SPIKEVAX: Periodic safety update report assessment

18th December 2022 to 17th June 2023

This document consists of:

1. The PRAC assessment report of the SPIKEVAX periodic safety update report (PSUR) covering the period 18th December 2022 to 17th June 2023, and;

2. The SPIKEVAX PSUR itself.

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

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

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

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

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

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

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

EMA/PRAC/588046/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010897/202306

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

Period covered by the PSUR: 18/12/2022 To: 17/06/2023

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

Status of this report and steps taken for the assessment[1]

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	14 September 2023	14 September 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	13 November 2023	08 November 2023
☐	MS/PRAC members and MAH comments	13 December 2023	13 December 2023
☐	PRAC Rapporteur's updated assessment report following comments	28 December 2023	19 December 2023
☐	Oral explanation	n/a	n/a
☒	PRAC recommendation	11 January 2024	11 January 2024

Procedure resources	
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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for elasomeran (Spikevax), elasomeran / imelasomeran (Spikevax bivalent Original/Omicron BA.1), elasomeran / davesomeran (Spikevax bivalent Original/Omicron BA.4-5), andusomeran (Spikevax XBB.1.5).

2. Assessment conclusions and actions

This report assessed the 5th Periodic Safety Update Report (PSUR) for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, summarising the safety information gathered during a 6-month reporting period from 18 Dec 2022 to the data-lock point (DLP) 17 Jun 2023.

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

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

Andusomeran (Spikevax XBB.1.5) was approved in the EU after the DLP, on 15th September 2023.

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

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

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

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

At the time of the DLP of the 5th PSUR, elasomeran was authorised in 49 countries/regions for active immunisation of adults to prevent COVID-19 caused by SARS-CoV-2. Cumulatively, approximately 53,983 subjects were exposed in clinical trials. As of DLP of this report 978,005,565 doses of the three vaccines had been administered worldwide.

Signals

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

During the reporting period 4 signals were closed and 2 signals were ongoing at DLP. The closed signals - which also included responses to request for supplementary information - on Amenorrhea (re-evaluation), Diarrhoea (re-evaluation), Pemphigus and pemphigoid, and Idiopathic inflammatory myopathy/Myositis did not provide sufficient information of a causal association with elasomeran containing vaccines and the signal topics will be monitored by routine pharmacovigilance. For the ongoing signal of Sensorineural hearing loss, which was closed by the MAH after DLP, a signal evaluation report was presented. A hypothetical mechanism of action in which COVID-19 vaccination might result in otologic disorders was presented. However, the PRAC deemed that the data accumulated were not robust enough to support a causal association between sensorineural hearing loss and elasomeran exposure. For the ongoing signal of IgA Nephropathy flare up raised by the MAH, a signal evaluation report is expected presented with the next PSUR as the signal was closed after DLP.

Safety topics under monitoring

For the two safety topics under review Postural tachycardia syndrome (POTS), and secondary Hemophagocytic lymphohistiocytosis (sHLH) the data presented was inconclusive to draw firm conclusions on a causal relationship with elasomeran-containing vaccines. However, literature papers were published after DLP, and the MAH is requested to comment on these papers within the next PSUR.

The MAH presented an article by Uzun *et al.* that included 6 well-documented case reports of reportedly vaccine-induced liver injury. The observed liver injuries had a similar pattern to the one seen in autoimmune hepatitis. Furthermore, the authors mentioned literature case reports and observational studies which have been published after the topic "autoimmune hepatitis" was previously evaluated in PSUSA #3. Therefore, the MAH has been requested to present a cumulative review of autoimmune hepatitis with elasomeran, elasomeran/imelasomeran,elasomeran/davesomeran or andusomeran exposure within the next PSUR.

The signal of chronic urticaria was evaluated in the PSUR #3, however the signal was rejected. Based on new information on chronic urticaria, the PRAC has raised the signal in the current PSUSA procedure and provided a cumulative review on chronic urticaria and the vaccines. Causality assessment of all 360 cases of chronic urticaria in EVDAS has been performed with 58 cases assessed probably and 228 cases assessed possibly associated with the vaccines. Of these cases, 68 cases have been evaluated by the independent Danish Patient Compensation leading to patient compensation. The data show that there is a clear shared pattern between chronic urticaria and mechanical urticaria in time to onset of urticaria of 7-13 days and onset primarily after the third vaccine dose which is further supported by the literature. Based on the cumulative review, the PRAC considers that evidence exist of at least a possible causal association between chronic urticaria and the vaccines. The MAH agrees to include the ADR "Chronic urticaria" in the SmPC section 4.8 and PIL section 4 with the frequency "not known" as proposed by the PRAC.

Summary of safety concerns

No new and significant information was presented for the risks and missing information in the summary of safety concerns.

Conclusion

For the PSUR frequency it was concluded in the previous PSUSA (no 4.) to stay aligned with the EURD. A 6-monthly PSUR with DLP December 2023 is expected, and the first yearly PSUR is to be submitted with a DLP December 2024. This previous decision of future PSUR deadlines remains supported by the current evaluation of data.

No new significant information that would impact the benefit-risk balance was identified during the assessment of the data in this PSUR. In view of the data presented in the reviewed PSUR, the overall

risk-benefit balance of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and andusomeran is therefore considered unchanged in the approved indication.

3. Recommendations

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

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

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

Update of section 4.8 of the SmPC to add the adverse reaction 'Chronic urticaria' with a frequency 'Not known'. The Package leaflet is updated accordingly.

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

Summary of Product Characteristics

- Section 4.8

The following adverse reaction should be added under the SOC 'Skin and subcutaneous tissue disorders' with a frequency 'Not known':

Chronic urticaria

Package Leaflet

Section 4. Possible side effects

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

- rash elicited by external stimulus such as firm stroking, scratching, or pressure to the skin

(mechanical urticaria)

- raised, itchy rash with a duration of more than six weeks (chronic urticaria)

4. Issues to be addressed in the next PSUR

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

- The MAH is requested to provide a cumulative review of autoimmune hepatitis with elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran or andusomeran exposure in the next

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

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

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

[...]

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

If the MAH considers an update of the product information warranted, a wording and frequency for inclusion in the SmPC and package leaflet should be proposed with presentation of the used method for calculation of frequency.

- After DLP of the present PSUR, a paper including a case report and a literature review on secondary Hemophagocytic lymphohistiocytosis (sHLH) and COVID-19 vaccination has been published (Premec H, Živko M, Mijić M, Jelić-Puškarić B, Lalovac M, Filipec Kanižaj T, Sobočan N. Acute Liver Failure Caused by Secondary Hemophagocytic Lymphohistiocytosis After COVID-19 Vaccination - Case Report and Literature Review. Int Med Case Rep J. 2023 Aug 7;16:449-455. doi: 10.2147/IMCRJ.S417347. PMID: 37577009; PMCID: PMC10416787.). The MAH is requested to comment on this paper in the next PSUR and comply with appropriate measures based on the cumulative information including mechanism of actions concerning sHLH and elasomeran and andusomeran containing vaccines.
- Two papers concerning POTS and the association with COVID-19 vaccination have been published after the DLP of the present PSUR. The MAH is requested to comment on these in the next PSUR and comply with appropriate measures based on the cumulative information concerning POTS and elasomeran and andusomeran containing vaccines. The papers are the following:

  - Tv P, Tran TT, Hao HT, Hau NTH, Jain N, Reinis A. Postural orthostatic tachycardia syndrome-like symptoms following COVID-19 vaccination: An overview of clinical literature. Hum

Antibodies. 2023;31(1-2):9-17. doi: 10.3233/HAB-220013. PMID: 37248893; PMCID: PMC10357168.

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

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

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

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

5. PSUR frequency

☒No changes to the PSUR frequency

For the PSUR frequency it was concluded in the previous PSUSA (no 4.) to stay aligned with the EURD. A 6-monthly PSUR with DLP December 2023 is expected, and the first yearly PSUR is to be submitted with a DLP December 2024.

Annex: PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This is the periodic safety update single assessment (PSUSA) of the 5th periodic safety update report (PSUR) on elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran covering the period from 18 Dec 2022 to 17 Jun 2023.

Currently, the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates (EURD) and to stay aligned with the EURD, one additional 6-monthly PBRER (data lock point [DLP] 17 Dec 2023) will be submitted, then the first yearly PBRER (DLP 17 Dec 2024), to be followed by further yearly PBRERs. The first three PBRERs (PBRER#1, PBRER#2 and PBRER#3) submitted included the single International Nonproprietary Name (INN) elasomeran, however, beginning with the PBRER#4, bivalent vaccines; elasomeran/imelasomeran, and elasomeran/davesomeran were also included.

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

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has Anatomical Therapeutic Chemical (ATC) code: J07BN01 (previously J07BX03).

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; SARS-CoV-2). As per Company Core Data Sheet (CCDS) (v16.0, dated 03 Jan 2023), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals six months of age and older. Elasomeran/imelasomeran and elasomeran/davesomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

Elasomeran is Single-stranded, 5'-capped messenger Ribonucleic acid (RNA) (mRNA) produced using a cell-free in vitro transcription from the corresponding Deoxyribonucleic acid templates, encoding the full-length Spike protein of SARSCoV2, modified to introduce two proline residues to stabilize the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: 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, codonoptimized prefusion stabilized conformation variant (K983P and V984P) of the SARS-CoV-2 spike (S) glycoprotein (Omicron variant, B.1.1.529). Davesomeran is a single-stranded, 5'capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding Deoxyribonucleic acid templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). The S-proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

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

• Elasomeran 0.20 mg/mL dispersion for injection

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

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

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

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

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

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

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

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

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

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

Posology for primary series, a third dose in severely immunocompromised and booster doses for elasomeran-containing vaccines is provided in below Table 1.1.

