosis of ischaemic stroke, the potential causal association was confirmed and demonstrated a similar pattern to the overall reports. Amongst these 345 reports: • Ninety-nine (99) of the reports were deemed Unassessable. These reports did not include key clinical data elements to allow a causal assessment. These reports were all missing at least 3 critical data elements, including past medical history, concomitant medications, details of the clinical course of the events, information on the time to onset vis a vis vaccination, treatment details, diagnostic results, or age/gender. • Two hundred and forty (240) of the reports were deemed as Unlikely. These reports contained strong confounding factors that provide a plausible explanation for the event. These reports contained at least 2 or more risk factors for ischaemic stroke (as outlined in the background of this document), or other concurrent disease processes that are more likely the cause of the report of Ischaemic Stroke. • No reports described elements that would suggest either Probably/Likely or Certain causal association. Six (6) reports described a Possible causal relationship to mRNA-1273. **Additional Analysis: Concomitant/Co-Suspect Influenza Vaccination:** No pattern was noted concerning the concomitant use of influenza vaccine across the 663 reports. Only 8 (1.2%) of the reports described concomitant influenza vaccination (n=2) or influenza vaccine as a co-suspect (n=6). No reports described the influenza vaccination as "high-dose" or adjuvanted. Notably, reports of concurrent use occurred in older patients, range 71-94, average age 82. One patient did not have a reported age. In terms of case definition, 4 of these reports contained an Ischaemic Stroke term only. One described a TIA, not meeting the definition of stroke. Only 3 were likely or definite reports of ischaemic stroke. 2 these were strongly confounded. The remaining case is described in the table above, and the concomitant influenza vaccine use is highlighted. Given the small number of reports with concurrent influenza vaccination, and the limitations of post-marketing data, no conclusion regarding the concomitant use of Spikevax and influenza vaccine can be determined from review of the GSDB.

Discussion	A statistical signal for ischaemic stroke and administration of Spikevax vaccines, including concurrent administration of high-dose influenza vaccines, was presented by the CDC during the ACIP meeting on 27 Jun 2024. The signal was identified in the VSD for the time period of 10 Sep 2023, through 27 Apr 2024, evaluating first COVID-19 vaccine dose received during this period. Statistical signals were noted for both marketed mRNA COVID-19 vaccine: • For Pfizer vaccine, a statistical signal for ischaemic stroke was noted in the age group of 1864 years of age, in the 1–21-day window after vaccination. This signal was especially notable in the age group of 50-64 years of age and was not seen in those aged 18-49 upon sub-analysis. • For the Moderna vaccine, a statistical signal for ischaemic stroke was noted in the age group of 65 years plus, in the 1–42-day window after vaccination. • For Moderna, the signal was only statistically significant when the vaccine was given the same day as influenza vaccine. (2.53, 1.10-5.91), although the CI was quite wide. The CDC noted that there was a lack of consistent finding across age groups or risk interval. The concluded that this season's findings are consistent with CDC Immunisation Safety Office's prior interpretation based on data review in Oct 2023 that stated: "Available data do not provide clear and consistent evidence of a safety problem for ischaemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccines" still, the MAH considered this a validated signal, and undertook a signal evaluation of ischaemic stroke in association with all Spikevax variants, reviewing all available data. Review of RSI showed that ischaemic stroke is not labelled as ADR in the current Moderna mRNA 1273 CCDS. Ischaemic stroke is not labelled as an ADR in other COVID-19 vaccines label. In terms of clinical data, cases of ischaemic stroke from the mRNA-1273-301 study were reviewed. Seven (7) reports were identified. One (1) report occurred in a subject after receive placebo, and 6 reports occurred after receiving vaccination. Given the design of this study, in which all subject receiving placebo in part A were offered vaccination in the open-label Part B, this ratio of reports was in line with the exposure time to placebo and vaccine. Notably, none of these cases, other than the placebo case, occurred at least 60 days after vaccination, outside the window noted by the CDC and all occurred in elderly subjects who are at higher risk for ischaemic stroke. In terms the GSDB, 663 reports of ischaemic stroke were identified. Three hundred forty-five (345) of these reports were identified as at being at least a potential report of ischaemic stroke when case definitions based on the AHA/ASA Consensus Expert report were applied. Careful review of these reports, including review of age, gender, time to onset, dose number, clinical course, presenting symptoms, did not identify a consistent pattern suggesting a causal association with mRNA-1273. On an individual report basis, 99 of these reports were deemed to have an Unassessable causality as they did not provide sufficient information to review an association. A further 240 reports were deemed to have an Unlikely causality as they described patients with at least 2 risk factors for ischaemic stroke or had another concurrent disease process that provided a plausible explanation for the events.

	None of the reports described elements suggesting a Probably/Likely or Certain causal association with mRNA-1273. Only 6 reports were determined to have a Possible causal association. All 6 of these reports contained a relatively limited amount of clinical data, and all 6 described at risk factor for ischaemic stroke. Review of available epidemiological data focused on the US PASS mRNA-1273-P920. In this study, no increased risk ischaemic stroke following exposure to elasomeran/davesomeran or andusomeran was observed compared to influenza vaccinated cohort and medically-attended COVID-19 cohort within 1-28 days. The secondary analysis concluded no increased risk ischaemic stroke following exposure to Elasomeran/davesomeran or andusomeran with or without coadministration of influenza vaccine was observed compared to influenza vaccinated cohort and medically-attended COVID-19 cohort within 1-28 days. Further, the sensitivity analysis showed no increased risk of ischaemic stroke following exposure to elasomeran/davesomeran or andusomeran with or without coadministration of influenza vaccine was observed compared to influenza vaccinated cohort within 1-21- and 22-42-days. Review of the literature did not identify any articles that may provide sufficient evidence of a causal association between Ischaemic stroke and SPIKEVAX vaccination. Generally, ischaemic stroke was shown to be causally associated with COVID-19 infection, and several mechanisms of action for such an association were speculated in the literature. However, none of these mechanisms were demonstrated to be pertinent for vaccination, and the literature review failed to support a safety issue of concern. The results from the external safety databases (EVDAS, VAERS) showed ischaemic stroke did not meet the disproportionality threshold on a consistent basis. Overall, the review of the data from all the available data sources (MAH safety database, Clinical trial data, external safety databases, epidemiological studies, and literature review) showed that there is insufficient evidence to suggest a potential causal association between use of marketed Moderna vaccines targeting SARS-CoV-2 and ischaemic stroke at this point of time; the Company considers ischaemic stroke as a refuted signal. The findings are consistent with the known safety profile of the vaccine, and the benefits of vaccination in the prevention of COVID-19 is clear. The MAH will continue to monitor ischaemic stroke as part of its pharmacovigilance activities and will add ischaemic stroke as a close monitoring event.
Conclusion	The comprehensive evaluation of available data from CTs, pharmacovigilance databases, external databases, epidemiological studies, and published literature does not substantiate a relationship between the administration of marketed Moderna vaccines targeting SARS-CoV-2 and the occurrence of ischaemic stroke, including co-administration with influenza vaccines. While the CDC presented a statistical signal at the ACIP of an increased risk of ischaemic stroke in those over 65 years of age, especially with concomitant influenza use, these findings have not been corroborated by other data sources. The MAH concludes that there is insufficient evidence to support a causal association between SPIKEVAX administration (marketed Moderna vaccines targeting SARS-CoV-2) and ischaemic stroke; the Company considers ischaemic stroke as a refuted signal. The MAH will continue to monitor ischaemic stroke as part of its pharmacovigilance activities and will add ischaemic stroke as a close monitoring event.

	COVID-19 vaccination has been shown to reduce stroke risk over time, as it reduces COVID-19 infection and its sequalae. These findings are reassuring and suggest that vaccination with the COVID-19 vaccines is safe for older patients. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive.

16.2.6 Dermatitis allergic

Table 16-9 Dermatitis allergic

Signal evaluation criteria	Summary
Source	The MAH considered dermatitis allergic in association with Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) as a validated signal following a request from Saudi-FDA to present hypotension in next Spikevax PSUR. Saudi-FDA identified this signal from medical literature with elasomeran but did not share the source.
Background	Generally, a medical definition of allergic dermatitis was not consistently identified. When searching for this term, it usually returned allergic contact dermatitis. • Several sources noted the 2 terms as basically interchangeable, • True allergic contact dermatitis is Type IV, T-cell-mediated allergic reaction, and symptoms should be consistent with that. **Overview of Allergic Contact Dermatitis (ACD)** Allergic contact dermatitis as defined by Mayo Clinic and the American Academy of Allergy, Asthma, and Immunology is a skin reaction caused by exposure to allergens, triggering an immune response. This form of dermatitis is a delayed-type hypersensitivity reaction, typically occurring hours to days after contact with an allergen. Common allergens include metals (e.g., nickel), cosmetics, fragrances, medications, and plants such as poison ivy. **Incidence and Risk Factors** ACD can affect people of all ages, but it is more common in those with a genetic predisposition to allergies or those repeatedly exposed to allergens. Occupations like healthcare, construction, cosmetology, and food service often involve higher risk due to frequent exposure to irritants and allergens.
Methodology	The evaluation of the occurrence of dermatitis allergic in association with the administration of Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) used in the indication of Covid-19 was performed using several data sources. The methods of evaluation and the results obtained from each of the analysed data sources are described below: **Non-Clinical Data** There are no data to assess the effects of vaccine on Dermatitis allergic in (SPIKEVAX IB v. 9.0) **Clinical Trial Data** The Data from the CTs listed in the Table-xx was reviewed to identify cases reporting the MedDRA PTs in section 3.2.1.

	The topic of dermatitis allergic was reviewed in the clinical trial setting using the following search criteria using MedDRA PT: Dermatitis allergic. Any report with this MedDRA PT, within 2 weeks of vaccination were retrieved and reviewed.
Results	Review of clinical trial data showed the relevant data on dermatitis allergic from study mRNA-1273P301; mRNA-1273-P203 and mRNA-1273-P204, remaining studied had no reports related to dermatitis allergic. There were 14 reports of which 4 were reported within 2 weeks of the study vaccination. The cumulative search of the GSDB (Cumulative through 17Sep2024) retrieved 573 cases (2 cases were invalid). There were 576 events reported across the 573 cases (3 cases reported same PT more than once). The majority of cases were reported in the European Economic Area, the UK, and the United States. As a known factor, Female patients were accounted for the majority of cases (78.0%). There were cases (2.3%) for which gender information was not reported. A significant portion of cases (34.5%) had an unknown dose number. The average time to onset was approximately 2 weeks, but with a large standard deviation, indicating high variability among cases. The scientific literature search retrieved 476 literature hits of which, most of these (90%) articles discuss the different types of Dermatitis, such as, atopic Dermatitis, Psoriasiform Dermatitis, and Allergic Contact Dermatitis. Of the 40 articles, most described Dermatitis allergic and covid-19 infection or were associated with Dermatitis allergic and adenoviral vector vaccines. Review of these literature hits did not identify any articles that could provide sufficient evidence of an association between Dermatitis allergic and SPIKEVAX vaccination. • No new Individual Case Safety Reports (ICSRs) beyond what was already documented in the Company's safety database were identified. • There were few articles which speculated mechanism etc., but none of these articles confirmed a well-established mechanism associated with Dermatitis allergic and mRNA vaccination. However, there are multiple articles describing the association of Dermatitis allergic with COVID-19 infection were selected 3 articles describing the Dermatitis allergic with COVID-19 infection. • Battis N, Ekstein SF, Cosky E (Eugene P, Neeley AB. Patient Reported Association Between COVID-19 Infection or Vaccination and Onset of Allergic Contact Dermatitis. Dermatitis® 2024. • Daneshbod Y, Ahmed I, Kerstetter J. Psoriasiform Dermatitis Associated With the Moderna COVID-19 Messenger RNA Vaccine. Cutis. 2022;110(5):E1–4. • Sidlow JS, Reichel TR, Reichel M, Lowenstein EJ. Localised and generalised urticarial allergic dermatitis secondary to SARS-CoV-2 vaccination in a series of 6 patients. Jaad Case Reports. 2021;14:13–6. In summary, review of the literature did not identify any articles that may provide sufficient evidence of a causal association between Dermatitis allergic and SPIKEVAX vaccination.
Discussion	• No disproportionate reporting of Dermatitis allergic was observed in EVDAS or VAERS,

	• No pattern was identified regarding Dermatitis allergic during CTs, • Literature output review was inconsistent for Dermatitis allergic association with vaccination, • Post marketed data review showed that majority of cases were spontaneous type reports (of 571 cases only 4 were literature non-study reports) lacking important information (e.g medical history and/ or concomitant medications); there were 209 cases (36.6.%) unassessable; 145 (25.4%) cases reported confounding factors. Reported local events (rash, pruritus, erythema, swelling, etc.) are listed in current CCDS, • Review of labelling of other COVID-19 Vaccines revealed that Dermatitis allergic is not listed in other manufacturer's labels (Pfizer/BNT162b2, Janssen and Novavax).
Conclusion	Symptoms of dermatitis allergic are adequately reflected in current CCDS. Besides, the higher severity events of Hypersensitivity and Anaphylaxis are listed as well. The current CCDS (version 19.0) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified. The cumulative safety data evaluated does not provide a sufficient basis for new recommendations or product labelling changes and/or RMP, including relevant risk minimisation measures with regard to Dermatitis allergic. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive. The MAH will continue to monitor through routine pharmacovigilance activities.

16.2.7 Hypotension

Table 16-10 Hypotension

Signal evaluation criteria	Summary
Source	The MAH considered hypotension in association with Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) as a validated signal following a request from Saudi-FDA to present hypotension in next Spikevax PSUR. Saudi-FDA identified this signal from medical literature with elasomeran but did not share the source.
Background	Hypotension is a decrease in systemic blood pressure below accepted lower bound values, which is any blood pressure below 90/60: that is if the systolic blood pressure if below 90 mm Hg, or the diastolic is below 60 mmHg, it is considered hypotension. While much more rarely used, hypotension can also be considered when the mean arterial pressure (2/3 diastolic + 1/3 systolic) is below 65 mm Hg. While hypotension can be accompanied by symptoms, they are not necessary for diagnosis. In fact, the condition is often underdiagnosed because it is often not symptomatic. Hypotension may be subclassified as orthostatic in nature if there is a documented drop of 20 mm Hg systolic, or 10 mm Hg when the patient changes from lying to standing.
Methodology	The evaluation of the occurrence of Hypotension in association with the administration of Spikevax (all marketed Moderna vaccines targeting SARS-CoV-2) used in the indication of Covid-19 was performed using several data sources.

Results	**Non-Clinical Data** There are no data to assess the effects of vaccine on hypotension in (SPIKEVAX IB v. 9.0). **Clinical Trial Data** The topic of hypotension was reviewed in the clinical trial setting using the following search criteria using MedDRA PTs: Hypotension, Orthostatic hypotension, Diastolic hypotension. Review of clinical trial data showed the relevant data from study mRNA-1273-P301 and mRNA-1273P304, remaining studied had no reports related to hypotension. **Clinical Trial Study mRNA-1273 P301** In part A of this trial (the first portion which was blinded, with a 1:1 vaccine to placebo ratio), a total of 27 events of hypotension in 25 separate subjects was identified. **Clinical Trial Study mRNA-1273-P304** This trial did not have a placebo control, so all reports identified received mRNA-1273. Notably, these patients, who were all immunocompromised, had significant medical history and a number of potential confounders. A total of 4 reports were identified. Three had underlying liver disease/transplant, and 1 had underlying kidney disease/transplant leading to their immunocompromised status. They ranged in age from 49-67 year. No cases were identified in the paediatric trials (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P306). Overall, review of the data seen in clinical did not demonstrate any signal of concern for an association between mRNA-1273 immunisation and hypotension. **Company GSDB** Cumulatively, a total of 2,515 hypotension cases (2,515 events) of which 906 (36.0 %) were reported as serious cases were retrieved from the Company GSDB in association with SPIKEVAX. Out of the total 2515 cases, 99 cases reported a fatal outcome. Most reports came from the US and Europe. Almost two-thirds of the reports were non-serious. The age range of the reports was wide, with mild peaks at 25-39 years, and 50-64 years. No specific pattern in terms of dose number was noted, and number of reports declined with the number of doses, as would be expected given the use of the vaccine. Time to onset had an average of 10.8 days, but a median of just 1 day. This is consistent with many of reports describing vasovagal reactions to vaccination, as is seen with all vaccines. Most reports were either deemed to not be true reports of hypotension (n=231) or did not provide enough information to assign a definition (n=1487). Another 433 reports failed to provide a blood pressure measurement but did provide symptoms consistent with hypotension that were not due to another aetiology and were at least Potential reports of hypotension. Three hundred sixty-six (366) did meet the Definite case definition, providing a blood pressure below 90/60. Amongst these reports meeting the case definition, no pattern representing a safety concern for Spikevax was noted. Only 27 of these Definite reports were deemed to be possibly related to Spikevax. Most of these 27 reports did have potential confounders for the event of hypotension, and generally they provided very limited information that would allow a full review of a potential causal association. These 27 reports were mild in nature, often not requiring medical intervention beyond fluid intake. More than half were consistent with vasovagal symptoms commonly seen with all vaccines.

	Review of the GSDB identified no sentinel cases and did not demonstrate a consistent pattern that could represent a safety signal for Spikevax and a potential association with hypotension.
Discussion	Hypotension is often associated with other diseases, including COVID-19 itself. Vasovagal symptoms, due vasovagal hypotension, have been associated with all vaccines, and is related to vaccine process, not the vaccine itself. Review of multiple data sources failed to identify an association between Spikevax itself and events of hypotension: • Observed vs. expected analysis did not demonstrate an elevated reporting rate for hypotension. • Review of EVDAS and VAERS did not provide any significant disproportionality. • Review of the clinical trial data did not demonstrate any signal of a safety concern. • Review of the literature failed to identify an association between Spikevax immunisation and hypotension, nor an established mechanism for such an association. • Review of the Post-Marketing database did not identify any signal of concern.
Conclusion	Based on the review of all data presented in this report, the cumulative evidence shows an insufficient data to support a causal association between validated signal of hypotension and Spikevax vaccination; the Company considered Hypotension as a refuted signal. The current CCDS (version V19) is considered to adequately reflect the safety profile of SPIKEVAX. No new or emerging safety issues of concern were identified. The cumulative safety data evaluated do not provide a sufficient basis for new recommendations or product labelling changes and/or RMP, including relevant risk minimisation measures with regard to hypotension. The validated signal of hypotension is considered as refuted signal and closed at this point of time. The benefit-risk profile of the marketed Moderna vaccines targeting SARS-CoV-2 continues to remain positive. The MAH will continue to monitor hypotension through routine pharmacovigilance activities.

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 clinically relevant new safety information for this topic. The characterisation of this important risk as described in Section 16.4, remains valid.

A thorough evaluation of information receiving during this PBRER #7 reporting interval relating to the use of marketed Moderna vaccines targeting SARS-Cov-2 and known important identified risk of anaphylaxis has not identified any additional clinically relevant new safety information.

Table 16-11 Anaphylaxis

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
Source of New Information	• Moderna GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 132 o New and Significant Safety Information: There was no new and significant safety information identified. Refer to Section 11 for additional information.
Background	Anaphylaxis is a listed event for SPIKEVAX. The MAH's CCDS contains specific guidance that the vaccine is contraindicated in individuals with known severe allergic reactions to any component of the vaccine or to a previous dose of the vaccine, including, any subsequent doses should not be given to those who have experienced anaphylaxis to the first dose of SPIKEVAX. Further, it specifies that appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Guidance is also included for close observation for 15 mins for all persons receiving the vaccine and for 30-minutes for people with a history of allergic reaction/anaphylaxis to another vaccine. Anaphylaxis is considered an important identified risk only for the PBRER. Anaphylaxis was removed from the RMP as an important identified risk and reclassified it as an identified risk (not important). While anaphylaxis, remains as an identified risk for the product, as with any other biologicals, it does not have a considerable impact on the benefit-risk balance of the vaccine.
Methods of Evaluation	The MAH applied the MedDRA SMQ "anaphylactic reaction" (narrow scope) to retrieve all cases in the review period reporting AEs suggestive of anaphylaxis from the GSDB for individuals who received marketed Moderna vaccines targeting SARS-CoV-2. Cases were classified following the Brighton Collaboration case definition for Anaphylaxis [16,17]. The Company causality assessment was provided utilising the WHO-UMC standardised case causality assessment.
Results:	Refer to Appendix 12.7 for additional information. *Overview of Anaphylaxis Cases involving elasomeran:* It is important to note that the MAH terminated the distribution of elasomeran vaccine worldwide after June 2023. During the reporting period, the MAH received 36 serious cases (36 serious events) containing the reported PT of anaphylaxis. Of these, 26 cases were medically confirmed. The majority of cases (27 cases, 75.0%) were reported in females, compared to 8 cases (22.2%) in males, with 1 case (2.8%) lacking gender information. The mean age was 44.7 years (SD: 13.6), and median age was 46.0 years (range: 15.0 to 70.0 years).

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	There was one case ([redacted]) with a reported fatal outcome. This involved a male patient of unknown age, who after receiving the first dose of elasomeran reportedly developed multiple AEs. However, anaphylaxis was not a reported event in this case. The events experienced by this patient were likely complications arising from progression/worsening of the underlying pre-existing comorbidities involving multiple organs (generalised atherosclerosis, condition after a previous heart attack, cardiomyopathy, cirrhosis of the kidneys, lung changes including pleural and pericardial effusions, hyperaemic gastritis) and a concurrent infection which provided a more likely explanation of the reported events in this case (circulatory failure, shock due to pulmonary oedema). *Overview of Anaphylaxis Cases involving elasomeran/imelasomeran:* During the reporting period, no cases were received for elasomeran/imelasomeran. *Overview of Anaphylaxis Cases involving elasomeran/davesomeran:* During the reporting period, the MAH received 4 serious medically confirmed cases (4 serious events) containing the PT of anaphylaxis. The majority of cases (3 cases,75.0%) were reported in females, compared to 1 case (25.0%) in males. The mean age was 64.0 years (SD: 15.5) and median age was 58.0 years (range: 53.0 to 87.0 years). There was one case [redacted] with a reported fatal outcome. Anaphylaxis (PT) was not a reported term in this case, which involved an 87- year-old male patient with known concurrent Interstitial Lung Disease (ILD). The patient also experienced the event of shock, which occurred 8 months after vaccination with elasomeran/davesomeran. *Overview of Anaphylaxis Cases involving andusomeran:* During the reporting period, the MAH received 13 serious cases (13 serious events) containing the PT of anaphylaxis. There were 10 medically confirmed cases involving andusomeran. The majority of cases (8 cases, 61.5%) were reported in females, compared to 5 cases (38.5%) in males. The mean age was 72.2 years (SD: 20.1) and median age was 77.0 years (range: 29.0 to 95.0 years). One case was missing age information. There were 2 cases [redacted] with a reported fatal outcome. In both cases, anaphylaxis (PT) was not a reported term. Additionally, a delayed latency/ time to onset (TTO) of >1 day noted, which is atypical in the context of vaccine induced anaphylaxis. Alternative aetiologies provided a more likely explanation of the reported event(s) in both cases. *Overview of Anaphylaxis Cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula*

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	During the reporting period, the MAH received 3 serious cases (3 serious events) containing the PT of anaphylaxis. There were 2 medically confirmed cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The majority of cases (8 cases, 61.5%) were reported in females, compared to 1 case (33.3%) in males. The mean age was 44.0 years (SD: 26.9) and median age was 44.0 years (range: 25.0 to 63.0 years). One case was missing information on age. There were no cases with a fatal outcome. *Overview of Anaphylaxis Cases Involving SARS-CoV-2 JN.1 mRNA:* During the reporting period, the MAH received 4 serious medically confirmed cases (4 serious events) containing the PT of anaphylaxis. The majority of cases (3 cases, 75.0%) were reported in females, while 1 case (25.0%) was missing gender information. The mean age was 66.0 years (SD: 17.8) and median age was 60.0 years (range: 52.0 to 86.0 years). There were no cases with a fatal outcome. *Overview of Anaphylaxis Cases Involving SPIKEVAX NOS:* During the reporting period, the MAH received one serious medically confirmed case cases (one serious event; non-fatal) containing the reported PT of anaphylaxis. The reported case involved a female (1 cases, 100.0%).
Discussion	A total of 61 cases were reported during this period, containing the reported term of anaphylaxis across various Moderna SARS-CoV-2 vaccines, including 4 cases with fatal outcomes. These cases were assessed using the Brighton Collaboration Criteria (BCC) and the WHO causality criteria, as follows: • Level 1: 1 case (WHO causality: Unlikely), • Level 2: 3 cases (WHO causality: 1 possible, 2 probable), • Level 3: 2 cases (WHO causality: 1 probable, 1 possible), • Level 4: 32 cases (WHO causality: 1 possible, 31 unassessable), • Level 5: 23 cases (cases not meeting the BCC case definition of anaphylaxis). Analysis of reported cases of anaphylaxis, including the events following the administration of marketed Moderna vaccines targeting SARS-CoV-2 are consistent with the known safety profile of the vaccines. Overall, a causal association between the marketed Moderna vaccines targeting SARS-CoV-2 and the event of anaphylaxis is considered of at least a reasonable possibility.
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 anaphylaxis, reported in temporal association with the

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	administration of marketed Moderna vaccines targeting SARS-CoV-2 did not raise any safety issue of concern. The MAH will continue to monitor events for anaphylaxis using routine surveillance. The benefit-risk evaluation remains positive.