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

Strength	Vaccination Type	Age and Dose	Recommendations
Elasomeran 0.20 mg/mL concentration	*Primary series*	*Individuals 12 years of age and older* Elasomeran is administered as a course of 2 (two) 100 µg doses (0.5 mL each).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 through 11 years of age Elasomeran is administered as a course of 2 (two) 50 µg doses (0.25 mL each, containing 50 µg mRNA, which is half of the primary dose for individuals 12 years and older).	
	Third dose in severely immunocompromised	*Individuals 12 years of age and older* Elasomeran is administered as course of one dose of 0.5 mL, containing 100 µg mRNA.	A third dose may be given at least 28 days after the second dose.
		Children 6 through 11 years of age Elasomeran is administered as a course of one dose of 0.25 mL, containing 50 µg mRNA.	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran 0.25 mL, containing 50 µg mRNA.	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or a denoviral vector vaccine at least 3 months after

			completion of the primary series.
Elasomeran 0.10 mg/mL concentration and 50 µg dispersion for injection in pre-filled syringe	*Primary series*[*]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of 2 (two) 50 µg doses (0.5 mL each, containing 50 µg mRNA).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age Elasomeran is administered as a course of 2 (two) 25 µg doses (0.25 mL each, containing 25 µg mRNA each, which is half of the primary dose for children 6 years through 11 years of age).	
	Third dose in severely immunocompromised[†]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of one dose of 0.5 mL, containing 50 µg mRNA.	A third dose may be given at least 28 days after the second dose.
		Children 6 months through 5 years of age Elasomeran is administered as a course of one (one) dose of 0.25 mL, containing 25 µg mRNA.	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran, 0.5 mL, containing 50 µg mRNA.	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or a adenoviral vector vaccine at least 3 months after completion of the primary series.
Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*[‡]	*Individuals 6 years through 11 years of age* Dose is administered as one dose of 0.25 mL containing 12.5 ug of elasomeran and 12.5 ug of imelasomeran.	There should be an interval of at least 3 months between administration of elasomeran/imelasomeran and the last prior dose of a COVID-19 vaccine.

		Individuals 12 years of age and older Dose is administered as a course of one dose of 0.5 mL containing 25 µg of elasomeran and 25 µg of imelasomeran.	Elasomeran/imelasomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.
Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 12 years of age and older* Dose is administered as a course of one dose of 0.5 mL containing 25 µg of elasomeran and 25 µg of davesomeran.	There should be an interval of at least 3 months between administration of elasomeran/davesomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/davesomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

*For primary series for individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.
†For the third dose in severely immunocompromised patients 12 years of age and older, the 0.2 mg/mL strength vial should be used.
‡ For details on the primary vaccination course for ages 12 and above, the 0.2 mg/mL strength vial should be used.

Elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran may be used to boost adults who have received a primary series with elasomeran, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine.
The mRNA drug substance in mRNA-1273 is chemically similar to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs 1,2]. This nucleoside is included in mRNA-1273 drug substance in place of the normal uridine base to minimize the indiscriminate recognition of the mRNA-1273 by pathogen-associated molecular pattern receptors (e.g., toll-like receptors) [3]. The cap structure used in the mRNA is identical to the natural mammalian Cap one structure [4,5] and is presented in Figure 1-1 below.

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

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

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

This elicits both T-cell and B-cell responses to generate neutralizing antibodies, which may contribute to protection against COVID-19.

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

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

Table 1.2 Variants and WHO labels for mRNA-1273

Suffix	Variants
mRNA-1273.351	Beta
mRNA-1273.617.2	Delta
mRNA-1273.211	Bivalent: 1:1 ratio of prototype and beta (.351)
mRNA-1273.213	Bivalent: 1:1 ratio of beta (.351) and delta (.617)
mRNA-1273.214	Bivalent: 1:1 ratio of prototype and omicron BA.1 (.529)
mRNA-1273.222	Bivalent: 2 mRNAs: CS-023314 and CX-034476
mRNA-1273.529	Omicron BA.1
mRNA-1273.815	B.1.351 lineage S variant
nRNA-1273.231	1.5 sub lineage of SARS-CoV-2

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

The expressed Spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

Further details on mechanism of action, indications, pharmaceutical forms, and instructions for use are presented in the CCDS for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran (current v16 dated 03 Jan 2023) in PSUR Appendix 1.

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

1.2. Worldwide marketing authorisation status

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

First marketing approval for elasomeran/imelasomeran was granted by the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by Food and Drug administration on 31 Aug 2022.
Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for third doses in special populations (e.g., immunocompromised) and/or as a booster dose, including authorization for two bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) continue to expand.
Cumulative information on marketing authorizations in all countries and approval dates are provided in PSUR Appendix 2.

Rapporteur assessment comment:

The International Birth Date of elasomeran is 18 Dec 2020. The product is currently authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelasomeran was granted by the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by Food and Drug administration on 31 Aug 2022. The date of marketing authorization in the European Economic Area for the primary vaccination series in adults was 06 Jan 2021.

This section is acknowledged.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

During the reporting period, the following safety-related action was taken by ModernaTx, Inc:

A Spikevax Risk Management Plan (RMP) version 7.0 was submitted during the reporting period along with PBRER#4 within procedure European Medicine Evaluation Agency (EMEA)/H/C/Periodic Safety Update Single Assessment (PSUSA)/00010897/202212 to propose removal of the following safety concerns:

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

The evaluation of the PBRER#4 was still ongoing at the end of the reporting period.

Rapporteur assessment comment:

During the reporting period, a risk management plan (RMP) version 7.0 was submitted along with the previous PSUSA (EMEA)/H/C/PSUSA/00010897/202212 with the proposal to remove the following safety concerns:

Important potential risk: Vaccine-associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD).

Missing information: Use in immunocompromised subjects, Interaction with other vaccines, Use in frail

subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) and Use in subjects with autoimmune or inflammatory disorders.

The section is acknowledged.

1.3.2. Changes to reference safety information

The Reference Safety Information (RSI) for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in effect at the end of the reporting period (DLP 17 Jun 2023) and used for this report is the CCDS v16.0 (dated 03 Jan 2023). This CCDS was used to assess listedness of adverse reactions (ARs), risks in risk sections, and to support benefit-risk evaluation in this report. The RSI contains a complete review of the safety profile for the product. This document is provided in Appendix 1 (see PSUR).

During this reporting period, the RSI (CCDS) was updated from v15.0 (dated 15 Nov 2022) to v16.0 (dated 03 Jan 2023). The safety-related changes are summarized below in Table 4.1.

Table 4.1 CCDS safety-related changes during the reporting period

Version	Date	Summary of changes
16.0	03 Jan 2023	Section 4.8, Addition of elasomeran/davesomeran Adverse drug reaction details. Section 5.1, Addition of elasomeran/imelasomeran D91 persistence data and elasomeran/davesomeran clinical data

Rapporteur assessment comment:

The RSI used by the MAH for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran was the CCDS version 16.0 (03 Jan 2023) which was also in effect at the end of the reporting period of the current PSUR (DLP 17 Jun 2023). The MAH reports that the RSI was updated during the reporting period from version 15.0 (15 Nov 2022) to version 16.0 with the following safety-related changes:

Section 4.8: Addition of elasomeran/davesomeran Adverse drug reaction details.

Section 5.1: Addition of elasomeran/imelasomeran D91 persistence data and elasomeran/davesomeran clinical data.

This section is acknowledged

1.3.3. Estimated exposure and use patterns

1.3.3.1. Cumulative exposure in clinical trials

Cumulatively, 53,983 subjects are estimated to have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA-1273.617.2, mRNA-1273.529, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administration with mRNA-1010 or co-administration with mRNA-1345 in the mRNA clinical development program sponsored by ModernaTx, Inc. The total count of 53,983 represents unique subjects (Subjects enrolled in both trials P301 and P201 (Part C)/P205 or in both P204 and P306 and are

only counted once in total).

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

Table 5.1 Estimated Cumulative Subject Exposure from Clinical Trials

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P201	Placebo	42[a]
mRNA-1273-P201	mRNA-1273	558[a]
mRNA-1273-P201	mRNA-1273 Booster	344
mRNA-1273-P201	mRNA-1273.351 Booster	40
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	20
mRNA-1273-P203	Placebo	1,144[a]
mRNA-1273-P203	mRNA-1273 100 ug	2,582[a]
mRNA-1273-P203	mRNA-1273 50 ug	52[a]
mRNA-1273-P203	mRNA-1273.222 50 ug	388[a]
mRNA-1273-P203	EUA+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	2,767
mRNA-1273-P204	mRNA-1273.214 25 ug Booster	209
mRNA-1273-P204	mRNA-1273.214 50 ug Booster	6
mRNA-1273-P205	mRNA-1273 Booster	681[a]
mRNA-1273-P205	mRNA-1273.211 Booster	759[a]
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	135[a]
mRNA-1273-P205	mRNA-1273.213 Booster	951[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	424[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.231 Booster	45[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.815 Booster	42[a]
mRNA-1273-P205	mRNA-1273.529 Booster	508[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	1,167[a]
mRNA-1273-P205	mRNA-1273.815 Booster	8[a]
mRNA-1273-P205	mRNA-1273.231 Booster	6[a]
mRNA-1273-P206	mRNA-1273.214	54[a]
mRNA-1273-P301	Placebo	2,513[a]
mRNA-1273-P301	mRNA-1273	27,833[a]
mRNA-1273-P301	mRNA-1273 Booster	19,609
mRNA-1273-P304	mRNA-1273	81[a]
mRNA-1273-P304	EUA+mRNA-1273	71[a]
mRNA-1273-P304	EUA+mRNA-1273 Booster	82[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	87
mRNA-1273-P305	Overall (mRNA-1273, mRNA-1273.214, or mRNA-1273.529 booster)	3,548[a]
mRNA-1273-P306	mRNA-1273.214	391[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	5[a]
mRNA-1283-P101	mRNA-1273	22[a]
mRNA-1283-P201	mRNA-1273 Booster	57[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1283-P301	mRNA-1273.222	3,886[a,b]
mRNA-CRID-001	mRNA-1273	60[a]
mRNA-1073-P101	mRNA-1010+mRNA-1273 co-administration	101[a]
mRNA-1073-P101	mRNA-1273+Placebo	49[a]
mRNA-1083-P101	mRNA-1273.222	102[a,b]
mRNA-1230-P101	mRNA-1273.214	44[a,b]
mRNA-1345-P302	Overall (mRNA-1273.214 alone or co-administration with mRNA-1345)	1,690[a]

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

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

Age Range	mRNA-1273									mRNA-1283			mRNA-CRID	mRNA-1073	mRNA-1083	mRNA-1230	mRNA-1345	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	P301[c]	001	P101	P101[c]	P101[c]	P302	
<2 years	0	0	2,828	0	54	0	0	0	244	0	0	0	0	0	0	0	0	3,001[b]
2 to <6 years	0	0	4,244	0	0	0	0	0	686	0	0	0	0	0	0	0	0	4,458[b]
6 to <12 years	0	0	4,843	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4,843
12 to <16 years	0	3,251	0	0	0	0	0	0	0	0	0	98	0	0	0	0	0	3,349
16 to <18 years	0	1,070	0	0	0	0	0	1	0	0	0	56	0	0	0	0	0	1,127
18 to <65 years	508	0	0	3,871	0	22,826	184	2,349	0	27	51	5,200	56	127	622	291	1,070	34,182[b]
65 to <75 years	128	0	0	1,034	0	6,121	43	1,118	0	0	5	1,735	4	22	504	95	498	10,478[b]
75 to <85 years	21	0	0	236	0	1,309	7	75	0	0	1	485	0	1	92	6	115	2,167[b]
>=85 years	3	0	0	22	0	90	0	5	0	0	0	51	0	0	0	0	7	163[b]
Missing	0	0	0	0	0	0	0	0	0	0	0	146	0	0	0	0	0	146

Total	660	4,321	11,915	5,163	54	30,346	234	3,548	930	27	57	7,771	60	150	1,218	392	1,690	63,914[b][d]

[a]=Data from ongoing and completed trials till 17 Jun 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.
c=Study is currently blinded. This is the overall count including Placebo/comparators or other investigational products.
d=The total 63,914 includes subjects from three blinded studies which could not be further estimated based on age, gender, ethnic origin or racial group, thus does not match with estimates of 53,983.

1.3.3.2. Cumulative and interval exposure from marketing experience

Cumulatively, at the end of the reporting period, a total of 1,664,690,323 doses of elasomeran (original and bivalents including elasomeran/imelasomeran and elasomeran/davesomeran) had been distributed to 91 countries (a proportion of doses distributed have been subsequently donated via either bilateral agreements or collaborative efforts such as COVAX). North America, Europe, and Asia accounted for approximately 91% of elasomeran (original and bivalents including elasomeran/imelasomeran and elasomeran/davesomeran) doses distributed (Table 5.6). Cumulatively, 217,505,466 (13.1%) doses had been distributed in lower- and middle-income countries.

In this reporting period, between 18 Dec 2022 to 17 Jun 2023, a total of 110,940,854 doses of elasomeran (original and bivalents including elasomeran/imelasomeran and elasomeran/davesomeran) had been distributed and an estimated total of 65,177,752 doses had been administered. North America, Europe, and Latin America accounted for approximately 88% of elasomeran doses distributed (Table 5.6). During this reporting period, 9,016,390 (8%) elasomeran doses had been distributed in lower- and middle-income countries.

A total of 1,318,183,956 elasomeran doses had been distributed to 91 countries and estimated total of 774,433,074 doses had been administered cumulatively. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed. In the reporting period, a total of 2,594,240 elasomeran doses were distributed and estimated 1,524,116 elasomeran doses were administered.

A total of 128,997,293 booster doses of elasomeran/imelasomeran had been distributed to 42 countries and an estimated total of 70,948,511 doses had been administered. Latin America, North America, and Asia accounted for approximately 95% of doses distributed and approximately 89% of doses administered (Table 5.8). A total of 217,509,074 booster doses of elasomeran/davesomeran had been distributed to 41 countries and an estimated total of 119,629,991 doses had been administered. The United States, Canada, Europe, and Asia accounted for >95% of all doses distributed and administered (Table 5.9).

Table 5.6 Total doses distribnted and administered for elasomeran and elasomeran/imelasomeran and elasomeran/davesomeran

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	1,664,690,323	100.0	978,005,565	100.0	110,940,854	100.0	65,177,752	100.0
North America	633,723,694	38.1	348,548,032	36.0	1,935,954	1.7	1,064,775	1.6
US	573,221,554	34.4	315,271,855	32.6	1,433,804	1.3	788,592	1.2
All Europe	490,094,123	29.4	269,551,768	27.4	39,301,350	35.4	21,615,743	33.2
European Economic Area	419,450,593	25.2	230,697,826	23.4	33,001,750	29.7	18,150,962	27.8
Asia	383,818,236	23.1	211,100,030	21.4	57,766,520	52.1	31,771,586	48.7
Latin America	70,470,000	4.2	38,758,500	3.9	8,984,750	8.1	4,941,612	7.6
Africa	32,469,280	2.0	17,858,104	1.8	7,680	0.0	4,224	0.0
Oceania	27,731,200	1.7	15,252,160	1.5	1,554,600	1.4	855,030	1.3
Middle East	26,383,790	1.6	14,511,085	1.5	1,390,000	1.3	764,500	1.2
International donations	-	-	62,425,887	6.4	-	-	4,160,282	6.4

Table 5.7 Doses distribnted and administered for elasomeran

	Cumulative				Interval			
Region	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	1,318,183,956	100.0	774,433,074	100.0	2,594,240	100.0	1,524,116	100.0
North America	553,855,010	42.0	304,620,256	39.3	503,800	19.4	277,090	18.2
US	505,353,070	38.3	277,944,189	35.9	3,000	0.1	1,650	0.1
All Europe	341,040,600	25.9	187,572,330	24.2	115,200	4.4	63,360	4.2
European Economic Area	301,453,700	22.9	165,799,535	21.4	115,200	4.4	63,360	4.2
Asia	282,393,826	21.4	155,316,604	20.1	265,260	10.2	145,893	9.6
Latin	62,187,600	4.7	34,203,180	4.4	1,702,300	65.6	936,265	61.4

America								
Africa	32,369,680	2.5	17,803,324	2.3	7,680	0.3	4,224	0.3
Oceania	23,676,600	1.8	13,022,130	1.7	0	0.0	0	0.0
Middle East	22,660,640	1.7	12,463,352	1.6	0	0.0	0	0.0
International donations	-	-	49,431,898	6.4	-	-	97,284	6.4

Table 5.8 Doses distributed and administered for elasomeran/imelasomeran

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	128,997,293	100.0	70,948,511	100.0	1,583,320	100.0	870,826	100.0
North America	10,521,450	8.2	5,786,798	8.2	0	0.0	0	0.0
US*	21,600	0.0	11,880	0.0	0	0.0	0	0.0
All Europe	83,496,993	64.7	45,923,346	64.7	871,520	55.0	479,336	55.0
European Economic Area	58,739,963	45.5	32,306,980	45.5	871,520	55.0	479,336	55.0
Asia	29,554,550	22.9	16,255,003	22.9	220,200	13.9	121,110	13.9
Latin America	1,100,150	0.9	605,083	0.9	100,200	6.3	55,110	6.3
Africa	99,600	0.1	54,780	0.1	0	0.0	0	0.0
Oceania	2,891,400	2.2	1,590,270	2.2	391,400	24.7	215,270	24.7
Middle East	1,333,150	1.0	733,233	1.0	0	0.0	0	0.0

*The 21,600 doses of elasomeran/imelasomeran distributed by ModernaTx to the US were ultimately provided to UNICEF after the initial delivery.

North America: Canada and US

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

Asia: Bangladesh, Bhutan, Cambodia, 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

Table 5.9 Doses distributed and administered for elasomeran/davesomeran

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	217,509,074	100.0	119,629,991	100.0	106,763,294	100.0	58,719,812	100.0
North America	69,347,234	31.9	38,140,979	31.9	1,432,154	1.3	787,685	1.3
US	67,846,884	31.2	37,315,786	31.2	1,430,804	1.3	786,942	1.3
All Europe	65,556,530	30.1	36,056,092	30.1	38,314,630	35.9	21,073,047	35.9
European Economic Area	59,256,930	27.2	32,591,312	27.2	32,015,030	30.0	17,608,267	30.0
Asia	71,869,860	33.0	39,528,423	33.0	57,281,060	53.7	31,504,583	53.7
Latin America	7,182,250	3.3	3,950,238	3.3	7,182,250	6.7	3,950,238	6.7
Africa	0	.	0	.	0	0.0	0	0.0
Oceania	1,163,200	0.5	639,760	0.5	1,163,200	1.1	639,760	1.1
Middle East	2,390,000	1.1	1,314,500	1.1	1,390,000	1.3	764,500	1.3

North America: Canada and US
Europe: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Ukraine, Switzerland, United Kingdom
Asia: Bangladesh, Bhutan, Cambodia, Indonesia, Japan, Kyrgyzstan, Nepal, Pakistan, Philippines, Singapore, Taiwan, Tajikistan, Thailand, Turkmenistan, Uzbekistan, Vietnam, South Korea
Middle East: Israel, Kuwait, Qatar, Saudi Arabia, United Arab Emirates, Palestine
Latin America: Argentina, Bolivia, Chile, Colombia, Dominica, Grenada, Haiti, Mexico, Paraguay, Peru, St. Lucia, St. Vincent, and the Grenadines
Oceania: Australia, Fiji, Vanuatu
Africa: Angola, Benin, Botswana, Brunei Darussalam, Burkina Faso, Central African Republic, Democratic Republic of Congo, Egypt, Guinea, Kenya, Nigeria, Rwanda, Sao Tome and Principe, Tanzania, Tunisia, Uganda, Zambia.