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

Table 16-12 Myocarditis and Pericarditis

Important Identified Risk	Myocarditis and Pericarditis
Source of New Information	• Moderna GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 195 o New and Significant Safety Information: 1 o During the reporting period, the EMA requested to include MAH's reflection and discussion on the article "Myocardial injury safety signal for mRNA COVID-19 vaccines (Myocarditis After COVID Vaccination (MACiV) study findings)" [10] in the upcoming PBRER.
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 7 days after Dose 2.
Methods	Cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [16,17], and the CDC working case definition [18] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilising the WHO-UMC standardised case causality assessment (WHO 2013).
Results	*Myocarditis and Pericarditis Cases Involving Elasomeran* During the review period, the MAH received 185 serious cases (195 events) of myocarditis and pericarditis following receipt of elasomeran. Majority of cases were from health authorities. There were 114 medically confirmed cases, and 2 cases reported a fatal outcome (one case is a possible duplicate) for the events of myocarditis or pericarditis. A total of 103 (55.7%) cases involved males

Important Identified Risk	Myocarditis and Pericarditis
	and 79 cases (42.7%) involved females; 3 cases (1.6%) were missing gender information. The mean age of the patients was 42.7 (SD:15.3), with a median 42.0 years (range 17.0 to 84.0 years); 16 cases were missing age data (See Appendix 12.8). A total of 64 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 Brighton Collaboration case definition for myocarditis and pericarditis, 26 cases met Level 1 definition, 25 cases met Level 2 definition, 8 cases met Level 3 definition, 122 cases met Level 4 definition, and 4 cases met Level 5 definition. According to the CDC working definition, 14 cases were classified as "Confirmed"; 41 cases were classified as "Probable"; 126 cases were classified as "Unassessable"; and 4 cases were considered "Not a case" of myocarditis or pericarditis (Appendix 12.8). According to the WHO causality assessment, 39 cases considered "Possible"; 105 cases considered "Unassessable", 37 cases considered "Unlikely" related to the vaccine, and 4 cases were not assessed as they were not considered a case of myocarditis or pericarditis. There were 2 cases which reported a fatal outcome for the events of myocarditis and/or myopericarditis and/or Pericarditis and these are summarised below: [redacted] A 33-year-old female patient with medical history of asthma and family history of cardiomegaly, experienced Pericarditis constrictive, Pleural effusion, Re-expansion pulmonary oedema, Pericardial fibrosis, Cardiac valve disease, Oedema peripheral, Ascites, Congestive hepatopathy, Pneumothorax, Pulmonary oedema, Vasculitis, Cardiac failure, Pectus excavatum, Ventricular extrasystoles, Hepatosplenomegaly, Anaemia and Weight decreased. The event of pectus excavatum occurred about 8 months after 2nd dose of mRNA-1273 and Ventricular extrasystoles 10 months and all the other events occurred about one year and a half after the same dose. The patient received third dose with Tozinameran. It was reported that the patient initially presented with symptoms of increased work of breathing, wheeze on exertion and cough about 5 months after 2nd dose with mRNA-1273 vaccine; treatment for suspected asthma exacerbation was initiated, which later evolved into concerns of heart failure following persistent symptoms and abnormal chest radiograph findings. Despite various investigations and consultations, including CT and MRI imaging, a definitive diagnosis remained elusive, and a cardiac MRI was consistent with constrictive physiology. A possible diagnosis of transient viral cardiomyopathy was proposed. Later the patient experienced recurrent pleural effusions and persistent symptoms, prompting ongoing medical intervention and multidisciplinary collaboration. 1. 5 litres of pleural fluid was drained from her right-side lung. The fluid was found to be exudative in nature with fluid protein measured at 35 g/L. Reactive mesothelial cells were also found in subsequent cytology, but there were no malignant cells seen. There were no infective organisms. The pleural effusion was thought to be reactive in nature. Despite efforts to manage the

Important Identified Risk	Myocarditis and Pericarditis
	condition, the patient's clinical status progressively deteriorated, ultimately leading to a fatal outcome. The reported cause of death was Pleural fluid exudate, Constrictive pericarditis and Re-expansion pulmonary oedema. An autopsy was performed which determined cause of death was Hepatic congestion, Lung oedema, Ascites, Pericardial fibrosis, heart valve disorder, Vasculitis, Peripheral oedema and Collapse of lung. As per the BCC the case met Level 1 definition (autopsy report showed pericarditis). According to WHO causality, the assessment is Unlikely considering there is a long onset latency, and the patient's medical history and family history (cardiomegaly), third dose with Tozinameran, and suspected viral cardiomyopathy were considered as potential confounding factors. [redacted] This case appears to be a potential duplicate of the above-mentioned case [redacted]. *Myocarditis and Pericarditis Cases Involving Elasomeran/Imelasomeran* During the review period, the MAH received 5 serious cases (5 events) of myocarditis and pericarditis following the receipt of elasomeran/imelasomeran. There were 4 medically confirmed cases, and no cases reported a fatal outcome for the events of myocarditis or pericarditis. A total of 2 cases (40.0%) involved males and 3 cases (60.0%) involved females. The mean age of the patients was 53.2 (SD: 19.0), with a median 50.0 years (range 33.0 to 81.0 years) There were 3 events (60.0%) reporting an outcome of "Recovered." According to the Brighton Collaboration case definition for myocarditis and pericarditis, 1 case met Level 3 definition, and 4 cases met Level 4 definition. According to the CDC working definition (Gargano 2021), 1 case was considered "Probable"; and 4 cases were considered "Unassessable." According to the WHO causality assessment, 4 cases considered "Unassessable", and 1 case was considered "Unlikely" related to the vaccine. *Myocarditis and Pericarditis Cases Involving Elasomeran/Davesomeran* During the review period, the MAH received 1 serious case (1 event) of myocarditis and pericarditis following receipt of elasomeran/imelasomeran. This case involved a female with an unknown age. The event was reported as "Not recovered." According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, the case met Level 4 definition. According to the CDC working definition, the case was considered "Unassessable." According to the WHO causality assessment, the case was considered "Unlikely" related to the vaccine. *Myocarditis and Pericarditis Cases Involving Andusomeran* During the review period, the MAH received 33 serious cases (34 events) of myocarditis and pericarditis following the receipt of andusomeran. There were no cases reporting a fatal outcome for the events of myocarditis or pericarditis. A total of 17 cases (51.5%) involved males, 15 cases (45.5%)

Important Identified Risk	Myocarditis and Pericarditis
	involved females; 1 case (3.0%) was missing gender information. The mean age of the patients was 63.8 (SD: 22.4), with a median 70.0 years (range 12.0 to 90.0 years). There were 15 events (44.1%) reporting an outcome of "Recovered/ Recovering." According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, 1 case met Level 1 definition, 7 cases met Level 2 definition, 2 cases met Level 3 definition, 22 cases met Level 4 definition, and 1 case met Level 5 definition. According to the CDC working definition, 9 cases were considered "Probable", 23 cases were considered "Unassessable" and 1 case was considered "Not a case" of myocarditis. According to the WHO causality assessment, 6 cases was considered "Possible", 19 cases were considered "Unassessable", 7 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 SARS-CoV-2 JN.1 mRNA* During the review period, the MAH received 2 serious non-medically confirmed cases (2 events) of myocarditis and pericarditis following the receipt of SPIKEVAX 2024-2025 Formula. There were no cases reporting a fatal outcome for the events of myocarditis or pericarditis. One case involved a 32-year-old male, and the other case involved a 73-year-old female. The mean age of the patients was 52.5 (SD: 29.0), with a median 52.5 years (range 32.0 to 73.0 years). Both events reported an outcome of "Not Recovered/ Not Resolved." According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, both cases met Level 4 definition. According to the CDC working definition both cases were considered "Unassessable." According to the WHO causality assessment, both cases were considered "Unassessable." *Myocarditis and Pericarditis Cases Involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula* During the review period, no cases involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula were received. *Myocarditis and Pericarditis Cases Involving SPIKEVAX (NOS)* During the review period, the MAH received 18 serious cases (18 events) of myocarditis and pericarditis following the receipt of Spikevax (NOS). There were 16 medically confirmed cases and there were no cases with a fatal outcome for the events of myocarditis or pericarditis. A total of 8 cases (44.4%) involved males, 4 cases (22.2%) involved females; 6 cases (33.3%) was missing gender information. The mean age of the patients was 49.1 (SD: 26.2), with a median 51.0 years (range 17.0 to 84.0 years); 9 cases were missing age data. There were 2 events (20.0%) reporting an outcome of "Recovered." According to the Brighton Collaboration case definition for myocarditis and pericarditis in patients, 1 case met Level 2 definition, 17 cases met Level 4 definition. According to the CDC working definition, 1 case was considered "Probable", and 17 cases were

Important Identified Risk	Myocarditis and Pericarditis
	considered "Unassessable." According to the WHO causality assessment, 1 case was considered "Possible", and 17 cases were considered "Unassessable." <u>Review of the Literature article requested by EMA:</u> "Myocardial injury safety signal for mRNA COVID-19 vaccines (MACiV study findings)" The authors of the "MACiV Multicentre Study" provided an exploration of the clinical characteristics, myocardial injury, and outcomes of COVID-19 vaccine-associated myocarditis (C-VAM) in paediatric and young adult populations. The study addresses the gaps in understanding mid- and long-term myocardial health outcomes for these patients. The study population included patients <=30 years of age, and C-VAM occurred in adolescent males (91%) with a mean age of 15.7 years. Most of the patients (95%; n=306) were vaccinated with Pfizer vaccine, 5% received Moderna vaccine (n=16), and only 1 patient received Johnson& Johnson Vaccine. Symptoms, primarily chest pain, typically appear within 3 days of vaccination, often following the second dose of an mRNA vaccine. Hormonal differences, particularly the pro-inflammatory role of testosterone and the cardioprotective effects of oestrogen, likely contribute to the observed age and sex disparities. Most of this cohort of patients (96%) presented with elevated troponin levels, indicative of targeted myocardial injury rather than systemic inflammation, as systemic inflammatory markers were generally low. Late gadolinium enhancement (LGE) on cardiac MRI, a marker of myocardial injury, was present in 82% of cases, resembling patterns observed in viral myocarditis. Despite these findings, the initial clinical course was mild for most patients, with only 2% requiring inotropic support. At a median follow-up of 178 days, no cardiac deaths or heart transplantations were reported, underscoring the generally favourable mid-term prognosis of C-VAM. Persistent LGE was observed in 60% of patients at follow-up, though the severity was reduced, suggesting ongoing myocardial fibrotic remodelling. The authors speculated that persistence of LGE may raise concerns about potential long-term risks, such as dilated cardiomyopathy, arrhythmias, and ventricular dysfunction. Notably, most patients recovered from left ventricular ejection fraction (LVEF), and some patients continued to experience mild symptoms such as chest pain or fatigue. While the MACiV study provides valuable insights, its retrospective design introduces potential biases. The lack of endomyocardial biopsy data limits the ability to confirm the underlying pathology. The study did not directly compare C-VAM with SARS-CoV-2 myocarditis, although findings, such as LGE and myocardial fibrosis, resemble patterns in viral myocarditis. Additionally, the median follow-up period of 178 days is insufficient to fully assess long-term outcomes. **<u>Conclusion</u>** The MAH considered that the MACiV study (FDA funded study) showed most patients with myocarditis after COVID-19 vaccination experience a mild clinical course and demonstrate favourable short- to medium-term outcomes. The MACiV study reinforces that C-VAM has

Important Identified Risk	Myocarditis and Pericarditis
	significantly better outcomes compared to viral myocarditis. Key findings highlight that C-VAM predominantly affects young males, often after the second dose of an mRNA vaccine, and is characterised by localised myocardial injury rather than systemic inflammation. The authors theorised that persistent cardiac MRI abnormalities, such as LGE, may raise concerns about potential long-term risks, including myocardial fibrotic remodelling and future cardiac dysfunction, and indicated that these findings emphasise the importance of continued surveillance and follow-up to assess long-term myocardial health and outcomes. The study seems to have several strengths such as large sample size and multicenter design, comprehensive data collection (such as imaging data echocardiography, cardiac MRI), biomarker (such as troponin, c-reactive protein), use of advanced diagnostics such as Cardiac MRI (LGE to detect myocardial injury), comparison of C-VAM to multisystem inflammatory syndrome, and well defined primary and secondary outcomes. However, there are several limitations with this study such as retrospective design which could introduce biases (potential selection bias), lack of long-term follow-up data, absence of biopsy data, did not directly compare C-VAM with SARS-CoV-2 myocarditis, and the study primarily focuses on younger patients, limiting the applicability of findings to older adults. These limitations necessitate cautious interpretation of findings. The MAH acknowledges that there is limited long-term follow-up data on C-VAM. Of note it should be noted that, as part of additional pharmacovigilance activities, the MAH already has an ongoing PASS study mRNA-1273-P911 for the evaluation of long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA). The primary objective of the study is to characterise presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of SPIKEVAX. The secondary objective of the study is to compare presentation, clinical course, and long-term outcomes of vaccine-associated myocarditis with those of non-vaccine myocarditis, including myocarditis arising in COVID-infected individuals, and to characterise possible risk factors for adverse long-term outcomes of vaccine-associated myocarditis including demographic factors, lifestyle factors, and medical history. Results of the study will be shared once the study is completed. In conclusion, myocarditis is a rare adverse event and is adequately addressed in all mRNA COVID vaccine labels. The overall benefits of vaccination in preventing severe COVID-19 outcomes, including hospitalisation and death, far outweigh the risks. Long-term monitoring and research remain critical to addressing knowledge gaps and ensuring optimal management of affected individuals.
Discussion	A review of the data received during this reporting period showed there is a consistent decrease in reported cases of myocarditis and pericarditis across all vaccine formulations over time. The mean age varied across formulations was noted, and this probably could be due to potential differences in the populations receiving each vaccine formulation.

Important Identified Risk	Myocarditis and Pericarditis
	Elasomeran: Mean age of 42.7 years. Andusomeran: Older population, mean age of 63.8 years. SPIKEVAX 2024-2025 Formula: Mean age of 52.5 years Consistent male predominance is observed in cases involving myocarditis/pericarditis, across all formulations. Overall, the review showed that of the 244 cases: 147 (60%) cases were assessed as "Unassessable;" 46 cases (19%) were assessed as "Unlikely;" 46 (19%) cases were assessed as "Possible" and 5 cases (2%) were assessed as "Not a case of myocarditis/pericarditis". Review of these cases did not identify any significant safety issues of concern. Review of the article suggested by the pharmacovigilance risk assessment committee (PRAC) did not identify any significant safety issue of concern. However, there are critical gaps in understanding mid- and long-term myocardial health outcomes as data on long-term follow-up after vaccine induced myocarditis are very limited. Of note, as part of additional pharmacovigilance activities, the MAH continues to monitor this identified risk through an ongoing PASS study mRNA-1273-P911 (Long-term outcomes of myocarditis following administration of SPIKEVAX [COVID-19 vaccine mRNA]). Based on the analysis of all the safety data available as of 17 December 2024, 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. Please refer to Section 8 for results from the PASS study on the evaluation 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. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including PASS to further characterise them. The benefit-risk evaluation remains positive.

16.3.2 New Information on Important Potential Risks

16.3.2.1 Immunoglobulin A Nephropathy (IgAN) (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the important potential risks of IgA Nephropathy for marketed Moderna vaccines targeting SARS-CoV-2 has not identified any clinically relevant new safety information for this topic. The characterisation of

this important potential risk as described in Section 16.4, remains valid. IgA Nephropathy is monitored in accordance with a request from a Health Authority.

Table 16-13 IgA Nephropathy

Important Potential Risk	**IgA Nephropathy (Safety concern in PBRER only)**
Source of New Information	• Moderna GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 61 o New and Significant Safety Information: None (0).
Background	Following review of PBRER#4, a Health Authority requested the following information on IgAN: • The reporting of IgA Nephropathy is rare, and 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 characterisation in PBRER section 16.3 and 16.4, respectively.
Methods	Neither the Brighton Collaboration 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 utilising the WHO-UMC standard causality assessment.
Results	Refer to Appendix 12.9 for information about the medical topic. During the review period, the MAH received 21 reports (24 events) that had PTs within the HLT of Glomerulonephritis and Nephrotic Syndrome (note: the following case [redacted]) was captured for both elasomeran and SPIKEVAX BIVALENT.214 [elasomeran/imelasomeran]). Of the 20 remaining cases, 10 cases involved elasomeran, 8 cases involved SPIKEVAX (NOS) and 1 case each involved, elasomeran/davesomeran, and andusomeran. There were no reports involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA. All 20 reports were medically reviewed. Seven cases were classified as confirmed IgA nephropathy and one was classified as antineutrophil cytoplasmic antibodies (ANCA) due to the clinical presentation and a positive ANCA test, with the reporter noting that IgAN was a possible diagnosis due to haematuria (no confirmatory biopsy was ever done due to the underlying severity of disease); the remaining 12 cases involved other types of nephropathy or other conditions (e.g., glomerulonephritis minimal lesion, glomerulonephritis membranous, nephrotic syndrome, glomerulonephritis rapidly progressive, and C3 glomerulopathy). According to the WHO causality assessment, 4 cases considered "Unassessable", 3 cases considered "Unlikely" related to the vaccine, and 13 cases were not assessed as they were not considered cases

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)
	of IgA Nephropathy. Out of the 7 cases involving true IgA nephropathy by definition, no cases involved fatal outcomes. Of these 7 cases, the majority (4 cases) involved SPIKEVAX NOS, 2 cases involved elasomeran and 1 case involved mRNA-1273 BIVALENT .222. All of these 7 cases were serious. Six (6) cases were new onset (de novo) of IgA nephropathy, and 1 case was considered a IgA nephropathy flare because the patient was reported to have experienced exacerbation of IgA nephropathy that had been diagnosed prior to vaccination at age 18. More numbers of cases in females (6 cases; 85.7%) when compared to males (1 cases; 14.3%) were reported. The mean age was 50.3 years (SD: 15.2) and median age was 53.0 years (range: 27.0 to 67.0 years).
Discussion	During the reporting period in the MAH's GSDB, there were 7 (one case more likely ANCA with +ANCA test) cases of IgA nephropathy that were identified through medical review. Most of these cases (4 cases) were on SPIKEVAX NOS, 2 (2) cases involved elasomeran and one (1) case involved mRNA-1273 BIVALENT.222. Of the 7 cases of IgA nephropathy, 6 cases involved new onset (de novo) IgA nephropathy. None of these cases were considered WHO possible, 4 cases were unassessable due to confounding factors, underlaying condition and limited information, finally the remaining 3 cases, the WHO causality assessment was considered unlikely due to the long TTO of 3, 5 and 2 1/2 months. No new patterns were observed with regard to IgA nephropathy for marketed Moderna vaccines targeting SARS-CoV-2. Based on the analysis of all the safety data available as of 17-Dec-2024, 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 outweigh 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 the reports does not differ from the known safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to monitor events of 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 the known important missing information risks of marketed Moderna vaccines targeting SARS-CoV-2 before and during pregnancy has not identified any clinically relevant new safety information for this topic. The characterisation of these important risks as described in the approved RMP as of the DLP of this PBRER and in Table 16-14 remains valid.

Table 16-14 Use in Pregnancy

Missing Information	Use in Pregnancy
Source of New Information	• Moderna GSDB • Literature Sources -Search Criteria Applied: -Pregnancy Methods of Evaluation: Literature Search Methodology -Articles of Reference for Pregnancy with Company Comment • Retrieved: 992 • New and Significant Safety Information: Four (4) articles.
Background	Use of marketed Moderna vaccines targeting SARS-CoV-2 (SPIKEVAX Original [elasomeran], SPIKEVAX Bivalent .214 Original/BA.1 [elasomeran/imelasomeran], SPIKEVAX Bivalent .222 Original/BA.4/5 [elasomeran/davesomeran], SPIKEVAX 2023-2024 Formula [andusomeran]), SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA 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 marketed Moderna vaccines targeting SARS-CoV-2 will be used in women of child-bearing age, pregnancy exposures are likely to occur. Additionally, at the request of regulatory authorities, the use of marketed Moderna vaccines targeting SARS-CoV-2 before and 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 12.10 for Methods of Evaluation
Results	Refer to Appendix 12.10 for additional information. **Overview of Pregnancy Cases Who Received Elasomeran** During the review period, the MAH received 52 pregnancy cases (540 events) with 41 serious cases (198 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. A total of 33 cases were medically confirmed, and 4 cases reported a fatal outcome. During the review period, a larger proportion (78.8%) of cases were reported as "serious" compared

Missing Information	Use in Pregnancy
	to cumulative data (35.5%). Among the serious cases, there were cases which simply report "maternal exposure during pregnancy" in addition to known events that reflect expected reactogenicity and are reported as "serious" cases. Serious cases should be interpreted with caution as many do not meet the true definition of "serious" (death, life-threatening, hospitalisation, 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 regardless of case medical information. Serious cases will be presented in the *Serious Pregnancy-specific Events-Elasomeran* and *Fatal Pregnancy Cases-Elasomeran* sections below. Most (24; 45.3%) pregnancy-specific cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and consistent with what has been observed in previous review periods. During the review period, the most frequently reported PTs (4 events or more) indicating an adverse event/outcome for pregnancy cases were COVID-19 infection, pyrexia, headache, pain in extremity, fatigue, arthralgia, dizziness, hypertension, abortion spontaneous, cognitive disorder, myalgia, nausea, pain, vomiting, asthenia, thrombosis, and atrial septal defect. Most reported events reflect expected reactogenicity, were comparable with cumulative data, and consistent with the product safety profile for all marketed Moderna vaccines targeting SARS-Cov-2. During the review period, 4 pregnancy cases reported events of myocarditis and/or pericarditis after receipt of elasomeran. 2 (2) of these cases were reported in the prior reporting period but had updates made to the narrative during this review period. During this review period, case [redacted] had diagnostic data, concomitant medication, and event onset updates made to the narrative and case [redacted] had medical history and event updates made to the narrative. The MAH's original causality assessments for those 2 cases were not affected by the new information added during this review period. The remaining cases [redacted] **and** [redacted] have been reviewed in the Myocarditis/Pericarditis Section 16.3.1.2. *Pregnancy-specific Events – Elasomeran)* During the review period, of the 52 pregnancy cases received by the MAH, 48 cases reported a pregnancy-specific event 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). Of these 48 pregnancy cases (74 events) reporting a pregnancy-specific event, 37 cases were serious (48 serious events), 3 cases reported a fatal outcome, and 30 cases were medically confirmed. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome ("Maternal exposure during pregnancy," "Exposure during pregnancy," "Drug exposure during pregnancy," "Maternal exposure before pregnancy," "Foetal exposure during pregnancy," and "Maternal exposure timing unspecified"), the most frequently reported pregnancy-specific PT's that indicated an adverse pregnancy-specific clinical event/outcome were "Abortion spontaneous" (5 events) and "Atrial septal defect" (4 events). Consistent with cumulative data, the PT "Abortion

Missing Information	Use in Pregnancy
	spontaneous" has been the most frequently reported pregnancy-specific PT that indicates an adverse pregnancy-specific clinical event/outcome. (Refer to Spontaneous abortions, Stillbirths, and Foetal Deaths evaluations added below). A summary of all pregnancy outcomes associated with elasomeran exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. *Serious Pregnancy-specific Events– Elasomeran* During the review period, of the 41 serious pregnancy cases reported, when restricted to pregnancy cases reporting only pregnancy-specific events/outcomes, 29 serious cases (48 events) were identified. A total of 22 cases were medically confirmed, and 3 cases reported a fatal outcome. 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 adverse event, diagnostics, treatment, and outcome. Where data were available, confounding factors for spontaneous abortion/foetal deaths and complications of pregnancy [including advanced maternal age, concomitant medications, comorbidities (such as hypothyroidism, increased blood pressure, or tobacco abuse) and previous relevant obstetric history including foetal loss] were present. *Fatal Pregnancy Cases– Elasomeran* During the review period, 3 pregnancy cases were coded as fatal following receipt of elasomeran. Case [redacted] concerns a 33-year-old female with a medical history of cardiomegaly, who experienced the fatal event of pericarditis constrictive. However, this case appears to be misclassified as a pregnancy case given that no information regarding obstetric medical history (e.g., LMP, delivery date/neonate outcome) was provided that would suggest a recent pregnancy associated with elasomeran (this case has been reviewed in the Myocarditis/Pregnancy Section 16.3.1.2). The remaining 2 fatal cases are summarised below: [redacted] This RA case by a health-care professional concerns a neonate of unknown gender who experienced the fatal event of foetal hydrops approximately 4 months after maternal exposure to elasomeran (Reported as the second dose in the mother's COVID-19 vaccination schedule). As reported, the patient's mother was admitted approximately 3 months after vaccination due to the presentation of uterine contractions. Pregnancy of 28.6 gestational weeks was confirmed by ultrasound. The pregnancy was considered "uncontrolled" until gestational week 25. Venereal Disease Research Laboratory (VDRL) test was positive for syphilis at 25 weeks gestational age and treatment was initiated with intramuscular benzathine penicillin G 2,400,000 (3 doses) at 1 dose per week. An ultrasound performed at 3 months and 1 week after vaccination, indicated probable foetal hydrops that was later confirmed with a