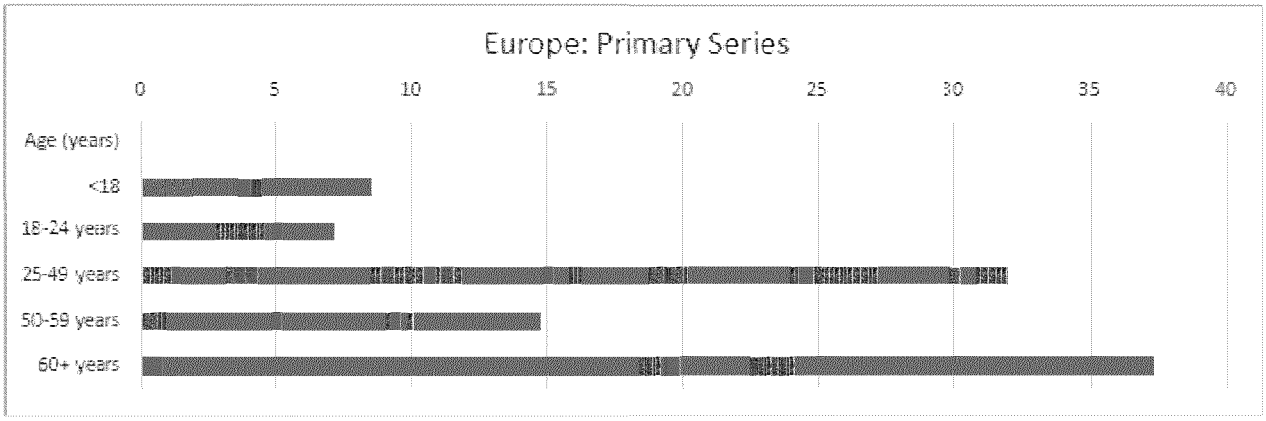
Summaries of ModernaTx, Inc. distribution administered by country and distribution by lots/batches are included in Appendix 12.1 [please see PSUR].

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

Available demographic characteristics of vaccine recipients (primary series boosters and elasomeran/imelasomeran and elasomeran/davesomeran) are shown for the European Economic Area (EEA) (Figure 5-4, Figure 5-5, Figure 5-6 and Figure 5-7) and Canada (Figure 5-8 and Figure 5-9) [please see PSUR]. In the EEA, the highest proportion of vaccinated individuals were among 25-49 years of age

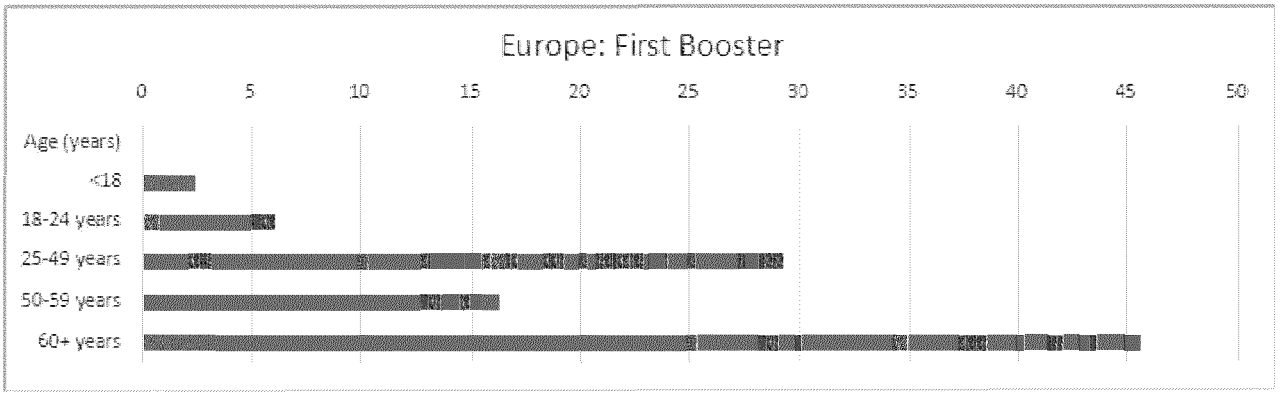
for primary series and 60 years and older for booster doses. In Canada, the highest proportion of vaccinated individuals were among 18-29 years for primary series and 60-69 years for booster doses. Information on distribution by gender was not published by European Center for Disease Prevention and Control (ECDC) at the time that the data were accessed (https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccinetracker. html#uptake-tab Accessed on June 18th, 2023).

Figure 5-4 EEA Recipients of All COVID-19 Vaccine Products for Primary Series by Age



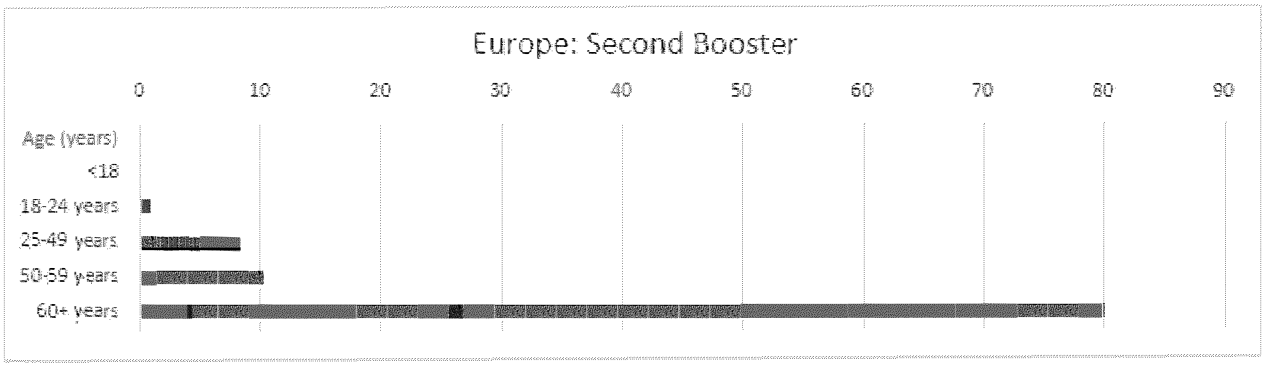
Data as of 16 Jun 2023 from ECDC [7].

Figure 5-5 EEA Recipients of All COVID-19 Vaccine Products for First Booster by Age



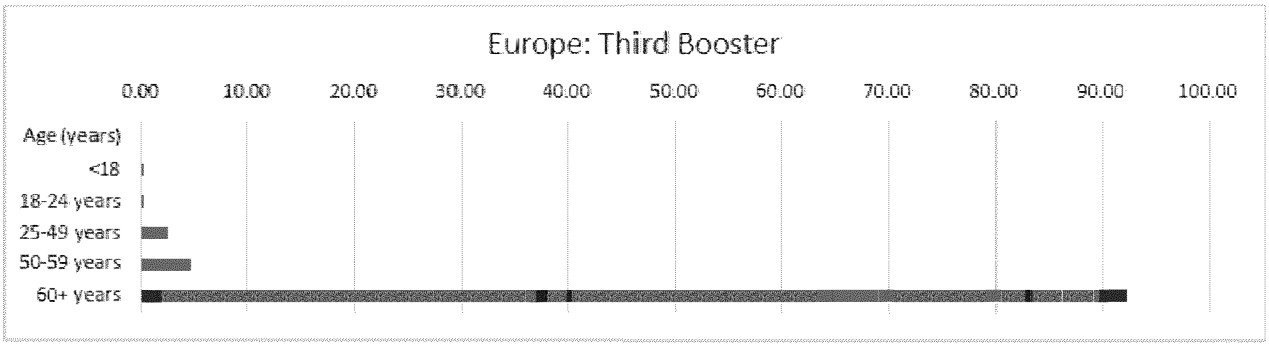
Data as of 16 Jun 2023 from ECDC [7].

Figure 5-6 EEA Recipients of All COVID-19 Vaccine Products for Second Booster by Age



Data as of 16 Jun 2023 from ECDC [7].

Figure 5-7 EEA Recipients of All COVID-19 Vaccine Products for Third Booster by Age



Data as of 16 Jun 2023 from ECDC [7].

Rapporteur assessment comment:

Patient exposure

Clinical trials

The estimated cumulative subject exposure in clinical trials is estimated to 53,983 subjects.

Post-marketing

The total cumulative exposure from marketing experience is estimated as 978,005,565 administered doses of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The estimated cumulative exposure for elasomeran alone is 774,433,074 administered doses. For elasomeran/imelasomeran the estimated cumulative exposure is 70,948,511 administered doses and for elasomeran/davesomeran 119,629,991 administered doses.

The total estimated interval exposure from marketing experience is estimated as 65,177,752 administered doses.

The estimated interval exposure for elasomeran alone is 1,524,116 administered doses. For elasomeran/imelasomeran the estimated interval exposure is 870,826 administered doses and for elasomeran/davesomeran 58,719,812 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 RMP and Summary of Product Characteristics (SmPC), instructions have been provided with our product for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability. ModernaTx, Inc. has also developed Traceability and Vaccination Reminder cards.

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

- Placeholder space for name of vaccine;
- Vaccine brand name and manufacturer name;
- Placeholder space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine;
- QR code that links to a website with additional information on product use; and
- Adverse event reporting information.

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

1.3.3.2.2. Post-authorization use in special populations

Use in elderly
Evaluation of information received during the PBRER reporting period relating to use of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in the elderly population has not identified any additional clinically relevant new safety information for this subpopulation. The number of cases received during this reporting period and the associated Marketing Authorization Holder (MAH) comment are presented by product in Table 5.10 [please see PSUR]. Refer to Appendix 12.3 for more information [please see PSUR].

Use in children
Evaluation of information received during the PBRER reporting interval relating to use of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in children, has not identified any additional clinically relevant new safety information for this subpopulation. The number of cases received during this reporting period and associated MAH comment are presented by age group in Table 5.11 [Please see PSUR]. Refer to Appendix 12.4 for additional information [Please see PSUR].