Missing Information	Use in Pregnancy
	diagnosis of foetal malformation incompatible with life. Co-suspect products were reported, including MMR (measles, mumps and rubella) and DT (diphtheria and tetanus) vaccines which were administered to patient's mother at an unspecified date. The mother was discharged from obstetrics and re-admitted one day after with pre-eclampsia (blood pressure: 160/120). Vital foetus positive uterine dynamics. Magnesium Sulfate infusion was prescribed. The decision was made to terminate the pregnancy, but then an emergency caesarean section was performed: Live foetus was born, weighing 1,760 grams, Apgar score 3/6, with foetal hydrops. Newborn died in Neonatal Intensive Care Unit (NICU) [hours of life was not reported]. Underlying maternal syphilis, other viral infections (Parvovirus B19-Herpes, but with no pathological confirmation provided) and rhesus incompatibility were suggested by the reporter as important confounders. No pathology reports regarding the placenta or neonatal autopsy were provided that confirmed characteristic findings in foetus and placenta suggestive of syphilis and placental vasculopathy. MAH Comment: This case was assessed as "Unlikely" given the lack of biological plausibility and underlying maternal syphilis as a potential alternative aetiology for the event. This case was also potentially confounded by maternal exposure to the co-suspect products MMR and DT; and the possibility of rhesus incompatibility and/or exposure to maternal viral infection (Parovirus B19 Herpes virus-CMV). [redacted] This RA case concerns a female neonate of unknown age, who experienced unexpected events of neonatal asphyxia, encephalopathy neonatal and neonatal behavioural syndrome that resulted in death. The events occurred almost 2 years after a dose of elasomeran (reported as the second dose in the mother's COVID-19 vaccination schedule). The mother of the baby had an emergency caesarean section at 33 and 4/7 weeks of amenorrhea from a bichorial-biamniotic twin pregnancy for placental abruption and foetal bradycardia. The mother had haemorrhagic shock due to placental detachment. The neonate was initially hospitalised in neonatology on continuous positive airway pressure (CPAP). Blood tests indicated poor neonatal adaptation with pHs of 6.79 and 7.04, lactates at 18, and Apgar score 0/0/1. The patient had severe asphyxia with hypoxic-ischaemic encephalopathy and multiorgan involvement. Despite immediate resuscitation and a recovery of the heart rhythm at 15 minutes of life, the clinical neurological evolution was unfavourable. The neonate died after 2 days of life. MAH Comment: This case was assessed as "Unlikely" given the long latency and etiopathogenesis of the events that were triggered by placental abruption. *Foetal Deaths– Elasomeran* The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA, and as stillbirth if they occur after 20 weeks gestational age. The threshold of 20 weeks is per the definitions applied in the US [19]. *Spontaneous and Missed Abortions – Elasomeran*

Missing Information	Use in Pregnancy
	During the review period, 5 serious pregnancy cases with a medical history of maternal exposure to elasomeran reported spontaneous abortion with 5 serious events. Of the 5 cases, 2 cases were medically confirmed, and no cases were coded as fatal. The mean age of the women was 35.4 years (SD: 6.6) and median age of 32.0 years (range 29.0 - 43.0 years). Analysis of event clustering by dose number and TTO was not meaningful as none of the events reported dose number and only 3 of the 5 events reported TTO. Of the events that reported TTO, 1 event was reported to occur between 7 to 13 days after an unspecified dose, 1 event was reported to occur 30 plus days after an unspecified dose, and 1 event was reported to occur prior to the first dose reported. Review of 5 cases reporting spontaneous abortion, showed 1 case reported long latency (2 years after the second dose mRNA-1273), 2 cases reported advanced maternal age (>40 years old), and the remaining 2 cases lacked critical information required for a meaningful medical assessment including GA, prior maternal obstetric and medical history, concomitant medications, etc. No significant safety issues of concern were identified. *Stillbirth – Elasomeran* Stillbirth has varying global definitions based on GA and foetal weight. For the purposes of this PBRER, and as described above, the MAH applied a definition of stillbirth as foetal death after 20 weeks gestational age [19]. Congenital anomalies, placental dysfunction associated with foetal 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, 1 pregnancy case reported stillbirth following maternal exposure to elasomeran and is summarised below: [redacted]: This RA case concerns a 32-year-old female patient with a pregnancy history of a vaginal delivery at 38 weeks of amenorrhea in a 3100-gram boy, who experienced the serious (due to medically significant) unexpected events of foetal death, premature separation of placenta, thrombocytopenia, disseminated intravascular coagulation and drug exposure before pregnancy. The events foetal death, premature separation of placenta, thrombocytopenia and disseminated intravascular coagulation occurred almost 9 months after maternal exposure to a dose of elasomeran (reported as the second dose in the mother's COVID-19 vaccination schedule). Based on information provided, a caesarean delivery occurred in the 29th week due to amenorrhea stemming from placental detachment. It was estimated that time of conception occurred approximately 3 months after the mother received Dose 1 of elasomeran and approximately 2 months after she received Dose 2 of elasomeran. The mother also tested positive for SARS-CoV-2 infection between 4 to 5 months after the time of conception. As reported, the mother presented with

Missing Information	Use in Pregnancy
	severe disseminated intravascular coagulation in the context of placental abruption and thrombocytopenia. Blood loss was estimated at 3000 ml, and the pregnancy ended with a lower transverse isthmic caesarean section following intrauterine foetal death. The outcome of the events was reported as "Recovered." MAH Comment: This case was assessed as "Unlikely" given the long latency to onset of events. The maternal SARS-CoV-2 infection that occurred between 4 to 5 months GA during this pregnancy and maternal history of amenorrhea (the underlying hormonal imbalance leading to amenorrhea can potentially increase risk of pregnancy complications including stillbirth) may be considered as plausible alternate aetiologies for the events that led to stillbirth. A summary of all pregnancy outcomes associated with elasomeran exposure 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-Authorisation Data (EMEA/CHMP/ 313666/2005)," are presented by individual vaccine in Appendix 12.10. *Congenital Anomaly– Elasomeran* During the review period, 19 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 19 pregnancy cases, 5 cases occurred among foetuses and neonates who were maternally exposed to elasomeran in-utero and 14 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. All 5 pregnancy cases ([redacted] **and** [redacted]), reported a live birth at delivery. Of the 11 events reported in those 5 cases, the event outcomes were reported as "Recovered/Resolved" for 2 events, "Not Recovered/Not Resolved" for 4 events, and "Unknown" for 5 events. Further review of the congenital anomalies, considering the GA at vaccination and foetal development, contributed to the assessment of causality. Many cases lacked GA at the time of vaccination and thus causality was 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 Analyses-Elasomeran:** • *Children <6 years of Age with a medical history of maternal exposure to elasomeran during pregnancy* During the review period, the MAH received 6 serious cases (15 serious events) among children under 6 years of age with a medical history of maternal exposure to elasomeran during pregnancy. Case [redacted] reported a fatal outcome and is described above in the *Fatal Pregnancy Cases-Elasomeran* section. Cases [redacted]

Missing Information	Use in Pregnancy
	and [redacted] reported congenital anomaly and are described in Appendix 12.10. The remaining case is summarised below: [redacted]: This spontaneous case reported by a family member or friend concerns a male infant, with no reported medical history, who experienced the serious (due to medically significant) unexpected, events of foetal growth restriction and premature baby, which occurred on an unknown date following maternal exposure to a dose of elasomeran (reported as the second dose in the mother's COVID-19 vaccination schedule). It was reported that the infant was born 31 days premature and was "very small". The reporter mentioned that the infant "stopped growing at 32 weeks old, was smaller than average, and his weight was less than average." It was also reported that the infant experienced a "utero growth restriction;" the child was now 2.5 years of age, and "was still wearing clothes appropriate for an infant 12-18 months of age." The event outcome for both foetal growth restriction and premature baby was reported as "Recovered/Resolved." MAH Comment: This case was considered "Unassessable" given the lack of information regarding maternal medical and obstetric history (including LMP, estimated date of delivery, and details pertaining to premature delivery), family history, diagnostic evaluation, and clinical course which precludes an informed assessment. No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period. No pregnancy cases associated with exposure to elasomeran were reported for the following subpopulations during the review period: • *Children 6 to 11 Years of Age,* • *Adolescents (12 to 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 in association with elasomeran. **Pregnancy Cases After Receiving Elasomeran/Imelasomeran** During the review period, no pregnancy cases were reported for individuals who received or had a medical history of maternal exposure to a BD of elasomeran/imelasomeran. **Pregnancy Cases After Receiving Elasomeran/Davesomeran** During the review period, no pregnancy cases were reported for individuals who received or had a medical history of maternal exposure to a BD of elasomeran/davesomeran. **Pregnancy Cases After Receiving Andusomeran** During the reporting period, the MAH received 15 pregnancy cases (49 events) with 2 serious cases (2 serious events) among individuals who received or had a medical history of maternal exposure to andusomeran. A total of 12 cases were medically confirmed, and no cases reported a fatal outcome. Most (10; 66.7%) of these pregnancy cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and consistent with what has been observed with marketed Moderna vaccines targeting SARS-Cov-2 in previous review periods.

Missing Information	Use in Pregnancy
	During the reporting period, the most frequently reported PTs continued to be events that reflect expected reactogenicity; this is comparable with cumulative data and consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2. However, during the reporting period, there also was an increase in number of events related to administration error, specifically administration of expired product (7 events; 14.3%). To date, no pregnancy cases associated with exposure to andusomeran have reported events of myocarditis and/or pericarditis. *Pregnancy-specific Events – Andusomeran* During the reporting period, The MAH received 15 pregnancy cases (2 serious cases) reporting 49 events (2 serious events) associated with exposure to andusomeran. Of the 49 events reported, only 15 events reported a pregnancy-specific PT. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome ("Maternal exposure during pregnancy" and "Foetal exposure during pregnancy") the only remaining PT that indicated a pregnancy-specific adverse clinical event/outcome was: "Jaundice neonatal." A summary of all pregnancy outcomes associated with andusomeran exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. *Serious Pregnancy-specific Events– Andusomeran* Of the 2 serious pregnancy cases reported during the reporting period, when restricted to pregnancy cases reporting only serious pregnancy-specific events, only 1 of those serious cases identified a serious pregnancy-specific event. Case [redacted] reported a 34-year-old female who experienced the serious PT "Jaundice neonatal." This case appears to be misclassified as a pregnancy case given that no obstetric medical history (e.g., LMP, delivery date/neonate outcome) was provided to suggest a recent pregnancy. Additionally, no information was reported that linked this case to a case involving a neonate who may have experienced this event. *Fatal Pregnancy Cases– Andusomeran* During the reporting period, no pregnancy case reported a fatal outcome in association with exposure to andusomeran. *Foetal Deaths– Andusomeran* The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [19]. *Spontaneous and Missed Abortions – Andusomeran* During the reporting period, no pregnancy cases with a medical history of maternal exposure to andusomeran reported events of spontaneous or missed abortion. *Stillbirth – Andusomeran* No pregnancy cases reported stillbirth following maternal exposure to andusomeran.

Missing Information	Use in Pregnancy
	Congenital Anomaly– Andusomeran No pregnancy cases reported congenital anomaly following maternal exposure to andusomeran. **Subpopulation Analyses-Andusomeran:** No pregnancy cases associated with exposure to andusomeran 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 associated with exposure to andusomeran have been identified. **Pregnancy Cases After Receiving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval in August 2024, the MAH has received 5 non-serious pregnancy cases (16 events) among individuals who received or had a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Four (4) of the 5 cases were medically confirmed. When age was reported, the pregnancy cases (2; 40.0%) occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been observed with marketed Moderna vaccines targeting SARS-Cov-2. Most of the PTs reported in these cases were related to errors in product administration and included: "Wrong product administered" (2 events), "Accidental overdose" (1 event), "Product administration error" (1 event), and "Underdose" (1 event). To date, no pregnancy cases associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have reported events of myocarditis and/or pericarditis. *Pregnancy-specific Events – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula* The MAH has received 5 non-serious pregnancy cases reporting 16 events associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Of the 16 events reported, only 5 events reported a pregnancy-specific PT. All 5 events reported the PT "Maternal exposure during pregnancy." There were no additional PTs reported that indicated a pregnancy-specific adverse event/outcome. A summary of all pregnancy outcomes associated with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. Serious Pregnancy-specific Events– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula

Missing Information	Use in Pregnancy
	No serious pregnancy cases associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have been reported. Fatal Pregnancy Cases– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases have reported a fatal outcome in association with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Foetal Deaths– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [19]. Spontaneous and Missed Abortions – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases with a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have reported events of spontaneous or missed abortion. Stillbirth – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases have reported stillbirth following maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Congenital Anomaly– SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula No pregnancy cases have reported congenital anomaly following maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. **Subpopulation Analyses- SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula:** No pregnancy cases associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have been reported for the following subpopulations during the review period: • Children <6 years of Age with a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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 associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula have been identified. **Pregnancy Cases After Receiving SARS-CoV-2 JN.1 mRNA** Since its approval in September 2024, the MAH has received 5 pregnancy cases (20 events) with 1 serious case (1 serious event) among individuals who received or had a medical history of maternal

Missing Information	Use in Pregnancy
	exposure to SARS-CoV-2 JN.1 mRNA. Three of the 5 cases were medically confirmed, and no case has reported a fatal outcome. Most of the cases did not report mother's age (4; 80.0%). The remaining case concerned a woman in the 25 to 39-year age group which is consistent with typical childbearing age and what has been observed with marketed Moderna vaccines targeting SARS-CoV-2 in previous review period. Most of the PTs reported predominantly reflect expected reactogenicity, consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2 and comparable with events reported for these vaccines in the prior review period. In addition, there were also reported PTs related to product storage and quality: "Product temperature excursion issue" (3 events; 15.0%) and "Poor quality product administered" (1 event; 5.0%). To date, no pregnancy cases associated with exposure to SARS-CoV-2 JN.1 mRNA have reported events of myocarditis and/or pericarditis. Pregnancy-specific Events – SARS-CoV-2 JN.1 mRNA The MAH has received 5 non-serious pregnancy cases reporting 20 events associated with exposure to SARS-CoV-2 JN.1 mRNA. Of the 20 events reported, only 5 events reported a pregnancy-specific PT. All 5 events reported the PT "Maternal exposure during pregnancy." There were no additional PTs reported that indicated a pregnancy-specific adverse event/outcome. A summary of all pregnancy outcomes associated with SARS-CoV-2 JN.1 mRNA exposure, 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. Serious Pregnancy-specific Events– SARS-CoV-2 JN.1 mRNA One serious pregnancy case has been reported in association with exposure to SARS-CoV-2 JN.1 mRNA and is summarised below: [redacted]: This spontaneous retrospective pregnancy case reported by a consumer concerns a female patient of unknown age with no reported medical or obstetric history who experienced the serious (due to medically significant) event of arthralgia among other non-serious events (Gait disturbance, Motor dysfunction, and Pain in extremity). The event was reported to occur 1 day following receipt of SARS-CoV-2 JN.1 mRNA (reported as the 6th dose in the patient's COVID19 vaccination series). Concomitant medication included sertraline. LMP and estimated date of delivery were not provided. Delivery occurred on an unknown date and was reported as "normal pregnancy outcome." No pregnancy-specific adverse outcomes were reported. The event outcome for arthralgia was reported as "Not Recovered/Not Resolved." MAH Comment: This case was considered "Unassessable" given the limited information provided regarding the age of the patient, maternal medical and obstetric history (including LMP, estimated date of delivery, and details associated with delivery), maternal family history, diagnostic/ laboratory evaluation and results, as well as clinical course. Concomitant use of sertraline was also considered a potential confounder.

Missing Information	Use in Pregnancy
	Fatal Pregnancy Cases– SARS-CoV-2 JN.1 mRNA No pregnancy case has reported a fatal outcome in association with exposure to SPIKEVAX 2024-2025 Formula (JN.1). Foetal Deaths– SARS-CoV-2 JN.1 mRNA The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the United States [19]. Spontaneous and Missed Abortions – SARS-CoV-2 JN.1 mRNA No pregnancy cases with a medical history of maternal exposure to SARS-CoV-2 JN.1 mRNA has reported events of spontaneous or missed abortion. Stillbirth – SARS-CoV-2 JN.1 mRNA No pregnancy cases have reported stillbirth following maternal exposure to SARS-CoV-2 JN.1 mRNA. Congenital Anomaly– SARS-CoV-2 JN.1 mRNA No pregnancy cases have reported congenital anomaly following maternal exposure to SARS-CoV-2 JN.1 mRNA. **Subpopulation Analyses- SARS-CoV-2 JN.1 mRNA:** No pregnancy cases associated with exposure to SARS-CoV-2 JN.1 mRNA have been reported for the following subpopulations: • Children <6 years of Age with a medical history of maternal exposure to SARS-CoV-2 JN.1 mRNA 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 associated with exposure to SARS-CoV-2 JN.1 mRNA have been identified. **Pregnancy Cases After Receiving SPIKEVAX (NOS)** It is important to note that for better attribution of case reports to marketed Moderna vaccines targeting SARS-CoV-2, 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, andusomeran, SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, and SARS-CoV-2 JN.1 mRNA. During the review period, the MAH received 8 pregnancy cases (36 events) with 5 serious cases (22 serious events) among individuals who received a vaccine classified as SPIKEVAX (NOS). A total of 6 cases were medically confirmed, and 1 case reported a fatal outcome. Most pregnancy cases (6; 75.0%) occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been observed with marketed Moderna vaccines targeting SARS-CoV-2 in the previous review period.

Missing Information	Use in Pregnancy
	Similar to the previous reporting period, many of the PTs reported predominantly reflect expected reactogenicity, consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2 and consistent with events reported for these vaccines in the prior review period. *Pregnancy-specific Events – SPIKEVAX (NOS)* During the reporting period, the MAH received 8 cases (5 serious) reporting 12 events (5 serious) associated with exposure to a vaccine classified as SPIKEVAX (NOS). All 12 events reported a pregnancy-specific PT. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome ("Maternal exposure during pregnancy" and Maternal exposure before pregnancy") the remaining PTs that indicated a pregnancy-specific adverse event/outcome were: "Abortion induced," "Foetal death," "Foetal malformation," "heart disease congenital," and "Peripartum cardiomyopathy." A summary of all pregnancy outcomes associated with exposure to vaccines classified as SPIKEVAX (NOS), 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-Authorisation Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.10. Serious Pregnancy-specific Events– SPIKEVAX (NOS) During the reporting period, the MAH received 5 serious pregnancy cases reporting 22 serious events following receipt or maternal exposure to a vaccine classified as SPIKEVAX (NOS). Case [redacted] reported maternal death and is summarised below in the *Fatal Pregnancy Cases-SPIKEVAX (NOS)* section. Case [redacted] reported stillbirth and is summarised below in the *Stillbirth-SPIKEVAX (NOS)* section. Cases [redacted] and [redacted] reported events of congenital anomaly and are summarised below in the *Congenital Anomaly-SPIKEVAX (NOS*) section. The remaining serious case is summarised below: [redacted] This spontaneous retrospective pregnancy case reported by a patient concerns a female of unknown age and no reported maternal medical, family, or obstetric history who experienced the serious (due to medically significant) unexpected AESI of peripartum cardiomyopathy and the serious (due to medically significant) unexpected event of ascites, among other non-serious events. The events occurred on an unknown date following receipt of a vaccine classified as SPIKEVAX (NOS) (reported as the third dose in the patient's COVID vaccination schedule. The patient received the first and second dose of "Moderna vaccine" in 2020). LMP and estimated date of delivery were not provided; as per the reporter, who was the patient, she estimated she was probably between 3 to 4 weeks pregnant at the time she received the booster. She reported that she found out that she was pregnant at the 7th week and had not exhibited any symptoms. She also reported that after the booster shot, she experienced the same muscle soreness and heaviness that she experienced with first and second shot. A week after giving birth, she experienced shortness of breath and was bloated, which lasted for a few months. Initial diagnosis was postpartum cardiomyopathy. Soon after, she had ascites which was addressed with unspecified diuretics. Additional information about clinical course, supportive diagnostic procedures, and treatment were not provided. The outcome of both serious events was reported as "Recovered."

Missing Information	Use in Pregnancy
	MAH Comment: This case was considered "Unassessable" given the limited information provided regarding the age of the patient, maternal medical and obstetric history (including LMP, estimated date of delivery, and details associated with delivery), maternal family history, concomitant medications, diagnostic/laboratory evaluation and results, as well as clinical course. Fatal Pregnancy Cases– SPIKEVAX (NOS) During the review period, the MAH received 1 fatal case that reported a maternal death following exposure to a vaccine classified as SPIKEVAX [NOS]. This case is summarised below: [redacted] This spontaneous prospective pregnancy case reported events associated with maternal exposure during pregnancy. This case concerns a 39-year-old female patient with no reported medical or obstetric history, who died on an unknown date following a dose of a vaccine classified as SPIKEVAX [NOS] (reported as a BD in the patient's COVID-19 vaccination schedule). It was reported that "a pregnant woman received a booster, had side-effects, and died." No information was reported regarding LMP, estimated date of delivery, or pregnancy outcome. No cause of death was provided, and it is unknown if an autopsy was performed. MAH Comment: This case was considered "Unassessable" given the limited details provided for medical review. Latency could not be established as the event onset date was not reported. No cause of death was reported, and it is unknown if an autopsy was performed. Additionally, limited information was provided regarding maternal medical and obstetric history (including LMP and estimated date of delivery), maternal family history, diagnostic/ laboratory evaluation and results, as well as clinical course. *Foetal Deaths– SPIKEVAX (NOS)* The MAH performed medical reviews of all reports coded as "foetal death" and "stillbirth." Foetal deaths are classified as spontaneous abortion if they occur before 20 weeks GA. The threshold of 20 weeks is per the definitions applied in the US [19]. *Spontaneous and Missed Abortions – SPIKEVAX (NOS)* During the review period, 1 serious pregnancy case with a medical history of maternal exposure to a vaccine classified as SPIKEVAX (NOS) reported spontaneous abortion with 1 serious event. Case [redacted] is summarised below in the *Congenital Anomaly-SPIKEVAX (NOS)*. *Stillbirth –SPIKEVAX (NOS)* During the review period, 1 pregnancy case reported stillbirth following maternal exposure to a vaccine classified as SPIKEVAX (NOS). This case is summarised below: [redacted] This literature-non-study case of maternal exposure during pregnancy concerns a 38-year-old female patient, with no reported medical history, who received an unspecified dose of a vaccine classified as SPIKEVAX (NOS) at 13 weeks GA and experienced the serious (medically significant) event of foetal death during the 22nd gestational week of pregnancy. It was reported that the patient's obstetric medical history did not indicate any observed events of arterial hypertension, diabetes, spontaneous miscarriage, or

Missing Information	Use in Pregnancy
	death in-utero. No concomitant or treatment medications were reported. No details of other vaccine doses were provided. No further clinical information was available for medical review. MAH Comment: This case was considered "Unassessable" given the limited information provided regarding maternal medical, family and obstetric history (including LMP and/or estimated date of delivery), concomitant medications, diagnostic/laboratory evaluation and results, as well as clinical course. The patient's age could also be considered a risk factor for stillbirth. *Congenital Anomaly*– SPIKEVAX (NOS) During the reporting period, 2 cases reported events of congenital anomaly in association with maternal exposure to a vaccine classified as SPIKEVAX (NOS). However, 1 case [redacted] appears to be misclassified as a pregnancy case given that the reported event of congenital heart disease was diagnosed in an adult patient. The remaining case describes an elective medical termination of pregnancy due to congenital anomaly and is summarised below: [redacted] This literature-non-study case of maternal exposure during pregnancy concerns a 42-year-old female patient, with the concurrent medical condition of diabetes mellitus, who underwent an elective medical termination of pregnancy due to congenital anomaly (foetal malformation). The medical termination of pregnancy was reported to occur 13 weeks following maternal vaccination with a vaccine classified as SPIKEVAX (NOS). No other information regarding the patient's obstetric history or treatment was reported. No further clinical information was available for medical review. MAH Comment: This case was considered "Unassessable" given the limited information provided regarding maternal medical, family, and obstetric history (including LMP and/or estimated date of delivery), concomitant medications, diagnostic/laboratory evaluation and results, or clinical course; as well, history of foetal malformations in the family. The patient's age and concurrent medical condition of diabetes mellitus could also be considered risk factors for foetal malformation. **Subpopulation Analyses-SPIKEVAX (NOS):** During the review period, no pregnancy cases associated with exposure to a vaccine classified as SPIKEVAX (NOS) were reported for the following subpopulations: • Children <6 years of Age with a medical history of maternal exposure to a vaccine classified as SPIKEVAX (NOS) 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 associated with vaccines classified as SPIKEVAX (NOS) have been identified.
Discussion	During the reporting period, the MAH received a total of 85 pregnancy cases (661 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

Missing Information	Use in Pregnancy
	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. 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. When data were available, it included important 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 review period, 2 cases reported stillbirth. Both cases of stillbirth had clear alternate aetiologies with no observed pattern or clear TTO cluster. This is consistent with cumulative data concerning stillbirth reported thus far for marketed Moderna vaccines targeting SARS-CoV-2. Published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth following 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 21 cases reporting congenital anomalies following maternal exposure to elasomeran (19 cases) and vaccines classified as SPIKEVAX [NOS)] (2 cases) during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunisation with marketed Moderna vaccines targeting SARS-CoV-2. During the reporting period, the only reports concerning children under 6 years of age exposed to marketed Moderna vaccines targeting SARs-CoV-2 were reported in association with elasomeran. Review of these 6 serious cases did not identify unusual patterns or safety concerns. During the reporting period, no pregnancy cases associated with exposure to marketed Moderna vaccines targeting SARS-CoV-2 were reported concerning children 6 to 11 years of age. Additionally, no pregnancy cases among adolescents associated with exposure to marketed Moderna vaccines targeting SARS-CoV-2 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. During the review period, in August 2024, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new variant KP.2. The new formulation was labelled SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Since that approval, the MAH has received 5 pregnancy cases reporting events after exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Review of all pregnancy-specific events and non-pregnancy-specific events for all pregnancy cases received following exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccination did not