During the reporting period, the MAH received 745 cases (121 serious, 685 medically confirmed, 6 fatal) with 1,749 events (275 serious) for children <18 years of age who received elasomeran as primary series, or booster with elasomeran/imelasomeran or elasomeran/davesomeran. When gender was known, no significant difference was noted in cases involving males (318, 42.7%) and females (350, 47.0%), with small proportion of cases (77, 10.3%) having no gender reported. The mean patient age was 6.9 years (standard deviation: 5.9) and median age of 4.0 (range: 0.0 to 17.0 years). The majority of these reports were spontaneous (429, 57.6%), with highest number of cases reported in United States (410, 55.0%) followed by Latin America (112, 15.0%) and Asia (97, 13.0%).

During the reporting period, when dose number and time to onset could be determined, events were most often reported after Dose 2 (250, 14.3%) followed by Dose 1 (214, 12.2%) and Dose 3 (171, 9.8%), typically within 7 days of vaccination.

As requested by a health authority, the MAH reviewed cases of Arrhythmia for children <18 years of age. The search retrieved one (1) case of Arrhythmia. For case details and MAH comments refer to Section 15.2.1.

The most frequently reported events in children were non-serious and often involved product use issues (Expired product administered (193, 11.0%), Wrong product administered (114, 6.5%) and Product storage error (80, 4.6%)) with no associated adverse events (AEs) reported. It should be noted that there were 393 (22.5%) events of Preferred term (PT) No adverse event.

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.

Paediatric population

One case of arrhythmia in the paediatric population was retrieved in the reporting period which is described further in section 2.3.2.1 as part of a Health authority request review.

Six fatal cases were reported of which two cases were confounded with birth defects, three cases had insufficient evidence for a causal association and one case was reported with myocarditis which is an important identified risk for elasomeran.

According to the MAH, no additional clinically relevant new safety information was identified in the reporting period for children aged <18 years.

This section is acknowledged

1.3.3.2.3. Other clinical topics

Overdose

Table 5.13 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 all the VAERs reports received from 2007-2018, more than three-fourths of the reports of an excess dose of vaccine did not describe an AE. Among reports where an AE was reported, most of the common events included expected conditions such as pyrexia, injection site erythema, pain, and headache. Although most of the reports were of other vaccines (e.g., trivalent inactivated influenza, varicella, hepatitis A, and measles, mumps, rubella, varicella), the percentage of the AEs among these vaccine reports were comparable to all reports submitted to VAERS during the same period [9].
Methods	The MAH queried the GSDB for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. The search criteria applied for identification of Overdose cases included the following terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.
Results	***Overdose Cases Involving use of Elasomeran*** During the review period, the MAH received 11 cases (11 events) of Overdose with 4 serious cases (1 serious event), and 1 case with a fatal outcome. All 11 cases were medically confirmed. The fatal outcome was due to the multiple underlying conditions including an aggravated small cell lung cancer. Additionally, the single serious overdose event in the fatal case was unrelated to elasomeran but associated with irbesartan. The reported events were "Accidental overdose" (6; 54.5%) and "Overdose" (5; 45.5%). There were 5 medically confirmed cases (5 events) involving booster dose with elasomeran, and there were no fatal cases. The reported events were "Accidental overdose" (4, 80%) and "Overdose" (1; 20%). ***Overdose Cases Involving use of Elasomeran/Imelasomeran*** During this review period, the MAH received 2 cases (2 events) of Overdose with no serious cases, and no fatal outcomes in patients who received elasomeran/imelasomeran. Both cases were medically confirmed. The reported events were "Overdose" (2; 100%). ***Overdose Cases Involving use of Elasomeran/Davesomeran*** During the review period, the MAH received 10 cases (10 events) of Overdose with no serious cases and no cases with a fatal outcome. There were 10 medically confirmed cases involving elasomeran/davesomeran. The reported events were "Overdose" (6; 60%) and "Accidental Overdose" (4; 40%).
Discussion	A review of the data received during the reporting period of this PBRER, showed that overall numbers of overdose were relatively small, ranging from 2 to 11 cases for the elasomeran original and bivalents (elasomeran/imelasomeran and elasomeran/davesomeran). All events of overdose were non-serious. One serious case for the elasomeran original reported a serious overdose event for irbesartan but not for the vaccine. Furthermore, in one serious case there was no causal relation between the elasomeran original and fatal outcome, which was due to multiple underlying conditions

	including an aggravated small cell lung cancer. 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 on 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, and elasomeran/davesomeran did not raise any safety issue of concern. The MAH will continue to monitor events of overdose using routine surveillance. The benefit-risk evaluation remains positive.

Refer to Appendix 12.5 [please see PSUR] for more detailed information.

Off-label

Table 5.14 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 authorization. Examples include the intentional use of a product in situations other than the ones described in the authorized product information, such as a different indication in terms of medical condition, a different group of patients (e.g., a different age group), a different route or method of administration or a different posology. The reference terms for off--label use are the terms of marketing authorization in the country where the product is used." (EMA Good Pharmacovigilance Practices Annex 1 – Definitions [Rev 4]) [10].
Methods	The search criteria applied for identification of Off-label use cases included the following terms: Off-label use, Off-label use of device, Intentional dose omission, Intentional product misuse, Intentional product misuse to child, and Intentional product use issue. If warranted, the Company causality assessment is provided utilizing the World Health Organization-Uppsala Monitoring Center (WHO-UMC) standardized case causality assessment for serious cases classified as meeting the definition of Off-label use.
Results	***Off-label Use Cases Involving use of Elasomeran*** During the review period, the MAH received 43 cases (45 events) of Off-label use with 35 serious cases (30 serious events), and 1 case with a fatal outcome. Of note, the patient with a fatal outcome had aggravated lung cancer, also reported the event of intentional product misuse (misuse of irbesartan, aminophylline, carbocisteine, methotrexate and others), and had no description of off-label use for elasomeran. There were 22 medically confirmed cases involving elasomeran. Most cases involved females (28 cases, 65.1%), males (14 cases, 32.6%); gender information missing in 1 case (2.3%). The mean age

	was 54.1 years (Standard deviation: 14.1) and median age was 52.5 years (range: 24.0 to 82.0 years). The country with the most frequent cases of Off-label use was Canada (21; 48.8%) followed by Germany (11; 25.6%). The events reported were "Off-label use" (42; 93.3%) and "Intentional product misuse" (3; 6.7%). ***Off-label Cases Involving use of Elasomeran/Imelasomeran*** During this review period, the MAH received 1 non-serious case (1 event) of Off-label use. The case involved a 63-year-old female. The case was received from Canada (1; 100%) and the event reported was "Off-label use" in elasomeran/imelasomeran. ***Off-label Cases Involving use of Elasomeran/Davesomeran*** During the review period, the MAH received 3 cases (3 events) of Off-label use with 1 serious case (1 serious event) and no case with a fatal outcome. There were 2 medically confirmed cases involving elasomeran/davesomeran. There were 2 cases reported in females (66.7%), and 1 case reported in males (33.3%). The mean age was 28.7 years (SD: 35.8) and median age was 28.7 years (range: 3.3 to 54.0 years). The country with the most cases of Off-label use was the United States (2; 66.7%) followed by Canada (1; 33.3%). The events reported were "Off-label use" (3; 100%).
Discussion	During the reporting period, the total number of off-label use cases decreased compared with last review period (60 vs 47 cases) as well as the number of medically confirmed cases (37 vs 25 cases). Same as the last review period, "off-label use" was the most frequently reported PT. Only isolated non-serious cases of off-label use were received from both elasomeran/imelasomeran and elasomeran/davesomeran boosters during the review period. One fatal case was reported by a consumer for elasomeran administration during this review period. Of note, the fatal outcome was most likely due to underlying aggravated lung cancer based on the information provided. Furthermore, the patient also reported the events of intentional product misuse and drug abuse of multiple other medications, but there was no description of off-label use for elasomeran. Off-label use observed during the review period did not change the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran exposure. The MAH will continue to monitor events for off-label use using routine surveillance. The benefit-risk evaluation remains positive.

Refer to Appendix 12.6 [please see PSUR] for more detailed information.

Rapporteur assessment comment:

Overdose

During the reporting period, eleven cases with overdose were identified for elasomeran, two cases for elasomeran/imelasomeran and ten cases for elasomeran/davesomeran. One case for elasomeran was fatal which was due to underlying conditions, including small cell lung cancer.

Off-label use

During the reporting period, 43 cases with off-label use were identified for elasomeran, one event for elasomeran/imelasomeran and three cases for elasomeran/davesomeran. One case with elasomeran was

fatal and according to the MAH most likely due to aggravated lung cancer.

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

The section is acknowledged

1.3.4. Data in summary tabulations

1.3.4.1. Reference information

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 was used for the coding of AEs/adverse drug reactions (ADRs) presented in this report. The line listings and summary tabulations are first arranged alphabetically by primary MedDRA System Organ Class (SOC) and then by the PT.

1.3.4.2. Cumulative summary tabulations of serious adverse events from clinical trials

A cumulative (18 Dec 2020 to 17 Jun 2023) summary tabulation of Serious Adverse Events (SAEs) from Company-sponsored CTs is provided in Appendix 3. Inclusion requirement parameters for the incorporation of data from Company sponsored-CTs are that the SAE occurred during active treatment, the SAE originated from a clinical study with mRNA-1273, mRNA-1273.214, mRNA-1273.222, mRNA-1273.815 and mRNA-1273.231, the event was assessed as serious, and the active treatment was mRNA-1273 or placebo.