Missing Information	Use in Pregnancy
	identify any new safety concerns. There were no cases that reported pregnancy-specific complications related with the administration of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. No unusual patterns or pregnancy-specific safety concerns have been identified with use during pregnancy. The current safety profile of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is consistent with the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to review cases involving exposure to the SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccine using routine surveillance. The most frequently reported PTs following SPIKEVAX 2024-2025 Formula (KP.2) vaccination were related to errors in product administration ("Wrong product administered," "Accidental overdose," "Product administration error," and "Underdose"). The other PTs reported were predominantly reactogenicity events, which is consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2 and consistent with events reported for those vaccines in prior review periods. No pregnancy-specific events indicating an adverse clinical outcome following SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccination have been reported. No pregnancy cases following SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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. 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. During the review period, in September 2024, the EMA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new variant JN.1. The new formulation was labelled SARS-CoV-2 JN.1 mRNA. Since that approval, the MAH has received 5 pregnancy cases reporting events after exposure to SARS-CoV-2 JN.1 mRNA. Review of serious pregnancy-specific events and non-pregnancy-specific events for all pregnancy cases involving exposure to SARS-CoV-2 JN.1 mRNA vaccination has not identified any new safety concerns. Overall, cases of pregnancy-specific complications were temporally related with the administration of SARS-CoV-2 JN.1 mRNA 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 SARS-CoV-2 JN.1 mRNA is consistent with the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to review cases involving exposure to SARS-CoV-2 JN.1 mRNA vaccine using routine surveillance. The most frequently reported PTs following SARS-CoV-2 JN.1 mRNA vaccination were related to product storage and quality ("Product temperature excursion issue" and "Poor quality product administered"). The other PTs reported were predominantly reactogenicity events, which is consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2 and consistent with events reported for those vaccines in prior review periods. No pregnancy-specific events indicating an adverse clinical outcome following SARS-CoV-2 JN.1 mRNA vaccination have been reported. No pregnancy cases following SARS-CoV-2 JN.1 mRNA vaccination have reported a fatal outcome, stillbirth, or congenital anomaly. No pregnancy cases

Missing Information	Use in Pregnancy
	have been reported in 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 immunisation with marketed Moderna vaccines targeting SARS-CoV-2. Furthermore, published literature has reported that there is transfer of maternal antibodies, reduction in SARS-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 SARS-CoV-2 infection may be more serious and cause complications for both the mother and the foetus. Four (4) articles published during the reporting period provided additional evidence supporting the use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy. A prospective cohort study from [20] demonstrated that both SARS-CoV-2 infection and COVID-19 vaccine (including marketed Moderna vaccines targeting SARS-CoV-2) exposure in-utero were not associated with an increased risk of adverse neurodevelopmental outcomes in infants up to 12 months of age. Similarly, a prospective study conducted by [21] in the United States suggested that the use of COVID-19 vaccines (including mRNA vaccines) was safe during pregnancy from the perspective of infant neurodevelopment up to 18 months of age. [22] conducted an observational population-based cohort study in Sweden and Norway which indicated that vaccination of pregnant individuals with mRNA COVID-19 vaccines was not associated with an increased risk of neonatal AEs in their infants. Lastly, [23] conducted a population-based retrospective cohort study and sibling matched analysis that demonstrated that mRNA COVID-19 vaccines (including marketed Moderna vaccines targeting SARS-CoV-2) given during the first trimester of pregnancy were not associated with an increased risk for major congenital anomalies in offspring, overall or grouped by organ system (for a summary of these articles please refer to Articles of Reference for Pregnancy with Company comment). Published literature supports the favourable benefit/risk profile of maternal immunisation 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-authorisation 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 missing information safety concern of all marketed Moderna vaccines targeting SARS-CoV-2 during breastfeeding has not identified any additional clinically relevant new safety information for this topic. The characterisation 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 while Breastfeeding

Missing Information	Use while Breastfeeding

Source of New Information	• Moderna GSDB
	• Literature Sources
	  • Search Criteria Applied: Appendix 13.4
	  • Retrieved: 992
	  • New and Significant Safety Information: None (0)

Background	Use of marketed Moderna vaccines targeting SARS-CoV-2 while breastfeeding 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 while breastfeeding have been identified.
Methods	Refer to Appendix 12.11 for Methods of Evaluation
Results	Refer to Appendix 12.11 for additional information. During the reporting period of this PBRER, a total of 36 lactation cases (137 events) were reported among individuals who received a marketed Moderna vaccine targeting SARS-CoV-2. No cases were reported among children under 6 years of age exposed via breastmilk from mothers vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2. There were no reports of adolescent mothers (12-17 years age group) who received a marketed Moderna vaccine targeting SARS-Cov-2 and were breastfeeding their newborn/infants. **Overview of Lactation Cases Who Received Elasomeran** During the review period, the MAH received 29 lactation cases (94 events) with 2 serious cases (2 serious events) among individuals who received elasomeran. A total of 26 cases were medically confirmed, and no cases reported a fatal outcome. Similar to the prior reporting period, the majority (27; 93.1%) of cases reported were non-serious. During the reporting period, no meaningful changes were observed in the age distribution of the cases of lactating women and their breastfeeding children. The majority of lactation cases (24; 82.8%) reported concerned individuals in the 25 to 39-year age group which is consistent with the expected age of lactating women. During the review period, the most frequently reported PTs (2 or more events; ≥2.0%) among individuals who received elasomeran were "Maternal exposure during breast-feeding," "Pyrexia,"

Missing Information	Use while Breastfeeding
	"Pain in extremity," "Fatigue," "COVID-19," "Headache," and "Nasopharyngitis." Most of the remaining reported events predominantly reflect expected events consistent with the product safety profile for marketed Moderna vaccines targeting SARS-Cov-2. After the exclusion of PTs that do not indicate a lactation-specific event (including "Maternal exposure during breast-feeding") the only reported PT's indicating a lactation-specific clinical adverse/outcome were "Lactation disorder" and "Lactation puerperal increased." There was no 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, the MAH received 2 serious lactation cases following receipt of elasomeran. Neither case [redacted] or [redacted] reported a serious lactation-specific event indicating a clinical adverse event/outcome for an infant/child or lactating woman. The only lactation-specific PT reported in both cases was "Maternal exposure during breastfeeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. Please note: Case [redacted] reported an event of spontaneous abortion, was medically reviewed, and presented as part of the analysis of cases reporting spontaneous or missed abortions in Section 16.3.5.1 (Use in Pregnancy). Similar to cumulative data, these cases lacked critical information required for a meaningful medical assessment including paediatric medical history, concurrent clinical events, evaluation and clinical course, as well as event outcome. However, 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. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with elasomeran or adolescent mothers (12-17 years age group) who received elasomeran and were breastfeeding their newborn/infants in association with exposure to elasomeran. No unusual patterns or lactation-specific safety concerns were identified in association with exposure to elasomeran. **Lactation Cases After Receiving BD 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 elasomeran/imelasomeran. **Lactation Cases After Receiving BD with Elasomeran/Davesomeran** 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 elasomeran/davesomeran. **Lactation Cases After Receiving BD with Andusomeran**

Missing Information	Use while Breastfeeding
	During the reporting period, the MAH received 5 lactation cases (3 serious) reporting 29 events (13 serious) among individuals who received a BD of andusomeran. One (1) case was medically confirmed, and no cases reported a fatal outcome. During the reporting period, no meaningful changes were observed in the age distribution of the cases of lactating women and their breastfeeding children. Most reported lactation cases (3; 60.0%) concerned adult women in the 25 to 39-year age group which is consistent with the expected age of lactating women. The other 2 cases involved a 43-year-old woman and a woman of unknown age. During the review period, the most frequently reported PTs (2 or more events; >6.0%) among individuals who received andusomeran were "Maternal exposure during breastfeeding," "Injection site pain," "nausea," and issues related to product administration ("Discontinued product administered"). The remaining reported events predominantly reflect expected reactogenicity. These events were comparable to cumulative data and are consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2. When restricted to lactation-specific events, the only PTs reported were "Maternal exposure during breast-feeding." No other PTs indicating a lactation-specific clinical adverse/outcome were reported. When compared to cumulative data, there was no significant change in the pattern of PTs reported. During the review period, the MAH received 3 serious lactation cases among women who received andusomeran. None of the 3 cases [redacted] reported a serious lactation-specific event indicating a clinical adverse event/outcome for an infant/child or lactating woman. The only lactation-specific PT reported in all 3 cases was "Maternal exposure during breastfeeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with andusomeran or adolescent mothers (12-17 years age group) who received andusomeran and were breastfeeding their newborn/infants in association with exposure to andusomeran. No unusual patterns or lactation-specific safety concerns were identified in association with exposure to andusomeran. **Lactation Cases After Receiving SPIKEVAX 2024-2025 Formula (KP.2)** The MAH received 1 medically confirmed non-serious case reporting 4 events involving a 65-year-old female who received a dose of SPIKEVAX 2024-2025 Formula (KP.) [reported as 8th dose in her COVID-19 vaccination series]. The only lactation-specific PT reported was "Maternal exposure during breastfeeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. This case appears to be misclassified as a lactation case given the individual's age (65 years old). The MAH requested further clarification for this case report. At the time of this PBRER, no response to this query had been received. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with SPIKEVAX 2024-2025 Formula (KP.2) or adolescent mothers (12-17 years age

Missing Information	Use while Breastfeeding
	group) who received SPIKEVAX 2024-2025 Formula (KP.2) and were breastfeeding their newborn/infants in association with exposure to SPIKEVAX 2024-2025 Formula (KP.2). No unusual patterns or lactation-specific safety concerns were identified in association with exposure to SPIKEVAX 2024-2025 Formula (KP.2). **Lactation Cases After Receiving SPIKEVAX 2024-2025 Formula (JN.1)** The MAH received 1 serious lactation case reporting 10 serious events involving a 38-year-old female who received a dose of SPIKEVAX 2024-2025 Formula [JN.1] (reported as the second dose in her COVID-19 vaccination schedule). The only lactation-specific PT reported was "Maternal exposure during breast-feeding." No other lactation-specific events indicating a clinical adverse event/outcome were reported. There were no lactation-specific events reported in children exposed via breastmilk from mothers vaccinated with SPIKEVAX 2024-2025 Formula (JN.1) or adolescent mothers (12-17 years age group) who received SPIKEVAX 2024-2025 Formula (JN.1) and were breastfeeding their newborn/infants in association with exposure to SPIKEVAX 2024-2025 Formula (JN.1). No unusual patterns or lactation-specific safety concerns were identified in association with exposure to SPIKEVAX 2024-2025 Formula (JN.1). **Lactation Cases After Receiving SPIKEVAX (NOS)** No lactation cases associated with exposure to vaccines classified as SPIKEVAX (NOS) have been reported. There were no lactation-specific events reported in children in association with exposure to vaccines classified as SPIKEVAX (NOS).
Discussion	During the reporting period of this PBRER, a total of 36 lactation cases (137 events) were reported among individuals who received a marketed Moderna vaccine targeting SARS-CoV-2. No cases were reported among children under 6 years of age exposed via breastmilk from mothers vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2. There were no reports of adolescent mothers (12-17 years age group) who received a marketed Moderna vaccine targeting SARS-Cov-2 and were breastfeeding their newborn/infants. There were 6 serious lactation cases received during the reporting period. However, no serious lactation-specific events were reported. The only lactation-specific PT reported in all 6 cases was "Maternal exposure during breastfeeding." 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 AEs 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 [24] [25] [26]. Similar to the prior reporting period, the most frequently reported PT was "Maternal exposure during breast-feeding." The only other lactation-specific PTs indicating a clinical adverse event/outcome were "Lactation disorder" and "Lactation puerperal increased." These were mild transient events which occurred within 2 days after vaccination. No clustering by dose or TTO or concerning patterns or notable trends of events reported were identified. The pattern of reports remains generally

Missing Information	Use while Breastfeeding
	consistent when compared with cumulative data and no new safety concerns were identified. 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 [25] [27] [28]. 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 [29] [30] [31]. 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-authorisation 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

Table 16-16 Long-term Safety

Missing Information	Long-term Safety
Source of New Information	As of the DLP of this PBRER, there have been 25 CTs, including 19 sponsored by ModernaTx, Inc., of which 5 CT (P203, P204, P205, P304, and P305) were completed during the reporting period, assessing the safety of mRNA-1273 and its variant containing vaccines. Cumulatively, 64,409 subjects have been or estimated to be exposed to either elasomeran, or its variants (mRNA 1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA 1273.617, mRNA 1273.617.2, mRNA-1273.529, mRNA-1273.231, 712, and mRNA-1273.815), and participants exposed to mRNA-1273 (or its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 active licensed sFLU vaccines, or mRNA-1345 in the mRNA

Missing Information	Long-term Safety
	clinical development programme sponsored by ModernaTx, Inc. The total count of 64,409 represents unique subjects (Subjects enrolled in both trials mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total).
Background	Per protocols, the clinical development programme had a safety follow-up period of 12 months or more in the ongoing studies that assessed long-term safety: mRNA-1273-P306, and the completed studies mRNA-1273-P301, mRNA-1273-P203, mRNA-1273-P204, and mRNA-1273-P205. Post-authorisation 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 characterised through continued trial follow-up, routine pharmacovigilance, and PASS as indicated in the current RMP. **Study mRNA-1273-P203** Study mRNA 1273 P203, completed during the current review period of this PBRER, was a Phase 2/3 clinical study that aimed to extend the age indication of mRNA-1273 to adolescents 12 to 17 years of age. In Part 1A and 1B, in the mRNA-1273 group Safety Set (N=2486), the median duration of follow-up was 347 days (range: 30 to 791 days) after Dose 1 and 316 days (range: 1 to 749 days) after Dose 2 (in participants who received Dose 2). In the placebo mRNA-1273 group, (N=96), the median duration of follow-up was 213 days (range: 46 to 505 days) after Dose 1 and 182 days (range: 37 to 471 days) after Dose 2 (in participants who received Dose 2). In the mRNA-1273-Part 1C-1 (booster group) Safety Set (N=1357), the median duration of follow-up was 365 days (range: 2 to 562 days) after the BD. In the placebo mRNA-1273-booster group, (N=51), the median duration of follow-up was 363 days (range: 192 to 381 days) after the BD. In Part 1C-2, in the Safety Set (N=155), the median duration of follow-up after the heterologous booster was 363 days (range: 179 to 463 days). In Part 2, in the Safety Set (N=52), 52 participants received Dose 1 and 50 participants received Dose 2. The median duration of follow-up after Dose 1 was 473 days (range: 29 to 520 days) and the median duration of follow-up after Dose 2 was 442 days (range: 0 to 492 days). **Study mRNA-1273-P204** Study mRNA 1273 P204, was a Phase 2/3, dose-escalation, age de-escalation, 3 parts study (Part 1, open-label) and randomised, observer-blind, placebo-controlled expansion study (Part 2) to evaluate the safety, reactogenicity, and effectiveness of mRNA 1273 (primary series and BD) and safety of mRNA 1273.214 (BD) in children 6 months through 11 years of age, assessing up to 3 dose levels (25, 50, and 100 µg) of mRNA 1273 in the primary series. Part 3 (open-label) evaluated an alternative primary series regimen of mRNA 1273 in the primary series (2 doses of mRNA 1273 25 µg on Days 1 and 29 followed by Dose 3 of mRNA 1273 25 µg at least 3 months and up to 5 months after Dose 2) in children 6 years through 11 years of age. Part 3 data are not in scope for this application. **mRNA-1273-P204 Primary series (Part 2)** In the 6 years through 11 years age group, during the Blinded Phase, the median duration of follow-up for participants who received the mRNA 1273 50 µg primary series (N=3007) was 78.0 days from Dose 1 and 48.0 days from Dose 2. The duration of follow-up was similar in the placebo group. In

Missing Information	Long-term Safety
	the long-term analysis (encompassing a period that covers the Blinded Phase and Open-Label Phase [ie, after study unblinding] up to the receipt of a BD, EOS, or database lock [17 May 2024], whichever occurred first), the median duration of follow-up for participants who received the mRNA 1273 50 µg primary series (including those in the placebo mRNA 1273 group) (N=3708) was 290.0 days from Dose 1 and 260.0 days from Dose 2. A total 3612 (97.4%) participants and 1042 (28.1%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety follow-up after Dose 2 of mRNA 1273, respectively. In the 2 years through 5 years age group, during the Blinded Phase, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (N=3031) was 217.0 days from Dose 1 and 186.0 days from Dose 2. The duration of follow-up was similar in the placebo group. In the long-term analysis, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (including those in the placebo mRNA 1273 group) (N=3671) was 362.0 days from Dose 1 and 330.0 days from Dose 2. A total 3116 (84.9%) participants and 1752 (47.7%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety follow-up after Dose 2 of mRNA 1273, respectively. In the 6 months through 23 months age group, during the Blinded Phase, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (N=1994) was 213.0 days from Dose 1 and 183.0 days from Dose 2. The duration of follow-up was similar in the placebo group. In the long-term analysis, the median duration of follow-up for participants who received the mRNA 1273 25 µg primary series (including those in the placebo mRNA 1273 group) (N=2438) was 345.0 days from Dose 1 and 314.0 days from Dose 2. A total 1968 (80.7%) participants and 956 (39.2%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety follow-up after Dose 2 of mRNA 1273, respectively. **mRNA 1273 BD (Study P204 Parts 1 and 2, 6 Years Through 11 Years)** A total of 2519 participants in the 6 years through 11 years age group received the mRNA 1273 25 µg BD following the mRNA 1273 50 µg 2 dose primary series in Study P204. The median interval between Dose 2 of mRNA 1273 in the primary series and the BD was 235.0 days. The median duration of follow-up after the BD was 369.0 days. A total of 2447 (97.1%) participants and 2262 (89.8%) participants had ≥6 months (ie, ≥168 days) and ≥12 months (ie, ≥336 days) of safety follow-up after the BD, respectively. **mRNA 1273.214 BD (Study P204 Parts 1 and 2, 6 Months Through 11 Years)** In the 6 months through 5 years age group, in Study P204 Part 2 (N=2766), the median interval between Dose 2 of mRNA 1273 in the primary series and the BD was 317.0 days. The median duration of follow-up after the BD was 184.0 days. A total of 2658 (96.1%) participants had ≥6 months (ie, ≥168 days) of safety follow-up after the BD. In the 6 years through 11 years age group, for Study P204 participants who received the mRNA 1273.214 BD (N=184), the median interval between Dose 2 of mRNA 1273 in the primary series and the BD was 385.0 days. The median duration of follow-up after the BD was 186.5 days. A total of 180 (97.8%) participants had ≥6 months (ie, ≥168 days) of safety follow-up after the BD.

Missing Information	Long-term Safety
	Study mRNA-1273-P205 Study mRNA-1273-P205 was an open-label, Phase 2/3 study with multiple, sequentially enrolled cohorts to evaluate the immunogenicity, safety, and reactogenicity of variant containing formulations of mRNA-1273 administered as BDs in adults aged 18 years and older. Across all study parts, a total of 5161 participants received a single BD of mRNA 1273 or its variant containing formulations in the study. Exposure and duration of follow-up details of mRNA 1273 and its variant containing formulations administered as a single BD in each study part are as follows: **Part A.1:** 300 participants received the mRNA-1273.211 50 µg single BD, and 593 participants received the mRNA1273.211 100 µg single BD. The median duration of follow-up after the BD was 373.0 days in the mRNA-1273.211 50 µg arm and 357.0 days in the mRNA1273.211 100 µg arm. Most participants (>95.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.211 BD. **Part A.2:** 135 participants received the mRNA-1273.214 50 µg single BD. The median duration of follow-up after the second BD was 177.0 days in the mRNA1273.214 50 µg arm. Most participants (>96.0%) had ≥5 months of safety follow-up after the mRNA-1273.214 second BD. **Part B:** 305 participants received the mRNA-1273 100 µg single BD. The median duration of follow-up after the BD was 358.0 and most participants (>93.0%) had ≥10 months of safety follow-up after the mRNA-1273 BD. **Part C:** 581 participants received the mRNA-1273.617.2 50 µg single BD, and 586 participants received the mRNA-1273.617.2 100 µg single BD. The median duration of follow-up after the BD was 360.0 days in the mRNA-1273.617.2 50 µg arm and 357.0 days in the mRNA-1273.617.2 100 µg arm. Most participants (>95.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.617 BD. **Part D:** 327 participants received the mRNA-1273.213 50 µg single BD, and 583 participants received the mRNA-1273.213 100 µg single BD. The median duration of follow-up after the BD was 359.0 days in the mRNA-1273.213 50 µg arm and 358.0 days in the mRNA-1273.213 100 µg arm. Most participants (>94.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.211 BD. **Part E:** 42 participants received the mRNA-1273.213 100 µg single BD and the median duration of follow-up after the BD was 359.5 days. All participants (100%) had ≥10 months of safety follow-up after the mRNA1273.213 BD. **Part F (Cohort 1):** 133 participants received the mRNA-1273.529 50 µg single BD. The median duration of follow-up after the BD was 357.0 days in the mRNA1273.529 50 µg arm. Most participants (>93.0% in each arm) had ≥10 months of safety follow-up after the mRNA-1273.529 BD. **Part F (Cohort 2):** 376 participants received the mRNA-1273.529 50 µg single BD, and 375 participants received the mRNA1273 50 µg single BD. The median duration of follow-up after the second BD was 358.0 days in the mRNA1273.529 50 µg arm and 358.0 days in the mRNA-

Missing Information	Long-term Safety
	1273 50 µg arm. Most participants (>94.0% in each arm) had ≥10 months of safety follow-up after the mRNA1273.529/mRNA1273 second BD. **Part G:** 437 participants received the mRNA-1273.214 50 µg single BD and the median duration of follow-up after the second BD was 358.0 days. Most participants (>96.0%) had ≥10 months of safety follow-up after the mRNA-1273.214 second BD. **Part H:** 510 participants received the mRNA-1273.222 50 µg single BD. The median duration of follow-up after the second BD was 179.0 days in the mRNA-1273.222 50 µg arm. Most participants (>96.0%) had ≥5 months of safety follow-up after the mRNA-1273.222 second BD. **Part J:** 50 participants each received the mRNA-1273.815 50 µg single BD or mRNA-1273.231 50 µg single BD. The median duration of follow-up after the third BD was 168.0 days in the mRNA-1273.815 50 µg arm and 169.5 days in the mRNA1273.231 50 µg arm. Most participants (>96.0%) had ≥5 months of safety follow-up after the mRNA1273.231/mRNA-1273.815 third BD.
Results	No long-term safety concerns were identified after completion of the studies mRNA-1273-P203, P204, and P205. Post-authorisation 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 characterised. In addition to routine pharmacovigilance activities, results from the following studies will be used to evaluate long-term safety of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran. **Ongoing Studies:** • Study mRNA-1273-P904 (final CSR: 31 Mar 2025), • Study mRNA-1273-P910 (final CSR: 30 Jun 2025), • Study mRNA-1273-P911 (final CSR: 31 Oct 2028), • Study mRNA-1273-P306 (final CSR: Feb 2026). **Completed Studies**: • Study mRNA-1273-P301 (final CSR: 20 Oct 2023), • Study mRNA-1273-P203 (final CSR: 08 Jan 2024), • Study mRNA-1273-P204 (final CSR; 22 Nov 2024), • Study mRNA-1273-P205 (final CSR: 09 Oct 2024).
Conclusion	As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor in the 4 completed study (mRNA-1273-P301, P203, P204, and P205) which are being assessed to characterise 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.

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 A health authority. The characterisation of the missing information within this PBRER 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 12.12.

Table 16-17 Use in Immunocompromised Subjects (Safety concern in PBRER only)

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)

Source of New Information	• Moderna GSDB
	• Literature Sources
	  • Search Criteria Applied: Appendix 13.4
	  • Retrieved: 215 articles
	  • New and Significant Safety Information: There was no new and significant safety information identified for the immunocompromised population.