1.3.4.3. Cumulative and interval summary tabulations from post-marketing data sources

A cumulative (18 Dec 2020 to 17 Jun 2023) and interval (18 Dec 2022 to 17 Jun 2023) summary tabulation of ADRs (serious and non-serious) is provided in Appendix 4. The ADRs presented in this tabulation were derived from spontaneous sources (healthcare professionals [HCPs], consumers, scientific literature, and regulatory authorities [RAs]) as well as serious ADRs from non-interventional studies and non-interventional solicited sources.

Rapporteur assessment comment:

No new important safety information is identified in the reporting period.

This section is acknowledged.

1.3.5. Findings from clinical trials and other sources

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

Completed clinical trials

There were no ModernaTx, Inc. sponsored CTs which were completed during the reporting period.

Ongoing clinical trials

There was a total of 12 ModernaTx, Inc. sponsored CTs ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P305, mRNA-1283-P101, mRNA-1283-P201, mRNA-1273-P206, mRNA-1283-P301, and mRNA-CRID-001), during the

current reporting period. Of these 12 ongoing CTs, four trials (mRNA-1283-P101, mRNA-1283-P201, mRNA1283-P301 and mRNA-CRID-001) included mRNA-1273 treatment arms. Cumulative exposure by study- has been presented in Table 7.1.

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

Table 7.1 Summary of Cumulative Subject Exposure by Study[a]

Study ID	Total subjects exposed
mRNA-1273-P203	4,321
mRNA-1273-P204	11,915
mRNA-1273-P205	5,163
mRNA-1273-P206	54
mRNA-1273-P301	30,346
mRNA-1273-P304	234
mRNA-1273-P305	3,548
mRNA-1273-P306	930
mRNA-1283-P101[b]	27
mRNA-1283-P201[b]	57
mRNA-1283-P301	7,771
mRNA-CRID-001[b]	60

[a]=The total count of 53,983 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) and hence the total of all studies varies from the total unique subjects exposed.
[b]=The counts from these studies do not include Investigational Product other than mRNA-1273, Comparator or Placebo.

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

Rapporteur assessment comment:

No clinical trials were completed during the reporting period. 12 trials were ongoing. The MAH reports that there was no clinically important information that arose from these studies during the reporting period. Endorsed.

Long-term follow-up

The Phase 3 study mRNA-1273-P301 includes a total of 24 months follow-up; no long-term safety concerns have been identified for the two-dose mRNA-1273 100 mcg primary series based on an interim analysis that includes 16,818.4 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). Participants completing CTs mRNA-1273-P101 (Division of Microbiology and Infectious Diseases [DMID] 20-0003), mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, and mRNA-1273-P306 are followed up for safety for 12 months.

In the adolescent Phase 3 Study mRNA-1273-P203, participants from the age of 12 through 17 years had a median follow-up of 342 days after Dose 1 and 312 days after Dose 2. In the paediatric Phase 3 Study

mRNA-1273-P204, participants 6 months through 11 years had a median follow-up ranging between 254 and 267 days across age groups.

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

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

New safety data related to fixed combination therapies

For elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, there were three combination therapies in which elasomeran, elasomeran/imelasomeran and/or elasomeran/davesomeran are part of the fixed combinations: mRNA-1073, mRNA-1230 and mRNA-1083. There are separate Development Safety Update Reports (DSURs) for each of these fixed combination therapies. No new safety information has been identified from the fixed combination therapies that are in development.

Rapporteur assessment comment:

The MAH reports that as of the DLP there were no significant safety findings identified from the CTs that investigate the long-term safety of elasomeran-containing vaccines.

There are three combination therapies in which elasomeran-containing products are involved. No new safety findings have been identified by the MAH.

This section is endorsed.

1.3.5.2. Findings from non-interventional studies

The following non-interventional study was completed during the reporting period:
mRNA-1273-P902
Title: Moderna mRNA-1273 Observational Pregnancy Outcome Study.

Status: Enrolment for this prospective pregnancy registry began in Oct 2021. Enrolment proceeded slowly and the study was replaced in the EU RMP by the ongoing study mRNA-1273-P905 and study mRNA-1273-P919 (planned), a US administrative claims-based study of pregnancy safety. No safety findings have yet been identified.

The following non-interventional studies were ongoing during the reporting period:
mRNA-1273-P901
Title: Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the US.

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

The final clinical study report (CSR) date for this study is currently anticipated to be submitted by 14 Apr 2025.

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

Prior analyses conducted from the P901 study assessing relative vaccine effectiveness of receipt of a single booster dose of the monovalent mRNA-1273 (following receipt of 2 doses of monovalent mRNA COVID vaccine) between 20 Oct 2021 and 31 Dec 2021 demonstrated rVE against hospitalization, SARS-CoV-2 infection and death to be 89.0% (95% Confidence Interval [CI]: 86.2%-91.2%), 61.3% (95% CI: 60.5% – 62.2%), and 96% (95% CI: 68.0%-99.5%), respectively among 431,328 immunocompetent adults receiving a single booster dose of mRNA-1273 (and a similar number of matched comparators who received a 2 dose mRNA monovalent COVID vaccine only) [11]. In addition, an analysis conducted between 01 Jan 2022 and Jun 30, 2022 among 30,809 SARS-CoV-2 cases and 92,427 matched controls looking at Omicron variant specific relative vaccine effectiveness of a booster dose of mRNA-1273 against hospitalization for COVID-19 demonstrated the rVE against BA.1, BA.2, and BA.4/5 Omicron sub-variants to be 88.8% (95% CI: 83.3-92.5); 75.0% (95% CI: 47.6-88.1); and 87.5% (95% CI: 51.8%-96.8%) [12].

<u>mRNA-1273-P903</u>
Title: Post-Authorization safety of SARS-CoV-2 mRNA-1273 vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity.

Status: This retrospective observational cohort study used secondary, de-identified individual level medical and pharmacy claims data provided by HealthVerity. Components of active vaccine surveillance via a historically controlled comparator and signal refinement using a SCRI design were implemented, and a final study report was submitted 30 Jun 2023.

Statistical Analyses: In the screening stage, incidence rates (IR) were calculated per 100,000 person-years following vaccination and were compared to IR calculated during two historical periods using incidence rate ratios (IRR). Where unadjusted IR >2.0 and ≥5 events, observed versus expected (O/E) ratios and 95% CIs comparing the number of events after vaccination to the expected number of events based on the historic rates were estimated. Where the lower bound of O/E ratio > 1, SCRI analyses were performed among vaccinated cases where ≥10 total cases were observed. All analyses were presented for any dose (referenced as dose-agnostic analysis) and for doses 1, 2 or 3 with stratification by age and sex. Analyses were presented separately for persons with immunocompromised conditions identified prior to

the index date, for heterologous booster dose recipients, and for elasomeran bivalent recipients as feasible. Pregnancy outcomes were presented separately with age strata limited to plausible values for women of childbearing age.

Results: The pre-COVID and COVID era cohorts included 50,015,708 individuals meeting study entry criteria. Of these individuals, 38,686,912 were at least 18 years of age and 11,328,796 were under 18 years of age. Among the historical comparator populations, there were 939,115 and 928,955 immunocompromised adults and 34,686 and 36,698 immunocompromised children in the pre-COVID and COVID eras, respectively. Among females of childbearing age (12-55 years) in the historical populations, after applying study inclusion criteria, there were 94,244 and 83,390 pregnant women in the pre-COVID and COVID eras, respectively. Within the pre-COVID comparator population, 5,276,278 adults and 1,803,180 individuals <18 years of age were vaccinated for influenza.

There were 6,824,063 adults and 9,046 children vaccinated with elasomeran who met study entry criteria through 31 Aug 2022 with 1-year of continuous medical and pharmacy enrolment prior to their elasomeran administration. Primary analyses among children (<18 years) were restricted to vaccinations occurring between 17 Jun 2022 and 31 Aug 2022 reflecting authorization of elasomeran in this age range in US children and adolescents. Among individuals receiving at least one dose of elasomeran, 70.1% of adults and 40.9% of children received a second dose. Among individuals who received a second dose, 38.4% of adults and 0.7% of children also received a third dose. There were 262,276 immunocompromised adults who were vaccinated with elasomeran, of which 68.6% received a second dose; 46.0% of immunocompromised adults with a second dose also received a third dose. Slightly more immunocompromised adults received a non-elasomeran COVID-19 vaccine during follow-up than the general population (4.8% vs. 4.3%). There were 23,713 pregnant women 12-55 years who received elasomeran and met study entry criteria to be included in the pregnancy-specific analyses, and 55.1% received a second dose of elasomeran. Of these, 4.2% also received a third dose.

Myocarditis: There were 276 cases of myocarditis included in dose-agnostic SCRI analyses considering a 7-day risk and 42-day control window; 56.1% occurred after the second dose of elasomeran. Dose-agnostic, dose 1, dose 2 and dose 3-specific SCRI analyses indicated an elevated rate of myocarditis within 7 days of vaccination, driven particularly by young adults (Dose 2 Event rate ratio [ERR] 8.47, 95% CI 4.55 – 15.77). The association was strongest for males 18-29 years of age following dose 2 (ERR 9.50, 95% CI 4.61–19.57), noting that increased risk was also present in other subgroups. Estimates after dose 3 showed numerical elevations that reached statistical significance in sensitivity but not primary analyses. In SCRI analyses among heterologous vaccine recipients and children, counts were too low to support meaningful inference.

The signal evaluation results for myocarditis were consistent with known safety profile of elasomeran vaccine.

Pericarditis: Among adults, there were 413 cases of pericarditis identified through 31 Aug 2022, most (55.7%) after the second dose of elasomeran. Dose-agnostic and dose 2-specific SCRI analyses indicate an elevated rate among males 18-29 years of age in the 7 days following elasomeran vaccination, primarily driven by the second dose (ERR 3.40, 95% CI 1.51 – 7.66).
SCRI analysis following a third or a heterologous dose was conducted, however counts were too low to support any meaningful inference. In children, no pericarditis events were observed following elasomeran administration.

The signal evaluation results for pericarditis were consistent with known safety profile of elasomeran vaccine.