Background	The topic of Immunocompromised is summarised because it is an area of missing information in 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 tumours 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": 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

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	population.
Results	Refer to Appendix 12.12 for additional information. **<u>Overview of Cases for Immunocompromised Individuals Who Received Elasomeran</u>** During this review period, the MAH received 89 cases (489 events) with 57 serious cases (206 serious events) among immunocompromised individuals who received elasomeran. A total of 62 cases were medically confirmed, and 2 cases reported a fatal outcome. Similar to the prior reporting period, there were more cases involving females (53; 59.6%) compared to males (34; 38.2%), with 2 cases (2.2%) that did not report gender information. The median age of patients was 58.0 years (range: 28.0 to 87.0 years). Similar to the previous review period, the most frequently reported MedDRA PTs (8 events or more; ≥1.6%) in immunocompromised individuals who received elasomeran included fatigue, headache, pyrexia, nausea, pain in extremity, arthralgia, and dyspnoea. Most of the events reported reflect expected reactogenicity and were comparable to those events reported in the general population. Events of COVID-19 infection among immunocompromised individuals was the most reported event during this review period (28; 5.7%). 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, 12 cases (including 11 serious cases and 0 fatal 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. **<u>Subpopulation Analyses:</u>** **<u>Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years old) – Elasomeran)</u>** During the review period, no cases were reported among immunocompromised individuals in these age groups who received elasomeran. **<u>Fatal Cases in Immunocompromised Individuals – Elasomeran</u>** During the reporting period, 2 cases reported a fatal outcome among immunocompromised individuals who received elasomeran. One case concerns a 75-year-old female patient with a relevant medical history of Rheumatoid arthritis who passed away due to asphyxia and aspiration. The asphyxiation due to aspiration of vomit occurred during SARS-CoV-2 PCR testing. The patient's elderly age and significant medical history and concurrent RA-ILD remained as potential confounders. The other case concerned a 66-year-old male patient with a medical history of Epstein-Barr virus infection, and concurrent medical condition of psoriasis that was treated with methotrexate and adalimumab. The patient experienced angioimmunoblastic T-cell lymphoma and passed away due to uncontrollable infection and disseminated intravascular coagulation. His death occurred 3 months after the second dose of elasomeran. His medical history of Epstein-Barr virus infection, and

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	concurrent medical conditions of psoriasis treated with methotrexate and adalimumab, and angioblastic T-cell lymphoma remain as confounders for the fatal events. Using the WHO-UMC causality assessment tool, both cases were assessed as "Unlikely," considering their elderly age, prolonged TTO and significant medical histories, and concurrent medical conditions which could provide alternative explanation for the occurrence of the fatal events. 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 13 cases (73 events) with 5 serious cases (45 serious events) for immunocompromised individuals who received a BD of elasomeran/imelasomeran. Nine (9) cases were medically confirmed, and no cases reported a fatal outcome. Similar to the previous reporting period, there were more cases reported for females (8; 61.5%) than males (5; 38.5%). The median age of patients was 63.0 years (range: 21.0 to 77.0 years). During the review period, the most frequently reported PTs (2 or more events; >2.0%) in immunocompromised individuals who received elasomeran/imelasomeran were fatigue, rash, headache, pyrexia, pain in extremity, syncope, lethargy, gastroesophageal reflux disease, burning sensation, and condition aggravated. Most of these events reflect expected reactogenicity and were comparable to events reported in the general population receiving elasomeran/imelasomeran. Events of COVID-19 infection were the most frequently reported PT in this subpopulation during this review period (6; 8.2%). 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, 1 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 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 2 cases (4 events) with 1 serious case (2 serious events) for immunocompromised individuals who received elasomeran/davesomeran. Both cases were medically confirmed, and neither case reported a fatal outcome. Similar to the previous review period, there were no meaningful changes in the gender distribution

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	of reports as a similar proportion of cases continued to be reported in both females (1; 50.0%) and males (1; 50.0%). The median patient age was 64.5 years (range: 63.0 to 66.0 years). No meaningful comparison of PTs reported during this reporting period can be made with the prior reporting period due to the significant decrease in the number of cases/events reported for immunocompromised individuals who received elasomeran/davesomeran During this reporting period, the only PTs reported in immunocompromised individuals who received elasomeran/imelasomeran were fatigue, condition aggravated, nail pigmentation, and rheumatoid arthritis. Note that during the review period, no 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, no cases were reported among immunocompromised individuals in these age groups who received elasomeran/davesomeran. 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** During the review period, the MAH received 224 cases (990 events) with 164 serious cases (554 serious events) for immunocompromised individuals who received andusomeran. A total of 46 cases were medically confirmed, and 3 cases reported a fatal outcome. Similar to the prior reporting period, there were more cases involving females (142; 63.4%) compared to males (71; 31.7%), with 11 cases (4.9%) that did not report gender information. The median age of patients was 65.0 years (range: 0.0 to 95.0 years). Similar to the previous reporting period, the most frequently reported PTs (21 events or more; >2.0%) in immunocompromised individuals who received andusomeran included fatigue, headache, pyrexia, nausea, arthralgia, chills, pain in the extremity, pain, and product expiration issues (PT: "Discontinued product administered"). Most of these events reflect expected reactogenicity and were comparable to cumulative data. These events were also comparable to events reported in the general population during this reporting period. Note that during the review period, 42 cases (34 serious cases and 0 fatal 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) – Andusomeran)**

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	During the reporting period, the MAH received 1 serious case reporting 3 events (1 serious) involving an immunocompromised child under 12 years of age who received a dose of andusomeran. **Case** [redacted] is a health authority report that concerns a [redacted]-day-old female who experienced the serious event of vomiting as well as the non-serious events of feeling hot and chills on the same day following a dose of andusomeran (reported as the second dose in the patient's COVID-19 vaccination schedule). However, it appears this case may be misclassified as a case involving a neonate considering the events occurred after the second dose and there is no information suggesting maternal exposure to andusomeran in-utero. Additionally, the patient's concurrent medical conditions (which included chronic kidney disease stage 5, diabetes, and immunodeficiency) are not compatible with reported age and seem to indicate that these events may have occurred in an older individual. **Use in Immunocompromised Adolescents (12-17 years old) – Andusomeran)** During the reporting period, the MAH received 1 non-serious case involving an immunocompromised 15-year-old female with a medical history of immunodeficiency who received an unspecified dose of andusomeran. It was reported that the wrong product was administered ("no drug effect") at the pharmacy where she received the vaccine. No other AEs or outcomes were reported. **Fatal Cases in Immunocompromised Individuals – Andusomeran** During the review period, 3 cases reported a fatal outcome among immunocompromised individuals following receipt of andusomeran. All 3 cases concerned individuals 75 years of age or older. According to the WHO causality assessment, all 3 cases were assessed as "Unlikely" given the patient's elderly age and significant medical history (1: Pulmonary embolism, deep vein thrombosis, plasma cell myeloma; 2): Type II diabetes, hypertension, myasthenia gravis; 3): Diffuse large B-cell lymphoma on chemotherapy) which provided alternative explanation for the fatal events. 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 SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** It is important to note that during the review period, in August 2024, the US FDA approved a new formulation for SPIKEVAX against COVID-19 variants, including the new variant KP.2. The new formulation was labelled SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Therefore, this will be the first PBRER review period where cases for immunocompromised individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula will be reviewed. Since its approval, the MAH has received 7 cases (15 events) including 1 serious case (1 serious event) for immunocompromised individuals who received a dose of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Five (5) cases were medically confirmed, and no cases reported a fatal outcome. There have been fewer cases reported for females (3; 42.9%) than males (4; 57.1%). The median age of patients was 66.5 years (range: 25.0 to 79.0 years).

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	Fifteen (15) PTs (1 event each) have been reported in immunocompromised individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. These PTs included anaphylactic reaction, contusion, COVID-19 infection, diarrhoea, gastrointestinal disorder, heart rate increased, lethargy, peripheral swelling, secretion discharge, skin haemorrhage, urticaria, vaccination site pain, as well as issues related to product quality and product storage. No specific pattern/trend were noted among the events reported for these cases. Note that no 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) – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval, no cases have been reported among immunocompromised individuals in these age groups who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. **Overview of Cases for Immunocompromised Individuals Who Received SARS-CoV-2 JN.1 mRNA** Since its approval, the MAH has received 12 cases (39 events) including 6 serious cases (17 serious events) for immunocompromised individuals who received a dose of SARS-CoV-2 JN.1 mRNA. Six (6) cases were medically confirmed, and 1 case reported a fatal outcome. More cases have been reported for females (9; 75.0%) than males (3; 25.0%). The median age of patients was 59.5 years (range: 16.0 to 84.0 years). The most frequently reported PTs (2 events or more; >5.0%) in immunocompromised individuals who received SARS-CoV-2 JN.1 mRNA included pyrexia, dizziness, erythema, malaise, pain in extremity, and syncope. Most of these events reflect expected reactogenicity and were comparable to events reported in the general population who received SARS-CoV-2 JN.1 mRNA. Note that 2 cases (1 serious case, no fatal 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) – SARS-CoV-2 JN.1 mRNA** Since its approval, no cases have been reported among immunocompromised individuals in this age group who received SARS-CoV-2 JN.1 mRNA. **Use in Immunocompromised Adolescents (12-17 years old) – SARS-CoV-2 JN.1 mRNA**

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	Since its approval, the MAH has received 1 non-serious case involving an immunocompromised 16-year-old female with a medical history of rheumatoid arthritis who received. The only reported PT was "Product selection error (Incorrect dose selected)." The event outcome was reported as "Unknown," and no other adverse events/outcomes were reported. **Fatal Cases in Immunocompromised Individuals – SARS-CoV-2 JN.1 mRNA** Since its approval, the MAH has received 1 case reporting a fatal outcome among an immunocompromised individual following receipt of SARS-CoV-2 JN.1 mRNA. This case concerns an 84-year-old male who experienced cerebral infarction and passed away approximately a month after the second dose of SARS-CoV-2 JN.1 mRNA. The patient's medical history included unspecified immunodeficiency and unspecified concomitant medications. According to WHO causality assessment, the case was considered "Unassessable" given the lack of information pertaining to adequate medical history, concomitant medications, diagnostics tests, clinical course of the events, etc., required for a meaningful medical assessment. The patient's elderly age and medical history could be considered as significant risk factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received SARS-CoV-2 JN.1 mRNA. **Overview of Cases for Immunocompromised Individuals Who Received a Vaccine Classified as SPIKEVAX (NOS)** It is important to 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 marketed Moderna vaccines targeting SARS-CoV-2. During this review period, the MAH received 17 cases (43 events) with 8 serious cases (14 serious events) among immunocompromised individuals who received a vaccine classified as SPIKEVAX (NOS). Thirteen cases (13) cases were medically confirmed, and reported a fatal outcome. Unlike the previous reporting period, there were fewer cases reported for females (5; 29.4%) when compared to males (11; 64.7%) during this reporting period and 1 case (5.9%) that did not report gender information. The median age of patients was 65.0 years (range: 32.0 – 79.0 years). Similar to the previous reporting period, most events predominantly reflect expected reactogenicity. During the reporting period, the most frequently reported PTs (2 events or more; >4.0%) were pain and pain in the extremity. Additionally, events of COVID-19 infection continued to be the most reported event for this subpopulation (5; 11.6%) when compared to cumulative data as well as the general population (122; 8.2%) during this review period. This may be due to an already exiting COVID-19 infection prior to vaccination, decreased immunogenicity of vaccination, and/or the susceptibility to constantly changing variants. Note that during the review period, 1 serious non-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.

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	Subpopulation Analyses: **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 classified as SPIKEVAX (NOS). **Fatal Cases in Immunocompromised Individuals – SPIKEVAX NOS** During the review period, 1 case reported a fatal outcome following receipt of a vaccine classified as Spikevax NOS. This case concerns a 42-year-old male with a medical history of myeloma (vincristine, doxorubicin [Adriamycin], Dexamethasone treatment), hypopharyngeal cancer (10 years post-transplant) allogeneic peripheral haematopoietic stem cell transplant and pharyngectomy, who died on unknown date after receiving an unspecified dose of a vaccine reported as Spikevax (NOS). The cause of death was not provided. According to WHO causality assessment, this case was assessed as "Unassessable", given the lack of information provided including cause of death, circumstances leading up to death, supportive diagnostic procedures and treatment, autopsy details, latency, etc. which precluded an adequate medical assessment. However, the conditions outlined in the patient's medical history were considered significant risk factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received a vaccine classified as SPIKEVAX (NOS).
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 AEs observed with all marketed Moderna vaccines targeting SARS-CoV-2 in this population were generally similar. Epidemiological studies have not indicated any increased risk of AEs in immunocompromised individuals following vaccination with a marketed Moderna vaccine 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. During the review period, there were 2 cases reported in adolescents. One (1) case was reported for a child 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 either strongly confounded by multiple comorbidities that provided alternate aetiologies or lacked key data elements required for a meaningful medical assessment.
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

Missing Information	Use in Immunocompromised Subjects (Safety concern in PBRER only)
	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 regarding 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 vaccines 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., 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 relation to the frail subpopulation has not identified any additional clinically relevant new safety information for this subpopulation.

It is important to note that the use of marketed Moderna vaccines targeting SARS-Cov-2 in frail subjects with unstable health conditions and co-morbidities is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a request from a health authority. The characterisation of the risk for this missing information as of the DLP of this PBRER and in Section 16.4, below, remains valid.

Table 16-18 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)

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	• Moderna GSDB
	• Literature Sources
	  • Retrieved: 26
	  • New and Significant Safety Information: There was no new and significant safety information identified.

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)
Background	Frail patients are considered at higher risk for complications due to coronavirus disease 2019 (COVID-19) infection including hospitalisations and deaths; and for this reason, are prioritised candidates for vaccination. Since frail subjects with unstable health conditions and co-morbidities were excluded from the registration CTs, the MAH is characterising safety through post-marketing routine monitoring of AEs in this special subpopulation. It is important to note that the use of marketed Moderna vaccines targeting SARS-Cov-2 in frail subjects with unstable health conditions and co-morbidities is no longer considered missing information within the RMP. It is included as missing information within the PBRER based on a request from a health authority. 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 SSP (see Appendix 12.13), 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 12.13 for more information. **Overview of Frail Cases Reported for Elasomeran:** During the review period, the MAH received 657 cases (4,161 events) with 453 serious cases (1,571 serious events) among frail individuals who received elasomeran. A total of 351 cases were medically confirmed, and 23 cases reported a fatal outcome. The majority of cases (638; 97.1%) received during this period were spontaneous reports. Similar to the prior reporting period, more cases were reported in females (357, 54.3%) compared to males (292, 44.4%) with 8 cases (1.2%) that did not report gender. The median patient age was 56.0 years (range: 18.0 to 100.0 years). Similar to the previous reporting period, a high proportion of reported cases in frail individuals was among the elderly (198, 30.1%). The most frequently reported MedDRA PTs (45 events or more; >1.0%) were fatigue, headache, pyrexia, dyspnoea, pain, pain in extremity, myalgia, arthralgia, asthenia, dizziness, and issues related to the interchange of vaccine products. These events were comparable to those reported in the general population and most events reflect expected reactogenicity. Events of COVID-19 infection were also frequently reported during this review period (98; 2.4%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. **Subpopulation Analyses:** **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – Elasomeran)** During the review period, no cases were reported among frail individuals in these age groups who received elasomeran. **Fatal Cases in Frail Individuals – Elasomeran** During the reporting period, the MAH received 23 cases (3.5%) that reported a fatal outcome among frail individuals following receipt of elasomeran. Most cases (15; 65.2%) involved individuals over the age of 65 years. Using the WHO-UMC causality assessment, most of the cases (20; 87.0%), were assessed as "Unlikely" due to the patient's medical history, comorbidities, or concurrent medical

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)
	conditions that provided alternate aetiologies. Three (3) cases (13.0%) were considered "Unassessable" given the lack of information (e.g. cause of death, autopsy details, circumstances surrounding the event, clinical course, diagnostic tests, etc.) required for a meaningful medical assessment. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received elasomeran. **Overview of Frail Cases reported for Elasomeran/Imelasomeran:** During the review period, the MAH received 24 cases (98 events) with 17 serious cases (59 serious events) among frail individuals who received elasomeran/imelasomeran. A total of 10 cases were medically confirmed, and 1 case reported a fatal outcome. Similar to the prior reporting period, cases were almost equally distributed across gender, with a similar number of cases reported in females (11 cases, 45.8%) compared to males (12 cases, 50.0%) and with 1 case (4.2%) that did not report gender. The median patient age was 63.0 years (range: 42.0 to 90.0 years). Similar to the previous reporting period, a high proportion of reported cases in frail individuals was among the elderly (7, 29.2%). The most frequently reported PTs (3 or more events; >3.0%) were fatigue, dyspnoea, headache, pyrexia, and pain in extremity. Most reported events reflect expected reactogenicity and were comparable to cumulative data reported for this subpopulation. These events were also comparable to those observed in the general population during this reporting period. Events of COVID-19 infection were also frequently reported during this review period (5 events; 6.9%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. **Subpopulation Analyses:** **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – Elasomeran/Imelasomeran)** During the review period, no cases were reported among frail individuals in these age groups who received elasomeran/imelasomeran. **Fatal Cases in Frail Individuals – Elasomeran/Imelasomeran** During the review period, the MAH received 1 case reporting a fatal outcome among a frail individual following receipt of elasomeran/imelasomeran. This case concerns a 90-year-old male with a medical history of heart failure, cardiac pacemaker insertion, ruptured abdominal aortic aneurysm, chronic kidney disease, who passed away following receipt of a dose of elasomeran/imelasomeran (reported as his fifth dose in his COVID-19 vaccine schedule). The cause of death was reported as natural cause along with multiple events. According to WHO-UMC causality assessment, this case was assessed as "Unlikely." The patient's elderly age (90 years old) and significant medical history were considered important confounding factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received elasomeran/imelasomeran.

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)
	Overview of Frail Cases Reported for Elasomeran/Davesomeran: During the review period, the MAH received 24 cases (72 events) with 13 serious cases (24 serious events) among frail individuals who received elasomeran/davesomeran. A total of 20 cases were medically confirmed, and 1 case reported a fatal outcome. Similar to the prior reporting period, more cases were reported in females (15; 62.5%) compared to males (8; 33.3%) with 1 case (4.2%) not reporting gender. The median patient age was 73.0 years (range: 7.0 to 87.0 years). Similar to the previous reporting period, a high proportion of reported cases in frail individuals was among the elderly (13, 54.2%). During the reporting period, the most frequently reported PTs (3 events or more; >4.0%) for frail individuals who received elasomeran/davesomeran were pyrexia, fatigue, myalgia, and swelling. Most events reported during this reporting period reflect expected reactogenicity and were comparable to cumulative data for this subpopulation. Additionally, these events were also comparable with events reported in the general population. **Subpopulation Analyses:** **Use in Frail Children (<12 years old)-Elasomeran/Davesomeran** During the reporting period, the MAH received 1 non-serious case (6 events) concerning a 7-year-old male with a medical history of asthma, who received Elasomeran/Davesomeran, and experienced reactogenicity events. **Use in Frail Adolescents (12-17 years old) – Elasomeran/Davesomeran)** During the review period, no cases were reported among frail adolescents who received elasomeran/davesomeran. **Fatal Cases in Frail Individuals – Elasomeran/Davesomeran** During the review period, the MAH received 1 case reporting a fatal outcome in a frail individual following receipt of elasomeran/davesomeran. This case concerns a 70-year-old male with a medical history that indicated multiple comorbidities (hyperlipidaemia, overweight, atrial fibrillation, and peripheral vascular disorder). Information including the cause of death, circumstances leading up to death, whether an autopsy was performed or not, details regarding previous vaccination dates and doses received, clinical symptoms, and concomitant medications were not provided. According to WHO-UMC causality assessment, this case was considered "Unassessable." The patient's elderly age and significant medical history could be considered as risk factors. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received elasomeran/davesomeran. **Overview of Frail Cases Reported for Andusomeran:** During the review period, the MAH received 546 cases (2,069 events) with 273 serious cases (871 serious events) among frail individuals who received andusomeran. A total of 291 cases were medically confirmed, and 18 cases reported a fatal outcome. Similar to the prior reporting period, more cases were reported in females (329; 60.3%) compared to males (198; 36.3%) with 19 cases (3.5%) not reporting gender. The median patient age was 75.0 years

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)
	(range: 0.0 to 98.0 years). Similar to the prior reporting period, a high proportion of reported cases in frail individuals was among the elderly (340, 62.3%). During the reporting period, the most frequently reported PTs (43 events or more; >2.0%) in frail individuals who received andusomeran included fatigue, headache, pyrexia, nausea, pain in extremity, as well as issues related to product expiration and discontinued product administration. Most of the reported events reflect expected reactogenicity and were comparable to cumulative data reported for this subpopulation. Additionally, these events were also comparable to events reported in the general population during this review period. **Subpopulation Analyses:** **Use in Frail Children (<12 years old)-Andusomeran** During the review period, the MAH received 10 cases (21 events) with 1 serious case (1 serious event) among frail children less than 12 years of age who received or had a medical history of maternal exposure to andusomeran. A total of 9 cases were medically confirmed, and no cases reported a fatal outcome. There was no meaningful comparison by gender as there were an equal number of cases reported in females (5; 50.0%) and males (5; 50.0%). The median patient age was 6.0 years (range: 0.0 to 10.0 years). The 1 serious case (**Case** [redacted] was a health authority report that concerns a [redacted]-day-old female who experienced the serious event of vomiting as well as the non-serious events of feeling hot and chills on the same day following a dose of andusomeran (reported as the second dose in the patient's COVID-19 vaccination schedule). However, it appears this case may be misclassified as a case involving a neonate considering the events occurred after the second dose and there is no information suggesting maternal exposure to andusomeran in-utero. Additionally, the patient's concurrent medical conditions (which included chronic kidney disease stage 5, diabetes, and immunodeficiency) are not compatible with reported age and seem to indicate that these events may have occurred in an older individual. **Use in Frail Adolescents (12-17 years old) – Andusomeran)** During the review period, the MAH received 5 cases (10 events) with 1 serious case (1 serious event) among frail adolescents 12 to 17 years of age who received andusomeran. All 5 cases were medically confirmed, and no cases reported a fatal outcome. There was no meaningful comparison by gender as there were a similar number of cases reported in females (2; 40.0%) and males (3; 60.0%). The median patient age was 14.0 years (range: 12.0 to 17.0 years). The 1 serious case concerned a 12-year-old female with a medical history of asthma who experienced the serious event of chest pain 1 day after receiving Dose 1 of andusomeran. The event outcome was reported as "Resolved." **Fatal Cases in Frail Individuals – Andusomeran** During the reporting period, the MAH received 18 cases (3.3%) that reported a fatal outcome among frail individuals following receipt of andusomeran. The majority of cases (16; 89%) concerned individuals over the age of 65 years. Using the WHO-UMC causality assessment, most of the cases (14; 89%), were assessed as "Unlikely" due to the patient's medical history, comorbidities, or

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)
	concurrent medical conditions that provided alternate aetiologies, Three (3) cases were considered "Unassessable" given the lack of information (including cause of death, autopsy details, circumstances surrounding the event, clinical course, diagnostic tests, etc.) required for a meaningful medical assessment. One (1) case was assessed as "Possible," however, the patient's medical history could be considered as an important risk factor. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received andusomeran. **Overview of Cases for Frail Individuals Who Received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval in August 2024, the MAH has received 45 cases (172 events) with 10 serious cases (24 serious events) among frail individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. A total of 35 cases were medically confirmed, and no cases reported a fatal outcome. More cases have been reported in females (27; 60.0%) compared to males (17; 37.8%). The median patient age was 64.0 years (range: 0.6 to 93.0 years). Additionally, a high proportion of cases in frail individuals was among the elderly (21, 46.7%). The most frequently reported PTs (4 or more events; >2.0%) in frail individuals who have received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula were fatigue, headache, malaise, myalgia, pain in extremity, pyrexia, as well as administration issues related to underdosing. Most of the reported events reflect expected reactogenicity and were comparable with events reported during this review period in the general population. **Subpopulation Analyses:** **Use in Frail Children (<12 years old)- SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval for EUA for use in children 6 months to <12 years of age, the MAH has received 6 non-serious medically confirmed cases (13 events) among frail children less than 12 years of age who received or had a medical history of maternal exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The median patient age was 5.5 years (range: 0.6 to 10.0 years). Five of these cases reported PTs indicating issues related to product administration (wrong product administered, overdose, or expired product administered). No additional adverse events/outcomes were reported in these cases. The remaining case reported only the non-serious event of urticaria in a 6-year-old male with a medically history of eczema, drug sensitivity, and allergy. **Use in Frail Adolescents (12-17 years old) – SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula** Since its approval, the MAH has received 2 cases (10 events) with 1 serious case (8 serious event) among frail adolescents 12 to 17 years of age who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Both cases were medically confirmed, and neither case reported a fatal outcome. There was no meaningful comparison by gender as there was an equal number of cases reported in

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)
	females (1; 50.0%) and males (1; 50.0%). The median patient age was 15.0 years (range: 14.0 to 16.0 years). The 1 serious case concerned a 14-year-old female with a medical history of asthma, Type 1 diabetes mellitus, and coeliac disease who experienced the serious events of blood glucose increased, blood ketone body increased, headache, peripheral coldness, pyrexia, vaccination site cellulitis, vaccination site inflammation, and vomiting on the same day following Dose 1 of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula) [reported as the fourth dose in patient's COVID-19 vaccine schedule. Previous doses were Pfizer's Comirnaty vaccine]. The event outcome was reported as "Recovering/Resolving." Potential confounders for this case include the patient's medical history of Type 1 diabetes mellitus as well as the concurrent vaccination with Prevnar in the same arm on the same day. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula **Overview of Cases for Frail Individuals Who Received SARS-CoV-2 JN.1 mRNA** Since its approval in Sep 2024, the MAH received 60 cases (198 events) with 26 serious cases (60 serious events) among frail individuals who received SARS-CoV-2 JN.1 mRNA. A total of 36 cases were medically confirmed, and 3 cases reported a fatal outcome. More cases were reported in females (33; 55.0%) compared to males (27; 45.0%). The median patient age was 73.0 years (range: 32.0 to 94.0 years). Additionally, a high proportion of reported cases in frail individuals was among the elderly (35, 58.3%). The most frequently reported PTs (4 events or more; >2.0%) in frail individuals who received SARS-CoV-2 JN.1 mRNA were dyspnoea, pyrexia, arthralgia, fatigue, dizziness, headache, nausea, pain in extremity, as well as issues related to product expiration. Most of the reported events reflect expected reactogenicity and were comparable with events reported during this review period in the general population. **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – SARS-CoV-2 JN.1 mRNA** Since its approval, no cases have been reported among frail individuals in these age groups who received SARS-CoV-2 JN.1 mRNA. **Fatal Cases in Frail Individuals – SARS-CoV-2 JN.1 mRNA** Since its approval, the MAH has received 3 cases reporting a fatal outcome among frail individuals following receipt of SARS-CoV-2 JN.1 mRNA. 2 (2) cases concerned individuals who were older than 65 years of age. The remaining case concerned an individual who was 64 years old. According to the WHO-UMC causality assessment, 2 cases were assessed as "Unlikely" due to the patient's medical history, comorbidities, or concurrent medical conditions that provided alternate aetiologies. The remaining case was considered "Unassessable" given the lack of information provided including additional medical history, concomitant medications, diagnostic/laboratory tests, circumstances surrounding the events, event details, cause of death, autopsy details etc. The patient's underlying history of COPD and previous strokes were considered significant risk factors.