Other Adverse Events of Special Interest (AESI): SCRI analyses were also indicated for the following AESI: acute kidney injury, acute respiratory distress syndrome, anaphylaxis, anosmia/ageusia, arrhythmia, Bell's palsy, chilblain-like lesions, cerebral venous sinus thrombosis, coagulation disorders, erythema multiforme, immune thrombocytopenia, meningoencephalitis, narcolepsy/cataplexy, non-hemorrhagic stroke, seizures/ convulsions, single organ cutaneous vasculitis, thrombosis with thrombocytopenia, Guillain-Barré syndrome (GBS), myositis, and transverse myelitis. SCRI analyses could be conducted for these AESI are reported where the threshold of ≥10 cases was met.

Anosmia/ageusia: There were 2,709 anosmia/ageusia cases observed among adults in the 28-day risk and 42-day control windows following elasomeran administration through 31 Aug 2022. An increased event rate of questionable clinical significance was observed in the 28-day risk window following all doses among adults (ERR 1.10, 95% CI 1.02 – 1.19 in dose-agnostic analysis). In SCRI analyses following a heterologous dose, no increase in risk window event rates were observed. Similarly, sensitivity analyses not censoring on COVID-19 diagnosis and washing out for history of COVID-19 led to similar conclusions as the primary analysis. Results for another sensitivity analysis using a 14-day risk window led to more varied event rate ratios but were genuinely attenuated. Only 3 events were observed for estimating the rate of anosmia/ageusia following the Omicron-containing bivalent booster, limiting interpretation. There were 14 children included in the dose-agnostic SCRI. No elevated rates of anosmia/ageusia were observed in analyses performed.

Anaphylaxis: There were 719 cases of anaphylaxis within the risk and control periods following elasomeran administration observed among adults through 31 Aug 2022. Increased event rates in the 2-day risk window following elasomeran vaccination were observed in the dose-agnostic and dose-specific analyses for most age and sex strata, with a larger ERR for females (e.g., ERR 4.70, 95% CI 3.79-5.84 in dose-agnostic analyses). Analyses following dose 3 were less interpretable given low counts. Dose-agnostic SCRI analysis excluding cases with allergen immunotherapy and separately not censoring on COVID-19 diagnoses led to similar conclusions as the primary analysis. Only 4 events were observed among adults when estimating the rate of anaphylaxis following the Omicron-containing bivalent booster, thus limiting interpretation. SCRI analyses of anaphylaxis among children were not conducted given the threshold of ≥10 events was not met.

The signal evaluation results for anaphylaxis were consistent with known safety profile of elasomeran original vaccine.

Myositis: There were 7,006 cases included in the dose-agnostic SCRI analysis, which did not show elevated rates overall (ERR 0.99, 95% CI 0.93-1.05) or in subgroups by age and gender. In dose specific analyses, elevated rates were observed isolated subgroups – males ages 18-29 after dose 1 (ERR 1.77, 95% CI 1.02-3.10) and males 30-39 after dose 2 (1.73, 95% CI 1.02-2.93). Low case counts did not allow for interpretable analyses of myositis following a heterologous dose or an Omicron-containing bivalent booster. In the adult immunocompromised population, there were 599 cases included in the dose-agnostic SCRI analysis (ERR 1.05, 95% CI 0.85-1.30). In this subgroup, elevated rates were observed in adults ≥75 years (ERR 2.37, 95% CI 1.11-5.06). In the dose 1- specific SCRI analyses, an increase in rates was observed among IC adults 18-29 years (ERR 3.82, 95% CI 1.25-11.67) and females 18-29 years (ERR 3.49, 95% CI 1.02-11.91). On the dose 2-specific SCRI analyses, an imprecise numerical elevation in rate was observed among IC males 40-49 years (ERR 3.00, 95% CI 0.90-9.96). No heterologous dose SCRI analysis was conducted given the threshold of ≥10 events were not met.

Given this extent of multiple testing and the absence of a consistent pattern in other subgroups, interpretation of this finding is unclear. For further details on signal evaluation, please refer to Section 16.2.4 [please see PSUR].

Single organ cutaneous vasculitis (SOCV): Among the 485 events among adults included in the dose-agnostic SCRI analysis, an elevated rate of SOCV was not observed (ERR 0.91, 95% CI 0.76-1.09). Within the dose 3-specific SCRI analysis, an elevated rate of SOCV was suggested in the 28-day risk window among males overall (ERR 2.37, 95% CI 1.12-5.02) and within males 50-64 years (ERR 3.22, 95% CI 1.12-9.23), however event counts were low and should be interpreted with caution. The dose 1- and 2-specific SCRI analyses yielded no observed elevated rates, nor in a dose-agnostic sensitivity analysis not censoring on COVID-19 diagnosis. Only 2 events were observed among adults for estimating the rate of SOCV following the Omicron -containing bivalent booster, thus limiting interpretation. SCRI analyses within adults with a heterologous dose and within children were not conducted due to insufficient event counts.
Acute kidney injury, Arrhythmia, cerebral venous sinus thrombosis, Chilblain-like lesions, erythema multiforme GBS, immune thrombocytopenia, narcolepsy, seizure, and transverse myelitis: No significantly elevated event rate ratios were observed.

Discussion
Results of this final report for study mRNA-1273-P903 are largely consistent with findings from the interim reports and its known safety profile, particularly for labeled events such as myocarditis and anaphylaxis. Additional monitoring of potentially artifactual increases isolated to specific subgroups for myositis and SOCV will be subject to continued monitoring in studies mRNA--1273--P904 and mRNA-1273-P920.

<u>mRNA-1273-P904</u>

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

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

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

The MAH identified more than 50 strata with standardized mortality ratio ≥2.0 based on ≥5 elasomeran exposed cases in at least one country for the AESIs diabetes type 1, idiopathic thrombocytopenia, heart failure, myocarditis, pericarditis, pulmonary embolism, splanchnic vein thrombosis, coagulation disorders, acute liver injury, acute kidney injury, generalized convulsions, acute respiratory distress syndrome, anosmia/ageusia, multisystem inflammatory syndrome, and death of any cause. There was a maximum of 11 to50 signals in at least one country for the AESIs microangiopathy, coronary artery disease,

arrhythmia, cerebrovascular disease, SOCV, encephalitis/meningoencephalitis, Bell's palsy, erythema multiforme, and anaphylaxis. The MAH did not identify any signals for narcolepsy, cerebral venous sinus thrombosis, Kawasaki disease, transverse myelitis, and sudden death. For the remaining AESIs, there was a maximum of 10 signals for each country. Most signals were detected in Spain (Information System for Research in Primary Care).

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

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

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

mRNA-1273-P905
Title: Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries.

Summary: For this observational cohort study carried using large administrative databases in Denmark, Norway, Italy, Spain, and the UK, with feasibility counts were described in the Mar 2023 interim study update. At this time, no safety findings have yet been identified given the early stage of the study.
mRNA-1273-P911

mRNA-1273-P911
Title: Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA).

Summary: The overarching goal of this study is to characterize presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (elasomeran). The first interim feasibility report was completed 31 Oct 2022. Cases of myocarditis identified in routine clinical practice meeting the CDC case definition, including those occurring following administration of elasomeran as well as cases not secondary to vaccines targeting SARS-CoV-2. At this time, no safety findings have yet been identified given the early stage of the study.

mRNA-1273-P915
Title: Survey on acute phase safety for persons with underlying diseases with high risk.

Status: The overarching goal of this post-marketing surveillance (PMS) activity to confirm the incidence of hypersensitivity reactions including shock and anaphylaxis observed after vaccination with this drug and

to explore risk factors in persons with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan.

A report for this database survey was submitted to Pharmaceuticals and Medical Devices Agency (PMDA) on 17 May 2023. Based on the analysis of 13,309 individuals, the occurrence of hypersensitivity in individuals at high risk for COVID-19 infection was consistent with the known safety profile of elasomeran.

mRNA-1273-P916
Title: Survey on Shock and Anaphylaxis for Persons with Underlying Diseases with High Risk.

Status: The overarching goal of this PMS activity is to identify the incidence of specified AEs in the acute phase observed after vaccination in subjects with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A report for this database survey was submitted to PMDA on 17 May 2023. Based on the analysis of 8,844 individuals, the occurrence of solicited AEs, particularly, reactogenicity had an occurrence of > 1% within 8-days of vaccination in individuals at high risk for COVID-19 infection.

mRNA-1273-P917
Title: Survey on non-acute phase safety for persons with underlying diseases.

Status: The overarching goal of this PMS activity is to identify hypotheses for the safety evaluation of this product by confirming the occurrence status of non-acute hospitalization associated serious events observed after vaccination in persons with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. The study is ongoing; however, no safety findings have been identified to date.

mRNA-1273-P918
Title: General Use Results Survey: Spikevax Intramuscular Injection (Previously COVID-19 Vaccine Moderna Intramuscular Injection) During the Early Phase of Treatment with Novel Corona Vaccine, Follow-up of Key Survey Participants.

Summary: The overarching goal of this PMS activity is to follow-up subjects who are vaccinated early after the marketing approval of this product in Japan for 11 months from the day after the day following the last day of the last vaccination with this drug as the primary immunization (the last day of the observation period in the health status investigation of preceding vaccinees) to 12 months after the last vaccination with this drug as the primary immunization, and to collect information on SAEs observed during the follow-up period and COVID-19. Enrolment for this survey ended in Dec 2022. There were 8,637 individuals in the safety and efficacy analysis set. At this time, no safety findings have yet been identified. The observation of the final subject was completed in Apr 2023, and final analyses are ongoing.

mRNA-1273-P922
Title: DisCOVEries II: An Observational Study to Evaluate the Immunogenicity of a COVID-19 Bivalent Booster as the Second Booster Dose Against Omicron BA.4/5.