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)
	Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received SARS-CoV-2 JN.1 mRNA. **Overview of Frail Cases Reported for a Vaccine Classified as SPIKEVAX (NOS):** It is important to 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 marketed Moderna vaccines targeting SARS-CoV-2. During the review period, the MAH received 47 cases (185 events) with 20 serious cases (50 serious events) among frail individuals who received a vaccine classified as SPIKEVAX (NOS). A total of 25 cases were medically confirmed, and 2 cases reported a fatal outcome. When compared to the prior reporting period, there was a slightly higher proportion of cases reported in females (24; 51.1%) than males (19; 40.4%) with 4 cases (8.5%) that did not report gender. The median patient age was 66.0 years (range: 28.0 to 89.0 years). Similar to the prior reporting period, a high proportion of reported cases in frail individuals was among the elderly (19, 40.4%). During the reporting period, the most frequently reported PTs (3 or more events; ≥1.6%) reported among frail individuals who received a vaccine classified as SPIKEVAX (NOS) were fatigue, illness, pain, immunisation reaction, pain in extremity, peripheral swelling, dizziness, hypersensitivity, syncope, as well as issues related to interchange of vaccine products. Most of the reported events reflect expected reactogenicity and were comparable to cumulative data for this subpopulation. Additionally, these events were also comparable to events reported in the general population during this review period. Similar to the prior reporting period, events of COVID-19 infection continued to be the most frequently reported event during this reporting period (10; 5.4%). This may be due to an already exiting COVID-19 infection prior to vaccination, and/or the susceptibility to constantly changing variants. **Use in Frail Children (<12 years old) and Adolescents (12-17 years old) – SPIKEVAX (NOS)** During the review period, no cases were reported among frail individuals in these age groups who received a vaccine classified as SPIKEVAX (NOS). **Fatal Cases in Frail Individuals – SPIKEVAX (NOS)** During the review period, 2 cases reported a fatal outcome among frail individuals following receipt of a vaccine classified as SPIKEVAX (NOS). Both cases were reported for individuals over 75 years of age. Using WHO-UMC causality assessment, both cases were assessed as "Unlikely" due to the patient's medical history, comorbidities, or concurrent medical conditions that provided alternate aetiologies. Based on current available information, no clustering or trends of safety concerns have been identified regarding frail individuals who received a vaccine classified as SPIKEVAX (NOS).
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

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)
	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. During the reporting period, there were 17 cases reported among frail children and 7 cases reported among frail adolescents in association with exposure to marketed Moderna vaccines targeting SARS-CoV-2. There was no clustering or trends among these cases that revealed any new or unusual pattern of events or safety concerns. Cases reporting a fatal outcome among frail individuals during the reporting period (3.4%) were either strongly confounded by advanced age and multiple comorbidities that provided alternate aetiologies or lacked key data elements required for a meaningful medical assessment.
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 the missing information of all marketed Moderna vaccines targeting SARS-CoV-2 in relation to individuals with known history of autoimmune and inflammatory disorders (MedHx AI/ID), has not identified any additional clinically relevant new safety information for this population.

Use in subjects with AI/ID is no longer considered missing information in the approved RMP. It is presented here as per request from a health authority. The characterisation of this missing

information as described in this PBRER and in Section 16.4, below, remains valid. The number of cases received during reporting period are presented by product in Table 16-19. Refer to Appendix 12.14 for further information on fatal cases.

Table 16-19 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 (Safety concern in PBRER only)
Source of New Information	• Moderna GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 1056 o New and Significant Safety Information: None (0).
Background	To date, CTs, and post-authorisation safety data have not identified any safety risks in individuals with AI/ID. 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 additional doses 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. 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 spontaneous reports for marketed Moderna vaccines targeting SARS-CoV-2 in people with a medical history of autoimmune and/or inflammatory disease, received for the review period (18 Dec 2023 to 17 Dec 2024). 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 utilising the WHO-UMC standardised case causality assessment.
Results	Refer to Appendix 12.14 for additional information. **Overview of MedHx AI/ID Cases Reported for Elasomeran** During this reporting period, 279 cases (184 serious, 151 medically confirmed, 7 fatal cases) with 1,920 events (590 serious) were reported in individuals with a known MedHx AI/ID after receiving elasomeran. Majority of cases (202; 72.4%) were reported in females compared to males (74 cases;

Missing Information	Use in subjects with autoimmune or inflammatory disorders (Safety concern in PBRER only)
	26.5%), with a small proportion of cases (3; 1.1%) having no gender reported. The mean patient age was 51.7 years (SD: 13.8) and median age was 50.0 years (range: 14.0 to 90.0 years). Of note, 13 cases (4.7%) were missing age-related information. The most frequently reported (>1%) serious events during this reporting period were COVID-19; Asthenia; Dyspnoea; and Fatigue. **Subpopulation Analysis:** **Use in Children <18 Years of Age with MedHx AI/ID (Elasomeran)** During this reporting period, there was 1 non-serious follow-up case reported in a 14-year-old male, who had inappropriate schedule of product administration (First dose was administered on 18 Feb 2021 and second dose was administered on 03 Mar 2021). There were no AEs reported. On 29 Jan 2024: Follow-up received during this PBRER reporting period was non-significant. No adverse event was added. **Fatal Cases in Individuals with MedHx AI/ID (Elasomeran)** During this reporting period, 7 cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran. Most of these cases (4 out of 7) were assessed as Unassessable due to limited information and remaining 3 cases were assessed as Unlikely. Refer to Appendix 12.14 for further information. **Overview of MedHx AI/ID Cases Reported for Elasomeran/Imelasomeran** During the reporting period, 10 cases (7 serious, 4 medically confirmed, 0 fatal) with 35 events (17 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 (6 cases; 60.0%) and males (4 cases; 40.0%). The mean patient age was 62.4 years (SD:6.5) and median age was 62.0 years (range: 56.0 to 77.0). Of note, 1 case (10.0%) was missing age related information. During this reporting period, Syncope, and Myocardial injury were reported in 2 cases, (11.8%), and all other serious events, each were reported once (5.9%) in individuals each 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, 10 cases (5 serious, 7 medically confirmed, 0 fatal) with 35 events (8 serious) reported in individuals with known MedHx of AI/ID after receiving elasomeran/davesomeran. The majority of cases were reported in females (8 cases; 80.0%) compared to males (2 cases; 20.0%). The mean patient age was 57.5 years (SD:15.0) and median age was 61.0

Missing Information	Use in subjects with autoimmune or inflammatory disorders (Safety concern in PBRER only)
	years (range: 27.0 to 75.0 years). All 10 cases report age related information. During this reporting period, the following serious events were reported Anaphylactic reaction; Acute macular neuroretinopathy; Aneurysm; Coagulopathy; Myasthenia gravis; Retinal vascular occlusion; TIA; and Ventricular tachycardia. Each event was reported once (12.5%) in individuals 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, 261 cases (181 serious, 61 medically confirmed, 6 fatal case) with 1114 events (573 serious) were reported in individuals with a known MedHx AI/ID after receiving andusomeran. The majority of cases (187; 71.6%) were reported in females compared to males (67 cases; 25.7%), with a small proportion of cases (7; 2.7%) having no gender reported. The mean patient age was 62.9 years (SD: 14.0) and median age was 64.0 years (range: 27.0 to 93.0 years). Of note, 33 cases (12.6%) did not provide age related information. The most frequently reported serious events during this reporting period reflected expected reactogenicity events, such as pyrexia, headache, and fatigue. This is 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, 6 cases with fatal outcome was reported in an individual with known MedHx AI/ID who received andusomeran. Refer to Appendix 12.14 for further information. **Overview of MedHx AI/ID Cases Reported for SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula.** During this reporting period, 11 cases (2 serious, 9 medically confirmed, with no fatal case) with 61 events (9 serious events) were reported in individuals with a known MedHx AI/ID after receiving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. The majority of cases (9; 81.8%) were reported in females compared to males (2 cases; 18.2%). The mean patient age was 53.4 years (SD: 25.6) and median age was 62.0 years (range: 5.0 to 79.0 years). There was no frequently reported serious events during this reporting period. None of the serious events were reported for the first time and most of the events were reactogenicity events (such as

Missing Information	Use in subjects with autoimmune or inflammatory disorders (Safety concern in PBRER only)
	pyrexia, headache, etc). These are consistent with cumulative reporting. **Subpopulation Analysis:** **Use in Children <18 Years of Age with MedHx AI/ID with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula**: During this review period, there was one non-serious case (MOD-2024-776023) involving a 14-year-old female administered SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula reported in children <18 years of age. **Fatal Cases in Individuals with MedHx AI/ID with SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula:** During this reporting period, there were zero (0) case with fatal outcome who received SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. **Overview of MedHx AI/ID Cases Reported for SARS-CoV-2 JN.1 mRNA** During this reporting period, 13 cases (6 serious, 6 medically confirmed, 0 fatal case) with 41 events (13 serious events) were reported in individuals with a known MedHx AI/ID after receiving SARS-CoV-2 JN.1 mRNA. The majority of cases (10; 76.9%) were reported in females compared to males (3 cases; 23.1%). The mean patient age was 58.0 years (SD: 21.7) and median age was 62.5 years (range: 16.0 to 91.0 years). Of note, 1 case (12.9%) did not provide age related information. There was no frequently reported serious events during this reporting period and none of the serious events reported more than once. None of the serious events were reported for the first time and most of these were reactogenicity events. This is consistent with cumulative reporting. **Subpopulation Analysis:** ***Use in Children <18 Years of Age with MedHx AI/ID with SARS-CoV-2 JN.1 mRNA*** During this review period, there was one non-serious case involving a 16-years-old female involving SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula were reported in children <18 years of age. ***Fatal Cases in Individuals with MedHx AI/ID with SARS-CoV-2 JN.1 mRNA*** During this reporting period, there were zero (0) cases with fatal outcome who received SARS-CoV-2 JN.1 mRNA. **Overview of MedHx AI/ID Cases Reported for SPIKEVAX (NOS):** 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 marketed Moderna vaccine targeting SARS-CoV-2. During this reporting period, 27 cases (18 serious, 19 medically confirmed, 0 fatal) with 80 events (28 serious) were reported in individuals with a known MedHx AI/ID after receiving SPIKEVAX (NOS). The majority of the cases involved females (20 cases, 74.1%) compared to males (7 cases, 25.9%). The mean patient age was 59.6 years (SD: 12.3) and median age was 61.0 years (range: 38.0 to 79.0 years). Of note, 2 cases (7.41%) did not provide age related information. During this reporting period, Rheumatoid arthritis was the only serious event reported more than

Missing Information	Use in subjects with autoimmune or inflammatory disorders (Safety concern in PBRER only)
	once (14.3%). All remaining events were reported once each (3.6%) in individuals with known MedHx AI/ID receiving SPIKEVAX (NOS). **Subpopulation Analysis:** ***Use in Children <18 Years of Age with MedHx AI/ID (SPIKEVAX [NOS])*** During this review period, no cases involving SPIKEVAX (NOS) 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 SPIKEVAX NOS.
Discussion	Based on the analysis of all the safety data available as of 17-Dec-2024, 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 outweigh any possible vaccine-associated risks. Review of the literature for use in AI/ID individuals did not identify any new safety concerns and support the positive benefit/risk profile of marketed Moderna vaccines targeting SARS-CoV-2. 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, in addition to their underlying autoimmune diseases, the cases had common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, and hyperlipidaemia, 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 reported AEs and administration of marketed Moderna vaccines targeting SARS-CoV-2 in individuals with AI/ID. Information presented in the 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 vaccines 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. Characterisation of Risks

Table 16-20 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-authorisation safety.
Characterisation of risk	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 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 tachypnoea on Day 29 after the first dose (which was reported on the day of the second dose), severe tachypnoea 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 dyspnoea (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 50-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, the booster phase of mRNA-1273-P301, of the 19,609 participants who received the 50 µg BD mRNA-1273, no anaphylaxis or severe hypersensitivity reactions were reported within 30 minutes after injection (mRNA-1273-P301 Final CSR, Section 7.3.1.5; data extraction 07 April 2023). In Study mRNA-1273-P203 that evaluated mRNA-1273 in healthy adolescents ages ≥12 to <18 years, there were no cases of anaphylaxis assessed as related to study vaccine (mRNA-

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	1273-P203 Parts 1A, 1B, 1C-1, 1C-2 and 2 Final CSR, Sections 7.2.2.3.3, 7.3.3.3.3, and 7.4.3.3.3; mRNA-1273-P203 Part 3 Final CSR, Section 7.3.4.3.2). In studies mRNA-1273-P204 and mRNA-1273-P306 that evaluated a 2-dose primary series and/or a BD of mRNA-1273 and mRNA-1273.214 in children ≥6 months to <12 years of age, no cases of anaphylaxis assessed as related to study vaccine by the Investigator or other severe hypersensitivity related events were reported or identified after analysis of events within the Hypersensitivity SMQ following the primary series and/or BD (mRNA-1273 or mRNA-1273.214) in either study (Module 2.5, Section 2.5.5.4.1). During the review period, the MAH received a total of 36 cases (36 serious, 1 fatal) of anaphylaxis related events in individuals after the administration of elasomeran. Twenty-six cases were medically confirmed. The majority of cases (27 cases, 75.0%) were reported in females, compared to 8 cases (22.2%) in males, with 1 case (2.8%) lacking gender information. The mean age was 44.7 years (SD: 13.6) and median age was 46.0 years (range: 15.0 to 70.0 years). There was one case with a reported fatal outcome. This case involved a male patient of unknown age, who after receiving the first dose of Elasomeran reported developed multiple AEs. However, anaphylaxis was not a reported event. The events experienced by this patients were likely complications arising from progression/worsening of the underlying pre-existing comorbidities involving multiple organs (generalised atherosclerosis, condition after a previous heart attack, cardiomyopathy, cirrhosis of the kidneys, lung changes including pleural and pericardial effusions and hyperaemic gastritis) and a concurrent infection which provided more likely explanation of the reported events in this case (circulatory failure, shock due to pulmonary oedema). During the review period, no cases were received from elasomeran/imelasomeran. During the review period, the MAH received 4 serious medically confirmed cases (4 serious events) anaphylaxis related events in individuals after the administration of elasomeran/davesomeran. Of these 3 cases (75.0%) were reported in female and 1 case (25.0%) was reported in male. The mean age was 64.0 years (SD: 15.5) and median age was 58.0 years (range: 53.0 to 87.0 years). There was one case, with a reported fatal outcome. Anaphylaxis (PT) was not a reported term in this case, which involved an 87-year-old male patient with concurrent ILD. The patient also experienced the event of shock, which occurred 8 months after vaccination with Elasomeran/davesomeran. During the review period, the MAH received 13 serious cases (with13 serious) anaphylaxis related events after the administration of andusomeran. There were 10 medically confirmed cases involving andusomeran. The majority of cases (8 cases, 61.5%) were reported in females, compared to 5 cases (38.5%) in males. The mean age was 72.2 years (SD: 20.1) and median age was 77.0 years (range: 29.0 to 95.0 years). One case was missing age information. There were 2 cases [redacted] with a reported fatal outcome. In both cases, anaphylaxis (PT) was not a reported term. Additionally, a delayed latency/ TTO

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	of >1 day noted, which is atypical in the context of vaccine induced anaphylaxis. Alternative aetiologies provided a more likely explanation of the reported event(s) in both cases. During the review period, the MAH received one serious medically confirmed case (One serious event) related to anaphylaxis after the administration of SPIKEVAX (NOS). The reported case involved a female (1 case, 100.0%). Review of the data received, 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 were not suggestive of a typical anaphylactic reaction, instead an important confounder of medical histories of atopy including different types of allergies (food, animals, medicines, etc.) were noted in most of the patient's reporting anaphylaxis, indicating that the reported events may be an expression of allergic reactions and not true cases of anaphylaxis. Additionally, analyses of cases of anaphylaxis, including the events reported after marketed Moderna vaccines targeting SARSCoV2 appear to be generally consistent in nature and severity to those reported with elasomeran. For the cases that involved a fatal outcome, the underlying pre-existing comorbidities involving multiple organs, concurrent infection and the alternative aetiologies, provided a more likely explanation for the reported 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 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 vaccines targeting SARS-CoV-2. Causal association between marketed Moderna vaccines targeting SARS-CoV-2 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 the vaccine. As per request from the PRAC, in their final assessment report for PBRER 4, anaphylaxis is retained as an important identified risk within the PSUR.

Important Identified Risk	**Anaphylaxis (Safety concern in PBRER only)**
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 HCP.

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 recognised 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 [32]. Evaluation of the post-authorisation 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 to note that cases of myocarditis and pericarditis have been identified in CTs of Novavax COVID-19 Vaccine (a protein subunit vaccine) and have also been reported during post-authorisation 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 [33] 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 hypothesise that release of S1 protein could result from cleavage via mammalian cell proteases or circulating proteases. The

Important Identified Risk	Myocarditis
	authors observed an increase in S1 over an initial period of one to 5 days, suggesting that mRNA translation begins immediately after vaccine inoculation. Interestingly, spike protein appears in 3 of 13 participants on average 8 days after S1 is produced.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and post-authorisation safety information, including PASS, as well as published literature information.
Characterisation 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 2 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. 2 other cases of suspected myocarditis were reported but were not adjudicated as myocarditis. The Certified in Medical Quality (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-authorisation safety data, cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [7], and the CDC working case definition [18] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilising the WHO-UMC standardised case causality assessment. Evaluation of the data in the safety database 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 mean age varied across formulations was noted, and this probably could be due to potential differences in the populations receiving each vaccine formulation. Consistent male predominance is observed in cases involving myocarditis/pericarditis, across all formulations. Most of the cases reported during the current review period were considered unassessable regarding the causality assessment given that important information was missing, including medical history and concomitant medication, information considered essential for understanding any associated risk factors/confounders for individuals within the reported age range and the occurrence of myocarditis/pericarditis. Review of the article suggested by the EMA [10] did not identify any significant safety issue of concern. 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 [34].

Important Identified Risk	Myocarditis
	A review of the data received cumulatively showed a continuous decreasing trend in the number of reported cases and that events of myocarditis and pericarditis continue to primarily occur within 7 days after vaccination. Based on the analysis of all the safety data available as of 17 Dec 2024, 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%) [35]. Among these, high mortality rates (51%–97%) have been described in several cases series. Although the incidence of myocarditis in the vaccinated population is higher than in unvaccinated individuals, the risk of myocarditis due to COVID-19 and its fatal outcome is much lower among vaccinated people. Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The annual prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. 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 [36]. 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 dyspnoea 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 [37]. HCP 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. HCP 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 [38].

Important Identified Risk	**Myocarditis**
	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 PASS to further characterise 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 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. HCP should be alert to the signs and symptoms of myocarditis. The benefits (prevention of COVID-19 disease and associated hospitalisations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended [18].
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 HCP 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 characterised 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 [39]. 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 hospitalised 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 Identified Risk	Pericarditis
	Important to note that cases of pericarditis have been identified in CTs of Novavax COVID-19 Vaccine (a protein subunit vaccine) and have also been reported during post-authorisation 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 [33] 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 hypothesise 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 5 days, suggesting that mRNA translation begins immediately after vaccine inoculation. Interestingly, spike protein appears in 3 of 13 participants on average 8 days after S1 is produced.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and post-authorisation safety information, including PASS, as well as published literature information.
Characterisation 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 2 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, 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 Clinical Events Adjudication Committee (CEAC) adjudicated this as a case of acute pericarditis.

Important Identified Risk	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 hospitalised 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-authorisation safety data, cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [7], and the CDC working case definition [18] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilising the WHO-UMC standardised case causality assessment. Evaluation of the GSDB 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 mean age varied across formulations was noted, and this probably could be due to potential differences in the populations receiving each vaccine formulation. Consistent male predominance is observed in cases involving myocarditis/pericarditis, across all formulations. Most of the cases reported during the current review period were considered unassessable regarding the causality assessment given that important information was missing, including medical history and concomitant medication, information considered essential for understanding any associated risk factors/confounders for individuals within the reported age range and the occurrence of myocarditis/pericarditis. 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 [34]. A review of the data received cumulatively showed a continuous decreasing trend in the number of reported cases and that events of myocarditis and pericarditis continue to primarily occur within 7 days after vaccination. Based on the analysis of all the safety data available as of 17 Dec 2024, 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

Important Identified Risk	Pericarditis
	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 [40]. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years [41]. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardised incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65 [42]. 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, tumours, 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 [43]. Pericarditis may result in one of 2 serious complications: cardiac tamponade and chronic constrictive pericarditis. Cardiac tamponade is considered a medical emergency and, if left untreated, can quickly become fatal. HCP should consult guidance and/or specialists to diagnose and treat this condition. CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, could consider proceeding with 2nd dose [44].
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 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. HCP should be alert to the signs and symptoms of pericarditis. The benefits (prevention of

Important Identified Risk	**Pericarditis**
	COVID-19 disease and associated hospitalisations, 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 HCP.

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 2024, 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 [45] 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 July 2022, Ma and Yu [46] 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 hyperglycosylated IgA1 in IgA nephropathy, the authors proposed 3 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

Important Potential Risk	**IgA Nephropathy (Safety concern in PBRER only)**
	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 authorisation safety data. Based on the analysis of all available safety data as of 17 Dec 2024, 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.
Characterisation 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 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 aetiology and pathophysiology of IgA nephropathy remain unknown. There were no reports from CTs 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 2024, 65 IgA nephropathy confirmed reports in 1,043,567,281doses administered, shows an approximate reporting rate < 1 case per 10 million doses. Of these, 42 cases were de novo, and 22 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 haematuria 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 [47].

Important Potential Risk	**IgA Nephropathy (Safety concern in PBRER only)**
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 March 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."
Impact on the benefit-risk balance of the product	Overall, based on the analysis of all available safety data as of 17 Dec 2024, 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 SARSCoV2.
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) [48]. Half of patients with IgA Nephropathy may progress to ESRD within 25 years of the disease. Overall, 65 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 marketed Moderna vaccines targeting SARS-CoV-2 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 SARS-CoV-2 infection and related complications in this population. There have been no specific safety concerns identified for COVID maternal immunisation. 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.

Missing information	Use in Pregnancy and While Breast-Feeding
	More specifically, a 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 3 weeks following a spontaneous abortion and 0.81 (0.69 to 0.95) for vaccination in the previous 5 weeks, showing no risk of early pregnancy loss after COVID-19 vaccination. Another important perinatal outcome of interest after maternal vaccination is risk of foetal anomalies. Given the importance of timing in pregnancy and risk of foetal anomalies, a large cohort study evaluated the association of COVID-19 vaccination during early pregnancy with risk of congenital foetal 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 haemoglobin A1c level in the first trimester and age at delivery, vaccination within the highest risk period for teratogenicity was not associated with presence of congenital anomalies identified by ultrasonography (adjusted odds ratio 1.05, CI: 0.72 to 1.54). Additional studies have not found an increased risk of congenital anomalies among pregnant people 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 [49], 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 the 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 neutralising 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 85 pregnancy cases (661 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

Missing information	Use in Pregnancy and While Breast-Feeding
	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 review period, 2 cases reported stillbirth. Both cases of stillbirth had clear alternate aetiologies with no observed pattern or clear TTO cluster. This is consistent with cumulative data concerning stillbirth reported thus far for marketed Moderna vaccines targeting SARS-CoV-2. 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 21 cases reporting congenital anomalies following maternal exposure to elasomeran (19 cases) and vaccines classified as SPIKEVAX [NOS] (2 cases) during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunisation with marketed Moderna vaccines targeting SARS-CoV-2. During the reporting period, there were 6 pregnancy cases reported among children under 6 years of age associated with exposure to a marketed Moderna vaccine targeting SARS-CoV-2 (All 6 cases were reported in association with exposure to elasomeran). Review of these 6 serious cases did not identify unusual patterns or safety concerns. During the reporting period, no pregnancy cases associated with exposure to marketed Moderna vaccines targeting SARS-CoV-2 were reported concerning children 6 to 11 years of age. Additionally, no pregnancy cases among adolescents associated with exposure to marketed Moderna vaccines targeting SARS-CoV-2 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.

Missing information	Use in Pregnancy and While Breast-Feeding
	Since SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula approval, the MAH has received 5 pregnancy cases reporting events after exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. Review of all pregnancy-specific events and non-pregnancy-specific events for all pregnancy cases received following SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccination did not identify any new safety concerns. There were no cases that reported pregnancy-specific complications related with the administration of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula. No unusual patterns or pregnancy-specific safety concerns have been identified with use during pregnancy. The current safety profile of SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula is consistent with the safety profile of marketed Moderna vaccines targeting SARS-Cov-2. The MAH will continue to review cases associated with exposure to SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccine using routine surveillance. The most frequently reported PTs following SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula vaccination were related to errors in product administration ("Wrong product administered," "Accidental overdose," "Product administration error," and "Underdose"). The other PTs reported were predominantly reactogenicity events, which is consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2 and consistent with events reported for those vaccines in prior review periods. No pregnancy-specific events indicating an adverse clinical outcome following SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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. 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. Since SARS-CoV-2 JN.1 mRNA approval, the MAH has received 5 pregnancy cases reporting events after exposure to SARS-CoV-2 JN.1 mRNA. Review of serious pregnancy-specific events and non-pregnancy-specific events for all pregnancy cases received following SARS-CoV-2 JN.1 mRNA vaccination did not identify any new safety concerns. Overall, cases of pregnancy-specific complications were temporally related with the administration of SARS-CoV-2 JN.1 mRNA 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 SARS-CoV-2 JN.1 mRNA is consistent with the safety profile of marketed Moderna vaccines targeting SARS-CoV-2. The MAH will continue to review cases associated with exposure to SARS-CoV-2 JN.1 mRNA vaccine using routine surveillance. The most frequently reported PTs following SARS-CoV-2 JN.1 mRNA vaccination were related to product storage and quality ("Product temperature excursion issue" and "Poor quality product administered"). The other PTs reported were predominantly reactogenicity events, which is consistent with the product safety profile for marketed Moderna vaccines targeting SARS-CoV-2 and consistent with events reported for those vaccines in prior review periods.

Missing information	Use in Pregnancy and While Breast-Feeding
	No pregnancy-specific events indicating an adverse clinical outcome following SARS-CoV-2 JN.1 mRNA vaccination have been reported. No pregnancy cases following SARS-CoV-2 JN.1 mRNA 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. 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 immunisation with marketed Moderna vaccines targeting SARS-CoV-2. Furthermore, published literature has reported that there is transfer of maternal antibodies, reduction in SARS-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 SARS-CoV-2 infection may be more serious and cause complications for both the mother and the foetus. Four (4) articles published during the reporting period provided additional evidence supporting the use of marketed Moderna vaccines targeting SARS-CoV-2 during pregnancy. A prospective cohort study from [20] demonstrated that both SARS-CoV-2 infection and COVID-19 vaccine (including marketed Moderna vaccines targeting SARS-CoV-2) exposure in-utero were not associated with an increased risk of adverse neurodevelopmental outcomes in infants up to 12 months of age. Similarly, a prospective study conducted by [21] in the United States suggested that the use of COVID-19 vaccines (including mRNA vaccines) was safe during pregnancy from the perspective of infant neurodevelopment up to 18 months of age. [22] conducted an observational population-based cohort study in Sweden and Norway which indicated that vaccination of pregnant individuals with mRNA COVID-19 vaccines was not associated with an increased risk of neonatal AEs in their infants. Lastly, [23] conducted a population-based retrospective cohort study and sibling matched analysis that demonstrated that mRNA COVID-19 vaccines (including marketed Moderna vaccines targeting SARS-CoV-2) given during the first trimester of pregnancy were not associated with an increased risk for major congenital anomalies in offspring, overall or grouped by organ system (for a summary of these articles please refer to Articles of Reference for Pregnancy with Company Comment). Published literature supports the favourable benefit/risk profile of maternal immunisation 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. During the reporting period of this PBRER, a total of 36 lactation cases (137 events) were reported among individuals who received a marketed Moderna vaccine targeting SARS-CoV-2. No cases were reported among children under 6 years of age exposed via breastmilk from mothers vaccinated with a marketed Moderna vaccine targeting SARS-CoV-2. There were no reports of adolescent mothers (12-17 years age group) who received a marketed Moderna vaccine targeting SARS-Cov-2 and were breastfeeding their newborn/infants.

Missing information	Use in Pregnancy and While Breast-Feeding
	There were 6 serious lactation cases received during the reporting period. However, no serious lactation-specific events were reported. The only lactation-specific PT reported in all 6 cases was "Maternal exposure during breastfeeding." 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 AEs 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. Similar to the prior reporting period, the most frequently reported PT was "Maternal exposure during breast-feeding." The only other lactation-specific PTs indicating a clinical adverse event/outcome were "Lactation disorder" and "Lactation puerperal increased." These were mild transient events which occurred within 2 days after vaccination. No clustering by dose or TTO or concerning patterns or notable trends of events reported were identified. The pattern of reports remains generally consistent when compared with cumulative data and no new safety concerns were identified. 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. The MAH is closely monitoring the safety profile of marketed Moderna vaccines targeting SARS-CoV-2 in this population through routine pharmacovigilance. 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. There were 6 serious lactation cases received during the reporting period.
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

Missing information	Use in Pregnancy and While Breast-Feeding
	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 programme had a safety follow-up period of 12 months in the completed studies that assessed long-term safety: mRNA1273-P203, mRNA-1273-P204, mRNA-1273-P205 (Parts A.1, B, C, D, F, and G), and 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) was 6 months and that for mRNA-1273-P301 is 24 months. As of the DLP of this PBRER, there have been 25 CTs, including 19 sponsored by ModernaTx, Inc., of which 5 CT (P203, P204, P205, P304, and P305) were completed during the reporting period, assessing the safety of mRNA-1273 and its variant containing vaccines. Cumulatively, 64,409 subjects have been or estimated to be exposed to either elasomeran, or its variants (mRNA 1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA 1273.617, mRNA 1273.617.2, mRNA-1273.529, mRNA-1273.231, 712, and mRNA-1273.815), and participants exposed to mRNA-1273 (or its variants) in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 active licensed FLU vaccines, or mRNA-1345 in the mRNA clinical development programme sponsored by ModernaTx, Inc. No long-term safety concerns were identified after completion of the studies mRNA-1273-P203, P204, and P205. Post-authorisation 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.
Anticipated risk/consequence of the missing information	The long-term safety profile continues to be characterised 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 (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#7, 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 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 aetiologies or lacked key data elements required for a meaningful medical assessment. 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.

Missing information	Use in Immunocompromised subjects (Safety concern in PBRER only)
	The Spikevax 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 hospitalisations and deaths; and for this reason, are prioritised candidates for vaccination. Since frail subjects with unstable health conditions and comorbidities were excluded from the registration trials, ModernaTx, Inc. is characterising safety through post-marketing routine monitoring of AEs in this special subpopulation. Frailty refers to a state of vulnerability to stressors characterised by a decreased physiological reserve, resulting in poor health outcomes compared to individuals of the same chronological age. 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#7, 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.

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)
	Cases with fatal outcome in the frail subpopulation in the reporting period (3.4%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate aetiologies or lacked key data elements required for a meaningful medical assessment. 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. 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 marketed 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 additional doses. Vaccination has been shown to elicit robust antibody responses, which are further enhanced additional doses to counteract waning immunity and provide long-term protection. Articles also emphasise the effectiveness of vaccines in preventing severe disease, hospitalisations, and mortality, particularly among high-risk populations. Moreover, vaccination remains a critical tool in reducing the burden of COVID-19 across all age groups, enabling better health outcomes and contributing to public health efforts to control the pandemic. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional BD in medical history AI/ID patients to achieve an adequate, more robust immune response to vaccinations. Thus far, there have been no specific safety concerns for individuals with medical history 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

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders (Safety concern in PBRER only)
	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 SOT recipients, including kidney and liver transplants (mRNA-1273-P304). A 100 microgram (0.5 mL) dose was administered, which was the dose authorised at the time of study conduct. In Part A, 128 SOT recipients received a third dose of elasomeran. In Part B, 159 SOT recipients received a BD at least 4 months after the last dose (fourth dose for mRNA vaccines and third dose for non-mRNA vaccines). Reactogenicity was consistent with the known profile of Spikevax (original). There were no unexpected safety findings. 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 Subjects with Autoimmune or Inflammatory Disorders as Missing Information from the EU RMP, was endorsed. As per request from the PRAC "*the topic of Use in Subjects with Autoimmune or Inflammatory Disorders 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	Based on the analysis of all the safety data available as of 17 Dec 2024, 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 cumulative. 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 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.

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders (Safety concern in PBRER only)
	For the fatal AI/ID cases in addition to their underlying autoimmune diseases, 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 minimisation measures in place for marketed Moderna vaccines targeting SARS-CoV-2.

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy and Effectiveness Information

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 2 major respiratory illness outbreaks during the 21st century: SARS, which occurred during 2002–04; and Middle East respiratory syndrome (MERS), which began in 2012 [50].

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 [51] [52]. The WHO declared COVID-19 a pandemic on 11 Mar 2020; however, by that time, there was already widespread community transmission in many locations. Evidence of transmission of SARSCoV2 from asymptomatic or pre-symptomatic individuals may account for an estimated 30-60% of transmission [53]. COVID-19 was the third leading cause of death during 2020 and 2021 and the fourth leading cause during 2022. According to the WHO, as of 17 Dec 2024, over 777 million confirmed cases and over 7 million deaths have been reported globally. As of Nov 2024, over 28.1 million COVID-19 hospitalisations have been reported to the WHO across 172 countries. The average weekly hospitalisations have substantially decreased, dropping from 40,000 in 2023 to 13,000 in 2024 (WHO, 2024). Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [51] [52].

Subjects with COVID-19 may experience a range of clinical manifestations, from no symptoms to

critical illness. Long-term sequelae in COVID-19 subjects with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnoea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae [54,55],[56]. Myocardial injury remains an identified risk among patients with severe COVID-19 [57]. Additionally, some patients develop serious medical complications, such as ventricular dysfunction, pulmonary function abnormalities, and AKI [58,59] [60-62]. 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 [63]. Smokers and individuals with substance use disorders are also at increased risk for severe COVID19 [63]. Globally, the number of new cases increased by over 3% during the 28-day period of 24 Nov 2024 to 22 Dec 2024 as compared to the previous 28-day period, with over 180 000 new cases reported. The number of new deaths decreased by over 27% as compared to the previous 28-day period, with over 2000 new fatalities reported. At the regional level, during the 7-day period from 08 Dec 2024 to 15 Dec 2024, the majority of newly reported cases to WHO were from the EU (8,429), followed by South-East Asia (932), the Americas (640), the Eastern Mediterranean (638), the Western Pacific (223), and Africa (85) [64]. Most individuals with COVID-19 have mild symptoms or moderate illness, with approximately 10-15% of cases that progress to severe disease and approximately 5% that become critically ill (need reference). While more serious long-term health complications are less common, COVID-19 sequelae have individual, global health, and severe socioeconomic consequences.

Since the outbreak of the COVID-19 caused by the 2019 novel CoV began in Wuhan, in Dec 2019, multiple viral variants have been detected, of which a small number are 'variants of concern' (VOC). According to the CDC, as of 17 Sep 2024, the dominant variant nationwide is recombinant variant (XEC), with 44% of cases, followed by KP.3.1.1, with 39% of cases, and MC.1, with 6% of cases. The WHO proposed labels for global COVID-19 VOC and variants of interest (VOI) [65]. According to the European Centre for Disease Prevention and Control (ECDC), since the last update on 29 November 2024, and as of 20 December 2024, no changes have been made to ECDC's variant classifications for VOCs, VOIs, variants under monitoring (VUMs), and de-escalated variants. VOI median proportions in the EU/EEA for week 48-49, based on 9 reporting countries are currently: KP.3: 40.9% (range: 19.0%-47.1%, IQR: 33.9%-42.1%) BA.2.86: 15.8% (range: 0.0%-27.5%, IQR: 11.8%-20.9%). The VUM median proportions in the EU/EEA for week 48-49, based on 9 reporting countries are currently: XEC: 49.5% (range: 36.8%-61.9%, IQR: 40.3%-50.0%).

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 favoured over the monovalent approach however, a monovalent Omicron could also be considered.

As 09 Dec 2024, the circulating VUM were recombinant Omicron subvariants of JN.1 (WHO, 2024), and are [65] presented in Table 17-1:

Table 17-1 Omicron subvariants under monitoring

Pango lineage# (+ mutation)	GISAID clade	Next strain	Relationship to circulating VOC lineages	Spike genetic features	Earliest documented samples
KP.2	GRA	24B	Sublineage of JN.1	JN.1 + S:R346T, S:F456L, S:V1104L	02 Jan 2024
KP.3	GRA	24C	Sublineage of JN.1	JN.1 + S:F456L, S:Q493E, S:V1104L	11 Feb 2024
KP.3.1.1	GRA	24C	Sublineage of JN.1	KP.3 + S:S31-	27 Mar 2024
JN.1.18	GRA	24A	Sublineage of JN.1	JN.1 + S:R346T	02 Nov 2023
LB.1	GRA	24A	Sublineage of JN.1	JN.1+ S:S31-, S:Q183H, S:R346T, S:F456L	26 Feb 2024
XEC	GRA		Sub-lineage of KP. 3.3 and KS. 1.1	JN.1 + S:T22N, S:F59S, S:F456L, S:Q493E, S:V1104L	26 Jun 2024

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 2024, over 777 million confirmed cases of COVID-19 and over 7 million COVID-related deaths have been reported globally. These figures are considered underestimates. As per estimates, COVID19 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 [66].

Elasomeran, an LNP-encapsulated mRNA vaccine expressing the prefusion stabilised spike glycoprotein, is enzymatically manufactured, directs vaccine antigen production in vivo, thus

avoiding the need for the lengthy processes to optimise the production and in vitro characterisation 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 immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 months of age and older.

Efficacy, Immunogenicity and Safety in Adults ≥18 years of age Efficacy and immunogenicity against COVID-19 disease were being evaluated in 25 CTs, including 19 sponsored by ModernaTx, Inc., of which 5 CT (P203, P204, P205, P304, and P305) were completed during the reporting period.

Efficacy, Immunogenicity and Safety in Adults >18 years of age

The efficacy of mRNA-1273 to prevent COVID-19 was demonstrated in adults age ≥18 years in Study mRNA-1273-P301. The primary efficacy endpoint was met, mRNA-1273 prevented COVID-19 starting 14 days after the second injection of vaccine, based on a total of 799 adjudicated COVID-19 cases (55 cases in the mRNA-1273 group and 744 cases in the placebo group). This was during an observation period of 5.3 months. The VE was 93.2% (95% CI: 91.0%, 94.8%; one-sided p value <0.0001), rejecting the null hypothesis of VE ≤30% and achieving the prespecified efficacy boundary based on the 1-sided nominal alpha of 0.0047 using the Lan-DeMets O'Brien Fleming spending function. Importantly, mRNA 1273 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 mRNA-1273 group. Subgroup analyses 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. Additionally, mRNA 1273 was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of mRNA-1273 (VE of 92.8% based on HRs).

mRNA-1273 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%.

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.

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 safety profile of the mRNA-1273 100 µg 2-dose primary series and the 50 µg BD is well characterised based on CTs data from 27,833 participants who received the primary series and 19,609 participants who received the BD. In addition, post-authorisation safety data collected in the GSDB after more than 1.8 billion doses were distributed worldwide support the safety profile identified in the clinical studies and have not identified any new vaccine-associated safety concerns.

Reactogenicity after vaccination with the 2-dose 100 ug mRNA-1273 primary series and the 50 ug BDs is well characterised based on the placebo-controlled data from Part A and data from other mRNA-1273 studies and includes injection site reactions, headache, fatigue, myalgia, arthralgia, axillary lymphadenopathy, nausea/vomiting, pyrexia, and chills within 7 days after vaccination. There is no evidence of increased reactogenicity in participants who received multiple doses of mRNA-1273 and no increased reactogenicity in participants who were SARS-CoV-2 positive prior to receiving the vaccine.

Cumulative follow-up after Dose 1 of the primary series (Part A and Part B) through end of study after the BD (Part C) includes a median follow-up of 655 days (range: 249 to 892 days) representing 35,913 person-years. Long-term follow-up data for participants who received the primary series do not suggest any long-term safety concerns after vaccination.

The majority of unsolicited AEs and SAEs reported during follow-up after the primary series and BD were due to underlying disease, intercurrent illness, or accidental injury. Fatal events were reported infrequently and were generally the result of underlying disease, accidental injury or acute infection, and no fatal events were considered related to vaccination after either the primary series or the BD. In participants who received the BD, 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.

Since Apr 2021, myocarditis and pericarditis have been considered an important identified risk that may occur following vaccination with a COVID-19 vaccine, especially in young men. Available data suggest that the course of myocarditis and pericarditis following vaccination is typically milder than viral myocarditis or pericarditis and is self-limited. Analysis of post-authorisation safety data has shown that this identified risk of myocarditis and pericarditis generally occurs within 7 days following vaccination against COVID-19 and more frequently occurs in people aged 12 to 40 years, particularly young people <30 years old.

In Study P301 (Part A and Part B), there were no reported Treatment Emergent AEs (TEAEs) of myocarditis after vaccination. In Part C, a total of 19,609 participants received the 50 µg BD and 1 confirmed case of myocarditis in a 42-year-old mixed race male occurred on BD-Day 1, which was confounded by a prior viral infection. This SAE was assessed as related to study vaccine by the Investigator and Sponsor and adjudicated as a probable case of acute myocarditis by the independent CEAC (mRNA-1273-P301-addendum 3 Section 7.3.2.3.2.4.1). However, the participant had a documented rhinovirus/enterovirus infection one month prior to the onset of myocarditis, which suggests a potential alternative aetiology. 2 other cases of suspected myocarditis were reported during the study, and both were adjudicated by the CEAC as not meeting the definition of acute myocarditis. Pericarditis was reported during the study but was not considered related to study vaccine in any of the cases.

Based on the data included in the final clinical study report for Study P301, the mRNA-1273 100 µg 2-dose primary series and the 50 µg BD are effective with an acceptable safety profile for the prevention of COVID-19, and the potential benefits outweigh the known and potential risks for mRNA-1273 vaccines.

Efficacy, Immunogenicity and Safety in Adolescents 12 to <18 years of age

mRNA-1273-P203 a completed Phase 2/3 randomised, placebo-controlled, observer-blind, multi-parts (Parts 1A [Blinded Phase], 1B [Open-label Phase], 1C-1 [50 µg BD], 1C-2 [50 µg mRNA-1273 BD Participants who had completed the primary series with a non-Moderna vaccine], and 2 [Open-label mRNA-1273 50 µg 2 dose primary series]) CT to evaluate the safety, reactogenicity, and effectiveness of mRNA 1273 SARS-CoV 2 Vaccine in adolescents ages 12 to 17 years in the US (NCT04649151

Overall, a total of 3733 participants were randomly assigned to study treatment in Part 1A: 1243 participants in the placebo group and 2490 participants in the mRNA-1273 group. In Part 1B, 96/1243 (7.7%) participants received Dose 1 and 93/1243 (7.5%) participants received Dose 2 of

mRNA 1273 100 µg. A total of 1408/3733 (37.7%) participants received the homologous BD of 50 µg mRNA-1273 in Part 1C-1. A total of 52 participants were enrolled and dosed in Part 2. Enrolment for Part 2 was early discontinued in August 2022 when an updated variant containing vaccine (mRNA 1273.222) was authorised for use as a BD.

VE in adolescents aged ≥ 12 to < 18 years was inferred by demonstrating noninferiority of both sera nAb GMTs and seroresponse rates (SRR) from adolescents compared with those from young adults enrolled in Study mRNA-1273-P301 (aged ≥ 18 to ≤ 25 years. The Geometric Mean Ratio (GMR) of adolescent (Study P203) to young adult (Study P301) nAb titres at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the pre-specified 1.5-fold noninferiority criterion (ie, lower bound of the 95% CI for GMR is > 0.67). The difference in adolescent to young adult nAb SRRs at Day 57 was 0.2 (95% CI: -1.8, 2.4), meeting the pre-specified 10% noninferiority criterion (lower bound of the 95% CI of the SRR difference is > -10%).

Review of final safety outputs for Study P203 show that mRNA-1273 administered as a 2-dose 100 µg or 50 µg primary series, and as 50 µg homologous or heterologous BD was well-tolerated and continued to demonstrate an acceptable safety profile.

- Reactogenicity after heterologous 50 µg BD and 50 µg primary series plus 50 µg BD was comparable to the known reactogenicity profile of mRNA-1273.
- The profile of unsolicited AEs throughout the study parts represented events typical for an adolescent population.
- There were no fatal AEs during the study.
- There were no additional AEs reported leading to discontinuation of study intervention and no AEs leading to discontinuation of study participation.
- No SAEs were assessed as related to study intervention by the Investigator.
- Review of AESIs and events of interest in selected SMQs did not identify any safety concerns.

Efficacy, Immunogenicity and Safety in Children 6 months to <12 years of age

Efficacy in children 6 through 11 years of age – primary series

Study mRNA-1273-P204, parts 1 and 2, is a completed Phase 2/3 randomised, placebo-controlled, observer-blind, CT that evaluated the safety, reactogenicity, and effectiveness of elasomeran in healthy children 6 months through 11 years of age in the United States and Canada (NCT04796896).

In Study P204, a total of 8032 participants (3007 participants in the 6 years through 11 years age

group, 3031 participants in the 2 years through 5 years age group, and 1994 participants in the 6 months through 23 months age group) received at least 1 dose of mRNA-1273 in the randomised placebo-controlled Blinded Phase of the study (Part 2) evaluating the mRNA-1273 2-dose primary series. The primary immunobridging criteria were met in all 3 paediatric age groups and across the selected mRNA-1273 doses (50 µg [6 years through 11 years age group] and 25 µg [2 years through 5 years and 6 months through 23 months age groups]) by meeting the prespecified noninferiority success criteria (GMR [lower bound of the 95% CI >0.667 and a point estimator ≥0.8] and SRR difference [lower bound of the 95% CI >-10% and a point estimator ≥-5%]) comparing nAb responses in the paediatric groups to those of adult participants 18 years through 25 years of age in Study P301. This was supported by the secondary endpoint of direct efficacy, which was observed for each age group. Study P204 allowed evaluation of vaccine efficacy against variants: in participants 6 years through 11 years of age, a vaccine efficacy of 76% (95% CI: -41.6%, 96.5%) was observed (during the Delta variant surge) and in participants 2 years through 5 years and 6 months through 23 months of age, vaccine efficacy of 46.6% (95% CI: 32.8%, 57.4%) and 43.2% (95% CI: 23.2%, 57.6%), respectively, was observed (during the Omicron variant surge). It should be noted that the lower bounds for efficacy for the 6 months through 23 months and 2 years through 5 years age groups continued to exceed 20%, indicating that even during circulation of a highly divergent VOC, Study P204 demonstrated clinically meaningful vaccine efficacy in these paediatric age groups.

Effectiveness of the mRNA-1273 BD in Children 6 Years Through 11 Years of Age

The administration of a 50 µg BD to adults increased the serum nAb levels and enhanced clinical effectiveness against COVID-19 hospitalisation and COVID-19-associated deaths [67] [68]. This prompted evaluation of a 25 µg BD of mRNA-1273 in 2,519 children 6 years through 11 years of age in Study P204. Administration of a 25 µg BD of mRNA-1273 at least 6 months after the primary series effectively boosted serum nAb levels, demonstrating the ability of the BD to recall memory responses. The prespecified success criteria for the primary immunogenicity objective (GMR [lower bound of the 95% CI >0.667] and SRR difference [lower bound of the 95% CI >-10%]) were met, thus establishing immunobridging to Study P301, and thereby inferring VE.

Effectiveness of the mRNA-1273.214 BD in Children 6 Months Through 5 Years of Age

Following Omicron's emergence, the Sponsor developed Omicron BA.1 variant containing formulation, mRNA-1273.214, which was evaluated in Study P306 Part 2 as a 10 µg BD in younger children 6 months through 5 years of age who had received the mRNA-1273 25 µg 2-dose primary series in Study P204. The mRNA-1273.214 BD induced a robust rise in nAb levels compared to the mRNA-1273 primary series. The effectiveness of the mRNA-1273.214 BD in participants 6 months through 5 years of age was inferred by successful Immunobridging to

responses after the 2-dose primary series in Study P204. Immune responses generated after administration of the mRNA-1273.214 BD in participants 6 months through 5 years of age who were pre-BD SARS-CoV-2 negative met the prespecified superiority (lower bound of the 95% CI of the GMR against Omicron BA.1 >1.0) and noninferiority (lower bound of the 95% CI of the SRR difference against Omicron BA.1 >-5%; lower bound of the 95% CI of the GMR against ancestral SARS-CoV-2 >0.667; and lower bound of the 95% CI of the SRR difference against ancestral SARS-CoV-2 >-10%) criteria when compared to those generated by mRNA-1273 2-dose primary series administration in participants 6 months through 5 years of age in Study P204. Thus, the results indicate that when emergent SARS-CoV-2 variants substantially diverge from the mRNA sequences included in primary series immunisation, administration of a BD with a formulation updated to contain the target variant mRNA sequences would induce superior nAb responses against such emergent SARS-CoV-2 variants as compared to the initial primary series immunisation.

Effectiveness of the mRNA-1273.214 Primary Series in Children 6 Months Through 5 Years of Age

Effectiveness of the mRNA-1273.214 BD that induced superior immune response against Omicron BA.1 compared to that induced by the original vaccine led to the assessment of the safety and effectiveness of the mRNA-1273.214 vaccine as a 25 µg 2-dose primary series in vaccine-naïve younger children 6 months through 5 years of age in Study P306 Part 1. The mRNA-1273.214 primary series induced nAb responses against Omicron BA.1 superior to those induced by the mRNA-1273 2-dose primary series in Study P204. The effectiveness of the mRNA-1273.214 primary series in participants 6 months through 5 years of age was inferred by successful immunobridging to responses after the primary series in Study P204. Immune responses generated after administration of the mRNA-1273.214 primary series in participants 6 months through 5 years of age met the prespecified superiority (lower bound of the 95% CI of the GMR against Omicron BA.1 >1.0) and noninferiority (lower bound of the 95% CI of the GMR against ancestral SARS-CoV-2 >0.667) criteria when compared to those generated by the mRNA-1273 2-dose primary series administration in the same age group in Study P204. The data provided further proof of principle that variant containing formulation components are immunogenic in previously unvaccinated individuals and inclusion of variants induces responses against the variant that are superior to those induced by original mRNA-1273 vaccine.

Co-Administration with Moderna Vaccine

Effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) BD in individuals who completed primary vaccination with another authorised or approved COVID-19 Vaccine (heterologous BD):

Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine.

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 randomised 1:1:1 to receive a BD of one of 3 vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralising antibody titres, as measured by a pseudovirus neutralisation 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.

POST-MARKETING STUDIES

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 (hospitalisations 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 [69] [68,70].

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 [68]. The three-dose VE was 29.4% (95% CI: 0.3%, 50.0%) against Omicron infection in immunocompromised individuals. The three-dose VE against hospitalisation with Delta or Omicron was >99% across the entire study population. Receipt of 3 doses of mRNA-1273 demonstrated high, durable VE against Delta infection but lower effectiveness against Omicron

infection, particularly among immunocompromised people. However, VE of 3 doses of mRNA-1273 remained high against hospitalisation 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 [70]. 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 BD vaccinated individuals matched to 431,328 2-dose mRNA-1273 vaccinated individuals. In this analysis, IR of symptomatic SARS-CoV-2 infection, COVID-19 hospitalisation 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 hospitalisation, 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 hospitalisation, 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.

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 hospitalisation, and COVID-19 associated death. Incidence of COVID-19-associated outcomes among immunocompromised individuals who received 3 doses of elasomeran (original) was compared to individuals who received 2 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, leukaemia, 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 2 doses of elasomeran (original) only.

The adjusted rVE of 3 doses versus 2 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 hospitalisation, 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 BD among individuals (including immunocompromised individuals) who previously received 2 or more doses of any monovalent mRNA COVID-19 vaccine only in preventing COVID-19-associated hospitalisation. Incidence of COVID-19-associated hospitalisation 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, leukaemia, 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 2 or more doses of any monovalent mRNA COVID-19 vaccine followed by a BD of elasomeran/davesomeran; 19,991 immunocompromised individuals received 2 or more doses of monovalent mRNA COVID-19 vaccine but no BD; 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 hospitalisation 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.

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 Grading of Recommendations, Assessment, Development, and Evaluations (Grade) framework.

Evidence from randomised controlled trials (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 hospitalisation, 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.

Co-administration studies

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 BD 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 BD 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 2 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 geometric mean concentration (GMC) and for all 4 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 2 doses of Shingrix (56 days apart). Elasomeran was either co-administered with the first dose of Shingrix (n=257) or sequentially administered 2 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.

17.2. Newly Identified Information on Efficacy and Effectiveness

Immunogenicity in Immunocompromised Adults

The completed Phase 3b mRNA-1273-P304 study evaluated the safety and immunogenicity of mRNA-1273 in 214 SOT recipients (kidney or liver) and 20 healthy controls. Participants were enrolled in 2 parts. In Part A, SOT participants received up to 3 100 µg doses of mRNA-1273, while healthy participants received 2 doses as a comparator group for cell-mediated and antibody responses. In Part B, a 100 µg BD was administered to participants at least 4 months after completing their primary series.

In Part A, 2 doses of mRNA-1273 elicited modest neutralising antibody (nAb) responses in SOT participants (GMC=85.0, GMFR=6.0), with 52.8% achieving seroresponse. Kidney SOT participants showed lower responses (GMC=54.2, GMFR=3.7) compared to liver SOT participants (GMC=187.9, GMFR=13.8). 3 doses significantly enhanced nAb levels (GMC=538.4, GMFR=25.0), with 75.8% of SOT participants achieving seroresponse. Liver SOT participants reached nAb levels comparable to healthy participants (GMC=1340.2 vs. 1658.4), while kidney SOT responses remained lower (GMC=353.5).

In Part B, the 100 µg BD further increased nAb levels in SOT participants (GMC=901.3, GMFR=5.1). Liver SOT participants experienced a threefold increase in nAb responses (GMC=3946.0), and kidney SOT participants showed slight improvement (GMC=430.7). Responses persisted through 6 months post-BD (GMC=682.4). Binding antibody (bAb) responses followed similar trends, with lower levels against Omicron compared to other variants. SARS-CoV-2-positive SOT participants at baseline had higher initial nAb levels but exhibited post-vaccination increases similar to baseline-negative participants. Healthy participants demonstrated robust nAb responses post-Dose 2 (GMC=1658.4, GMFR=148.4) and sustained high levels post-BD (GMC=9943.5).

The study demonstrated that 3 doses and a booster of mRNA-1273 were safe and well-tolerated. However, kidney SOT participants and those on multiple immunosuppressants consistently exhibited reduced antibody responses compared to liver SOT participants and healthy adults.

The completed mRNA-1273-P305 study was a Phase 2/3, randomised, observer-blind, active-controlled trial assessing the immunogenicity and safety of the Omicron BA.1 monovalent vaccine (50 µg) and the bivalent vaccine (original and Omicron BA.1, 50 µg) compared to mRNA-1273 (50 µg) in individuals aged 16 years and older. In Part 1, 720 participants (363 in the Omicron BA.1 monovalent arm and 357 in the mRNA-1273 arm) showed balanced baseline characteristics. At Days 29 and 85, the Omicron BA.1 monovalent vaccine elicited a non-inferior neutralising antibody (nAb) response against Omicron BA.1 compared to mRNA-1273, meeting primary immunogenicity objectives. In Part 2, 2,824 participants (1,422 in the bivalent arm and 1,402 in the mRNA-1273 arm) also showed balanced baseline characteristics. The bivalent vaccine elicited a superior nAb response against Omicron BA.1 and a non-inferior response against the ancestral strain compared to mRNA-1273 at Days 29 and 85. Both vaccines demonstrated durable nAb responses through Month 12, with elevated geometric mean concentrations and fold-rises in the PPSI-negative population. These findings support further development of variant containing COVID-19 mRNA vaccines.

Immunogenicity of mRNA Vaccines for SARS-CoV-2 Variants in Children

P306 is an ongoing, open-label, Phase 3 study evaluating the safety and immunogenicity of mRNA vaccines for SARS-CoV-2 variants in participants aged 6 months to <6 years. The study planned for 480 participants in both Part 1 and Part 2. As of November 2024, 391 participants were analysed in Part 1 and 539 in Part 2. The majority of participants were White (57.3%) and non-Hispanic or Latino (84.4%), with enrolment distributed across the eligible age range.

In Part 1, the mRNA-1273.214 primary series elicited superior neutralising antibody (nAb) responses against BA.1 (GMR: 50.8; 95% CI: 44.9, 57.6) and noninferior responses against D614G (GMR: 1.19; 95% CI: 1.05, 1.36) compared to mRNA-1273. Day 57 SRRs were 95.6% for BA.1 and 92.9% for D614G. In Part 2, the mRNA-1273.214 BD demonstrated superior nAb responses against BA.1 (GMR: 12.1; 95% CI: 10.7, 13.6) and noninferior responses against D614G (GMR: 3.05; 95% CI: 2.73, 3.41) compared to mRNA-1273. SRRs were 99.0% for BA.1 and 100% for D614G after the BD. nAb levels declined over 6 months but remained above baseline or pre-booster levels. No severe COVID-19 cases or related deaths were reported, and most infections were asymptomatic.

Non-interventional studies (NIS)

Study mRNA-1273-P934 is a NIS that compares the real-world effectiveness of a first original booster dose (1.BD) of mRNA-1273 versus BNT162b2. This retrospective cohort study used Medicare FFS claims data from October 2020 through August 2022. Individuals who received a BD of mRNA-1273 (2.4 million) or BNT162b2 (1.6 million) after ≥1 dose of mRNA-based primary vaccine series were followed from 14 days after index until receipt of an additional booster dose, outcome occurrence, end of continuous enrolment, or end of study period. IPTW was applied to adjust for baseline confounding. Comparative VE against COVID-19 hospitalisation (principal or secondary diagnosis) and differences in total expenditures during hospitalisation and up to 90 days post-discharge were estimated. After IPTW, individuals who received mRNA-1273 as a booster had a reduced risk of hospitalisation (HR 0.789; 95% CI: 0.766, 0.813) compared to BNT162b2.

Study mRNA-1273-P942 is a non-interventional, retrospective cohort study using administrative claims data to evaluate the effectiveness of mRNA-1273.815 in preventing COVID-19 associated hospitalisation and medically-attended COVID-19. This study compared individuals vaccinated with mRNA-1273.815 versus matched individuals ("referent") who had not received mRNA-1273.815 at the time of the corresponding matched individual's vaccination date. Data accrual occurred from 01 Sep 2022 to 21 Feb 2024 (latest available data), and individuals were eligible for cohort entry between September 12, 2023 (approval date for monovalent XBB.1.5) to 20 Feb 2024 (one day prior to end of last available data at time of analysis). Individuals were matched on age, sex, geographic region within the US, and race. The eligible follow-up period was from 20 Sep 2023 through 21 Feb 2024. Individuals were censored on occurrence of the outcome (for each outcome separately), receipt of a dose of any 2023-2024 COVID-19 vaccine (mRNA-1278.815 or other), death, end of follow-up, or disenrollment. IPTW was used to adjust for potential confounding. Hazard ratios (HRs) were used to estimate VE in the weighted study population. The estimated VE and 95% CIs were reported as (1-HR) * 100%. The final study population included 903,349 vaccinated and 903,349 matched referent patients. The median follow-up was 111 days in the vaccinated group and 99 days in the referent group for the primary outcome. For the primary outcome of COVID-19 associated hospitalisation (coded in the primary position), the weighted incidence rate per 1,000 person-years was 4.10 in the vaccinated group, and 9.34 in the referent group. The estimated VE was 56% (95% CI: 52%, 60%). A similar VE was observed across all subpopulations, ranging from 52% in immunocompromised patients, to 62% in patients aged 50-64 years. For the secondary outcome of medically-attended COVID-19, the estimated VE was 24% (95% CI: 22%, 25%). In this large-scale, real-world study involving over 900,000 vaccinated patients, the mRNA-1273.815 vaccine demonstrated protection against COVID-19-related hospitalisations and medically-attended COVID-19 relative to those not having received mRNA-

1273.815. The current study included a substantial proportion of participants who had previously received COVID-19 vaccine doses, highlighting the incremental protection provided by the additional dose regardless of prior vaccination history.

In the mRNA-1273-P943 real-world study, Moderna estimated the VE of mRNA-1273.815 (XBB.1.5-containing mRNA COVID-19 vaccine) administered between 12 Sep 2023 and 31 Dec 2023 at preventing COVID-19 illness requiring hospitalisation, as well as medically-attended COVID-19, in adults ≥ 18 years. This observational, matched cohort study used aggregated medical and pharmacy claims data from HealthVerity. Adults vaccinated with mRNA-1273.815 between 12 Sep 2023, and 31 Dec 2023, were followed through 26 Jan 2024. Vaccinated individuals were matched 1:1 with individuals unvaccinated with any 2023-2024 COVID-19 vaccine on demographic and clinical characteristics. The primary outcome was COVID-19 hospitalisation, and the secondary outcome was medically-attended COVID-19. IPTW and Cox-proportional hazards regression were utilised to estimate VE. The study included 1,272,161 vaccinated individuals matched 1:1 with unvaccinated, with a maximum follow-up of 128 days (median 84 days). The VE against COVID-19 hospitalisation was 51% (95% CI: 48%-54%). Subgroup analyses showed a VE of 56% (95% CI: 51%-61%) among adults 65 and older and 46% (95% CI: 39%-52%) in immunocompromised adults. For medically-attended COVID-19, the VE was 25% (95% CI: 24%-27%). Time-varying analyses showed that while VE declined over time, the effect remained significant. During the 2023-2024 respiratory season, which included the emergence of JN.1, the mRNA-1273.815 vaccine significantly protected against COVID-19-related hospitalisations and medically-attended COVID-19 across diverse adult populations. These results support the continued use of updated COVID-19 vaccines to mitigate severe outcomes and maintain public health safety. The consistent effectiveness across subpopulations underscores the vaccine's role in protecting high-risk groups and the general adult population. The durability of effectiveness over time further emphasises the vaccine's importance in ongoing COVID-19 management.

The mRNA-1273-P946 study aimed to evaluate the VE of mRNA-1273.815, a 2023–2024 Omicron XBB.1.5-containing mRNA COVID-19 vaccine, at preventing COVID-19–related hospitalisations and any medically-attended COVID-19 in adults. In a linked electronic health record–claims dataset, Moderna identified US adults (≥18 years) who received the mRNA-1273.815 vaccine (exposed cohort) between 12 Sep 2023 and 15 Dec 2023, matched 1:1 to individuals who did not receive a 2023–2024 updated COVID-19 vaccine (unexposed cohort). Cohorts were balanced using IPTW on demographics, vaccination and infection history, and underlying medical conditions. Study cohorts were followed until 31 Dec 2023 for COVID-19–related hospitalisations and medically-attended COVID-19. Cox regression was used to estimate

HRs and VE. Subgroup analyses were performed for adults ≥50 years, adults ≥65 years, and individuals with underlying medical conditions. Overall, 859 335 matched pairs of mRNA-1273.815 recipients and unexposed adults were identified. The mean (standard deviation) age was 63 (16) years. More than 60% of individuals in both cohorts had an underlying medical condition. Among the overall adult population, VE was 60.2% (95% CI, 53.4–66.0) against COVID-19–related hospitalisation and 33.1% (30.2–35.9) against medically-attended COVID-19 over a median follow-up of 63 (interquartile range: 44–78) days. VE estimates by age and underlying medical conditions were similar. These results demonstrate the significant protection provided by mRNA-1273.815 against COVID-19–related hospitalisations and any medically-attended COVID-19 in adults, regardless of vaccination history, and support Centres for Disease Control and Prevention recommendations to stay up to date with COVID-19 vaccination to prevent COVID-19–related outcomes, including hospitalisations.

17.3. Characterisation of Benefits

There is an established safety profile of 3 or more doses of marketed Moderna vaccines targeting SARS-CoV-2, from data in clinical studies and post licensure data with more than 1.8 billion doses of distributed worldwide and more than 1 billion doses estimated to have been administered globally as of 17 Dec 2024.

Further, safety for bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran), as well with the 2023-2024 monovalent variant vaccine (andusomeran), SARS-CoV2 JN.1, and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula has been demonstrated in adults including young adults (18 to < 25 years) in clinical studies and post-authorisation settings.

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 programme, 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 titres as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a 2 dose primary series (2 doses of 100 µg in adolescents, 2 doses of 50 µg elasomeran in older children and 2 doses of 25 µg of elasomeran in younger children and infants/toddlers).

mRNA 1273.214 50 µg elicited a superior neutralising 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 [71] elasomeran/imelasomeran elicited a superior neutralising antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunisation, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralising 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 neutralise divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted individuals, and rates of COVID-19, hospitalised COVID-19 and hospitalised COVID-19 death are lower in boosted versus non-boosted individuals.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR AUTHORISED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

SARS-CoV-2 evolution is complex and remains unpredictable. There is no indication that SARSCoV-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 [72].

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 [73]. While less pathogenic as compared to the delta variant, the Omicron variant was significantly more transmissible than previous variants [74-76]. As a result, soon after its emergence, Omicron rapidly became the dominant circulating variant worldwide [77]. During the 05 Jun 2024 Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, the FDA initially authorised MAHs based on the available evidence that the 2024-2025 formula should be monovalent JN.1 strain COVID-19 vaccines (FDA, 2024). This recommendation was updated by the agency on 13 Aug 2024 to indicate a change in preference to the KP.2 strain. On 22 Aug 2024, the FDA approved and granted EUA for SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, an updated mRNA COVID-19 vaccines (2024-2025 formula) to include a monovalent component that corresponds to the Omicron variant KP.2 strain of SARS-CoV-2 (FDA, 2024). The MHRA

and EU approved mRNA-1273.167, updated 2024-2025 formula vaccine targeting JN.1, on 02 Sep 2024 and 09 Sep 2024 respectively.

After more than 4 years of marketed Moderna vaccines targeting SARS-CoV-2 post-authorisation 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, and certainly have been reported less frequently with the variant containing vaccines. This is consistent with post-marketing surveillance, results from the PASS mRNA-1273-P903, mRNA-1273-P920, and multiple published studies containing real-world safety information. The continuous evaluation of post-authorisation 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.

18.2. Benefit-Risk Analysis Evaluation

There is an established safety profile of elasomeran and its variant containing formulations, from data in clinical studies and post licensure data with approximately more than 1.8 billion doses that had been delivered to countries worldwide, and an estimated more than 1 billion doses administered as of 17 Dec 2024. Further, safety of the bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran), andusomeran, SARS-CoV-2 JN.1 mRNA and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula, has been demonstrated in individuals 6 months of age and older in clinical studies and post-authorisation settings.

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 randomised placebo-controlled phase of the study, supported the US EUA (authorisation on 18 Dec 2020) and Biologics License Application (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 [78]. 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 favourable 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 [68], thereby prompting the authorisation 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 neutralise divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted individuals, and rates of COVID-19, hospitalised COVID-19 and hospitalised COVID-19 death are lower in boosted versus non-boosted individuals [68,69].

VE data show that despite the epitope divergence from the original strain, elasomeran continues to protect adults against severe outcomes associated with Omicron, including hospitalisation and death (VE ~ 80%) [68] .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 hospitalisations are occurring in unvaccinated individuals [79-82].

Paediatrics

The tolerability and safety of elasomeran in the paediatric 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 2 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 paediatric vaccines for the respective age groups. Across all paediatric age groups, the AE profile of elasomeran in the paediatric populations is characterised 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 2024 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.

Myocarditis / Pericarditis

A review of the post-authorisation 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.

Immunocompromised

Based on the data presented in this PBRER, elasomeran administered as 2 100 µg doses (for individuals >12 years of age), 2 50 µg doses (for individuals 6 to 11 years of age), or 2 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 COVID19.

Conclusion

Post-authorisation 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 clinical studies presented herein, and the ongoing post-authorisation surveillance, the MAH considers that the known and potential benefits outweigh the known and potential risks for Marketed Moderna vaccines targeting SARSCoV-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 characterise important risks. Routine pharmacovigilance continues to 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; SPIKEVAX XBB.1.5, SPIKEVAX 2023-2024 Formula, SARS-CoV2 JN.1, SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula 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 Centre 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 Centre of Virology and Biotechnology (EpiVacCorona).
- Recombinant vaccine: Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences (ZF2001).
- Protein subunit vaccine: Centre 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 SARSCoV-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	• 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

Decision Factors	Evidence/ Uncertainties	Conclusions
	adolescents are as susceptible to infection with SARSCoV2 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 [73]. Omicron shares antibody escape site mutations with the Beta variant and it also exhibits transmissibility advantages [83-85]. 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, XBB.1, KP.2, KP.3, KP.3.1.1, JN.1.18, LB.1, XEC) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). The ECDC lists JN.1 as VOI as of 26 Jan 2023 [86]. 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 Health and Human Services (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. Globally, the number of new cases decreased by 30% during the 28-day period of 01 Dec 2024 to 29 Dec 2024 as compared to the previous 28day period, with over 150.000 new cases reported.	develop symptomatic COVID-19 primary infection at significantly lesser rates. Complications are rare but may be severe (e.g., MIS-C). • The Omicron variant became the epidemiologically dominant variant in multiple countries in 2022 and its subvariants, with JN.1 and KP.2 the most prevalent in Dec 2024. • 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 hospitalised 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) 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."

Decision Factors	Evidence/ Uncertainties	Conclusions
Medical Need for Treatment of Condition/ Disease	According to the WHO, as of 21 Dec 2024, over 777 million confirmed cases and over 7 million deaths have been reported globally. As of November 2024, over 28.1 million COVID-19 hospitalisations have been reported to the WHO across 172 countries. The average weekly hospitalisations have substantially decreased, dropping from 40,000 in 2023 to 13,000 in 2024 (WHO, 2024). Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [52,87]. Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults [88-90]. However, COVID-19 can also lead to severe outcomes in children and adolescents [91,92]. As of 17 Dec 2024, confirmed COVID-19 mortality has surpassed 1.1 million deaths in the US, as reported by the CDC. 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 hospitalisations were in patients with one of the listed pre-existing conditions. Elasomeran/imelasomeran elicited a superior neutralising antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunisation, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralising 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	• Since Dec 2020, elasomeran and other COVID-19 vaccines have been available under EUA, conditional approvals, and full approval worldwide. • As of 17 Dec 2024, more than 1.8 billion doses of marketed Moderna vaccines targeting SARS-CoV-2 (i.e., elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, andusomeran, SARS-CoV2 JN.1, SPIKEVAX 2024-2025 Formula [KP.2]) have been delivered to 97 countries, and over 1 billion doses are estimated to have been administered globally. North America, Europe, and Asia accounted for approximately 85% of marketed Moderna vaccines targeting SARS-CoV-2 doses distributed and administered. Andusomeran was introduced as a new marketed Moderna vaccine targeting SARS-CoV-2 in Sep 2023. As of 17 Dec 2024, 108,692,842 doses of andusomeran had been delivered to 23 countries and an estimated total of 54,346,421 doses were administered. Latin America, North America, and Asia accounted for approximately >93% of all doses delivered and administered. • SARS-CoV2 JN.1, SPIKEVAX 2024-2025 Formula [KP.2] were introduced as new marketed Moderna vaccines targeting SARS-CoV-2 in August 2024. As of 17 Dec 2024, over 24 million doses of SARS-CoV-2 JN.1 mRNA have been delivered to 15 countries and an estimated 12.3 million administered globally. Europe and Asia accounted for approximately 90% of all doses delivered and administered. Over

Decision Factors	Evidence/ Uncertainties	Conclusions
	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.	23 million doses of SPIKEVAX 2024-2025 Formula (KP.2) have been delivered to 3 countries in North America and an estimated 11.8 million have been administered. • 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 2 dose primary series. Additionally, approvals and/or authorisations for additional doses in special populations (e.g., immunocompromised) and/or as a BD, including authorisation for 2 bivalent vaccines (elasomeran/imelasomeran, and elasomeran/davesomeran), as well as andusomeran, SARS-CoV-2 JN.1 mRNA and SARS-Co-V-2 KP.2 mRNA (COVID-19 Vaccine, mRNA) 2024-2025 Formula , continue to expand.
Key Benefits	The efficacy of elasomeran to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273-P301. Analysis of the 04 May 2021 dataset showed that elasomeran 100 µg was 98.2% effective in preventing severe COVID-19. Subgroup 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 SARSCoV-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	• The efficacy of elasomeran to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273 P301. • Demonstration of elasomeran capacity to greatly enhanced immune responses compared to pre-boost levels after the administration of a BD of 50 µg at least 6 months after administration of the second of 2 doses of the elasomeran primary series has been confirmed in Study mRNA-1273-P201 Part A, Part B, and P301, as well as Study DMID 21-0012. • In Studies mRNA-1273-P203 and mRNA-1273-P204 the coprimary immunogenicity objectives were met in all age groups, demonstrating noninferiority to

Decision Factors	Evidence/ Uncertainties	Conclusions
	(including both symptomatic and asymptomatic infections) caused by the original and variant strains and sequelae including severe disease, hospitalisation, and death. Real-world effectiveness studies report COVID-19 mRNA VE ranging from 86-89% for SARS-CoV-2 infection, 65-92% for asymptomatic infections, 85 to 97% for symptomatic disease, 87 to 98% for hospitalisation 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 analyses, 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 titres. Across the full paediatric programme, the effectiveness of elasomeran was demonstrated from 6 months to 17 years. In Studies mRNA1273-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 titres as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a 2 dose primary series (2 doses of 100 µg in adolescents, 2 doses of 50 µg elasomeran in older children and 2 doses of 25 µg of elasomeran in younger children and infants/toddlers). mRNA 1273.214 50 µg elicited a superior neutralising 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	young adults (18 to 25 years of age) in the pivotal efficacy trial, Study mRNA-1273-P301. • The GMT ratio of nAb titres as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a 2 dose primary series (2 doses of 100 µg in adolescents, 2 doses of 50 µg elasomeran in older children and 2 doses of 25 µg of elasomeran in younger children and infants/toddlers). • VE data show that despite the epitope divergence from the original strain, elasomeran continues to protect adults against severe outcomes associated with Omicron, including hospitalisation and death (VE ~ 80%) [68]. • Elasomeran/imelasomeran elicited a superior neutralising antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunisation, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralising antibody response against the Omicron BA.4 and BA.5 subvariants. • Supportive data from the first bivalent vaccine (mRNA1273.211) demonstrate a durable neutralising 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

Decision Factors	Evidence/ Uncertainties	Conclusions
	BD of elasomeran [71] elasomeran/imelasomeran elicited a superior neutralising antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunisation, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralising 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 neutralise divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted individuals, and rates of COVID-19, hospitalised COVID-19 and hospitalised COVID-19 death are lower in boosted versus non-boosted individuals.	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 SARSCoV-2 status. • Variant containing bivalent boosters induce immune responses that are durable, and cross neutralise divergent SARS-CoV-2 strains.
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 randomised, stratified, observer-blind,	• 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

Decision Factors	Evidence/ Uncertainties	Conclusions
	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. During the reporting period, 4,601 subjects were estimated to be exposed to either mRNA-1273, or its variants (mRNA-1273.214, mRNA-1273.222, mRNA-1273.815, SPIKEVAX KP.2, and mRNA-1273.167), and subjects exposed to mRNA-1273 (or its variants) co-administered active licensed sFLU vaccines in the mRNA clinical development programme sponsored by ModernaTX. Cumulatively, 64,409 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, mRNA 1273.617.2, mRNA-1273.529, mRNA-1273.231, 712, 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-admin with mRNA-1010, active licensed sFLU vaccines, or mRNA-1345 in the mRNA clinical development programme sponsored by ModernaTx, Inc. The total count of 64,409 represents unique subjects (Subjects enrolled in both trials mRNA-1273-P301 and mRNA-1273-P201 (Part C)/P205, both mRNA-1273-P204 and mRNA-1273-P306, and both mRNA-1083-P101 and mRNA-1083-P301, are only counted once in total), or co-administered active licensed sFLU vaccines (Fluzone HD or Fluarix) in the mRNA clinical development programme 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).	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 2 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 paediatric vaccines for the respective age groups. Across all paediatric age groups, the AE profile of elasomeran in the paediatric populations is characterised 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

Decision Factors	Evidence/ Uncertainties	Conclusions
	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 authorisation. 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 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	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 favourable; those individuals who are hospitalised have lengths of stay of around 2 to 4 days on average. • A review of the post-authorisation 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-authorisation safety information, the general safety

Decision Factors	Evidence/ Uncertainties	Conclusions
	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 2 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 paediatric vaccines for the respective age groups. Across all paediatric age groups, the AE profile of mRNA-1273 in the paediatric populations is characterised 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 coexisting 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	profile of elasomeran continues to appear well-tolerated and with an acceptable safety profile.

Decision Factors	Evidence/ Uncertainties	Conclusions
	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 hospitalisation, 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 Cardiac magnetic resonance (CMR) imaging-detectable consequence [93].	

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, authorised as a suspension for injection for active immunisations 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-authorisation NIS conducted to date support the positive safety and efficacy profile of marketed Moderna vaccines targeting SARS-CoV-2.

During the reporting period of this PBRER, seven (7) signals were closed by the MAH during the reporting period. Based on scientific evaluation of the available information, all 7 closed signals

were refuted (CVT; Dermatitis allergic; ED; Hypotension; Ischaemic stroke; Pre-eclampsia, gestational hypertension and GD (P919); and Renal Failure).

The data included in this PBRER#7 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 v19.0, dated 13 Jun 2024) 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 Market Authorisation Status
Appendix 3	Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials
Appendix 4	Cumulative and Interval Summary Tabulations of Serious and NonSerious 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, Characterising, 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, Characterising, 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 (if desired by the MAH)
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