Status: A six-month observational prospective study (with an optional long-term follow-up of up to 12 months), to investigate antibody levels with respect to time since receiving a bivalent COVID-19 booster dose. The protocol was approved on 06 Dec 2022. At this time, no safety findings have been identified.

mRNA-1273-P928
Title: Relative Effectiveness of mRNA-1273 in Adults with At-Risk Clinical Conditions.

Status: This is an Observational retrospective cohort study.

Part I: To determine the rVE of 2 doses of the mRNA-1273 vaccine vs. 2 doses of the BNT162b2 vaccine and 2 doses of the mRNA-1273 vaccine vs. 1 dose of the Ad26.COV2.S vaccine in individuals aged 18 years and older who have at least one underlying medical condition (endpoints: medically-attended COVID-19 illness/COVID-19 illness in outpatients/ COVID-19 illness requiring hospitalization).

Part II: To determine the rVE of a single homologous booster dose of the mRNA-1273 vaccine vs. a single homologous booster dose of the BNT162b2 vaccine in adults aged 18 years and older who have at least one underlying medical condition associated with higher risk for severe COVID-19 (endpoints: medically-attended COVID-19 illness/ COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization). Protocol was approved on 02 Mar 2023 and interim updates were done on 12 May 2023. At this time, no safety findings have been identified.

mRNA-1273-P930
Title: Relative effectiveness of the BNT162b2, mRNA-1273, and Ad26.COV2.S COVID-19 Vaccines in adults in the US.

Status: This is an Observational retrospective cohort study.

Part I: To determine the rVE of 2 doses of the mRNA-1273 vaccine vs. 2 doses of the BNT162b2 vaccine and 2 doses of the mRNA-1273 vaccine vs. 1 dose of the Ad26.COV2.S vaccine in individuals aged 18 years and older (endpoints: medically-attended COVID-19 illness/COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization).

Part II: To determine the rVE of a single homologous booster dose of the mRNA-1273 vaccine vs. a single homologous booster dose of the BNT162b2 vaccine in adults aged 18 years and older (endpoints: medically attended COVID-19 illness/ COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization). Accepted for publication (Open Forum Infectious Diseases).

This retrospective observational study follows a cohort during two distinct periods that reflect vaccination guidelines. The first period began in Feb 2021, when COVID-19 vaccines become available, until booster doses were recommended in Oct 2021. The second period began in Oct 2021, when individuals started receiving their booster dose until the end of Jan 2022, when the omicron variant wave was rapidly progressing throughout the United States. P930 was approved by Patient Review and Coordination in Apr 2022. At this time, no safety findings have yet been identified given the early stage of the study.

mRNA-1273-P931
Title: Comparative Effectiveness of the Bivalent COVID-19 mRNA Vaccines (ORIGINAL AND OMICRON BA.4/BA.5) in Adults in the US.

Status: The goal of this study is to determine the rVE between the two mRNA Bivalent vaccines against COVID-19-related hospitalization/outpatient visits in adults 18 years or older. The protocol was approved on 11 May 2023 and first interim updates were done on 22 May 2023. At this time, no safety findings have been identified given the early stage of the study.

mRNA-1273-P932
Title: Real-world comparative effectiveness of a third dose of mRNA-1273 versus BNT162b2 among immunocompromised adults in the US.

Status: The goal of this retrospective database study is to compare the real-world effectiveness of a third dose of the Spikevax vaccine vs. a third dose of the Comirnaty vaccine against breakthrough COVID-19 hospitalizations among immunocompromised adults in the US. This protocol for this study was approved on 01 Mar 2023, and analyses were initiated in Jun 2023. Analyses are ongoing with final completion expected by 21 Oct 2023. At this time, no safety findings have been identified given the early stage of the study.

mRNA-1273-P933
Title: Real world comparative effectiveness of a booster dose of Spikevax versus Comirnaty among adults age 65+ in the US.

Status: The goal of this retrospective database study is to compare the real-world effectiveness of a 1st booster dose of the Spikevax vaccine vs. a 1st booster dose of the Comirnaty vaccine against breakthrough COVID-19 hospitalizations among adults age 65+ who have completed a primary series of an mRNA-based COVID-19 vaccine. This protocol for this study was approved on 01 Mar 2023, and analyses were initiated in Jun 2023. Analyses are ongoing with final completion expected by 21 Oct 2023. At this time, no safety findings have been identified given the early stage of the study.

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

mRNA-1273-P910
Title: Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2.

Summary: The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and elasomeran bivalent vaccination. Startup activities including creation of the case adjudication system are currently in progress.

mRNA-1273-P919
Title: An Observational Study to Assess Maternal and Infant Outcomes Following Exposure to SPIKEVAX During Pregnancy.

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

mRNA-1273-P920
Title: Post-marketing safety of an Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine in the United States.

Status: The overarching aim of this study is to characterize the safety of the Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine as used in routine clinical practice.
Preliminary analyses are ongoing.

mRNA-1273-P921
Title: Evaluation of Post-marketing safety of Spikevax (elasomeran) in the Kingdom of Saudi Arabia.

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

mRNA-1273-P923
Title: Post-marketing safety of Spikevax vaccine in South Korea.

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

mRNA-1273-P924
Title: Post-marketing Surveillance: Use-Result Surveillance with Spikevax Bivalent.

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

Rapporteur assessment comment:
The MAH reported status from PAS studies included in the EU RMP and presented post-marketing surveillance (PMS) activites.
No new safety information that has not been assessed in other procedures has been presented.
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: Vaccine in chronic lymphocytic leukaemia (CLL).

Title: Vaccine responsiveness in patients with CLL.

Summary: In this prospective study, 60% of patients with CLL developed SARSCoV-2 antibodies and 80% developed functional T-cell responses after vaccination. For this study enrolment has been completed, first patient first visit dated 01 Sep 2020 and final CSR was completed on 07 Mar 2023. The total number of subjects enrolled was 36. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short tittle: COVERALL Initial

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: The objective for this study was to have a head-to-head comparison BNTI 62b2 and mRNA-1273. The start date for this study was Dec 2021 and end date was Jun 2022. The total number of subjects enrolled till DLP was 601 subjects. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

The following Investigator-sponsored Studies were ongoing during the reporting period:
Short Tittle: T-Cell immunity

Title: T-Cell immunity

Description for T-Cell immunity: Recently, two mRNA vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have become available, but there is also an emergence of SARS-CoV-2 variants with increased transmissibility and virulence. A major concern is whether the available vaccines will be equally effective against these variants. The vaccines are designed to induce an immune response against the SARS-CoV-2 spike protein which is required for viral entry to host cells. Immunity to SARS-CoV-2 is often evaluated by antibody production, while less is known about the T-cell response. Here we developed, characterized, and implemented two standardized, functional assays to measure T-cell immunity to SARS-CoV-2 in uninfected, convalescent, and vaccinated individuals. The MAH found that vaccinated individuals had robust T-cell responses to the wild type of spike and nucleocapsid proteins, even more so than convalescent patients. The MAH also found detectable but diminished T-cell responses to spike variants (B.1.1.7, B.1.351, and B.1.1.248) among vaccinated but otherwise healthy donors. Since decreases in antibody neutralization have also been observed with some variants, investigation into the T-cell response to these variants as an alternative means of viral control is imperative. Standardized measurements of T-cell responses to SARS-CoV-2 are feasible and can be easily adjusted to determine changes in response to variants. Estimated completion date is 25 Feb 2024.

Summary: Enrolment is complete, first patient first visit dated in 2022 and planned final report date is Sep 2023. The total number of subjects enrolled was 50. No AEs have been reported and no significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: 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 dated 26 Oct 2022 and planned final report date is 31 Dec 2023. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: SCQM

Title: N/A

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

Short Tittle: CoviBoost 2

Title: AP-HA

Summary: For this study enrolment was complete, first patient first visit was 22 Aug 2022 and planned final report date is Aug 2023. The total number of subjects enrolled was 414. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: SCQM Extension

Title: N/A

Summary: For this study enrolment was complete, first patient first visit was 03 Apr 2021 and planned final report date is Sep 2023. The total number of subjects enrolled was 917. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: MIViral

Title: N/A

Summary: For this study enrolment was complete, first patient first visit was in Oct 2022 and planned final report date is Dec 2023. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: N/A

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

Summary: Objective of this study is to identify predictors of hospitalization for fully vaccinated patients presenting to an emergency department (ED) and identify predictors of severe outcomes in fully vaccinated hospitalized patients. No subjects have been enrolled/exposed for this study at DLP of this PBRER. This study started on 15 Jun 2023 and the projected end date for this study is Jan 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: VI

Title: VI

Summary: Objective of this study is to determine the correlation of pre-existing antibodies against influenza or COVID with the kinetics of infectious viral load. No subjects have been enrolled in this study at DLP for this PBRER. This study started in Feb 2023 and the projected end date for this study is in Jun 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

License partner studies

Completed clinical trials

Sponsored by Glaxo SmithKline (GSK):
Protocol or Study Number: 217670 (ZOSTER-091)

A Phase 3, randomized, open-label, controlled, multicenter study to evaluate the immune response and safety of both herpes zoster subunit vaccine in healthy adults aged 50 years and older and the influenza virus vaccine in healthy adults aged 18 years and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.

Country-US

Dosing details: mRNA-1273 50 µg per dose (embedded in SM-102 LNPs); water for injections q.s. 0.5 mL.

- Flu D-QIV: Flu Quadrivalent Influenza vaccine 15 µg per strain/dose;
- HZ/su: Varicella-Zoster Vaccine gE (50 µg) and AS01B: QS-21 (50 µg), MPL (50 µg), liposomes; water for injections q.s. 0.5 mL.

Summary: Total enrolment was 2,013 subjects and actual subjects exposed to mRNA-1273 was 1,534. Start date for this study was 07 Oct 2021 and end date was 28 Feb 2023 (Date of final CSR). No safety, efficacy, or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons.

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

Protocol or Study Number: mRNA-1273-P102/21-0002/NCT04785144

A Phase 1, open-label, randomized study to access the safety and immunogenicity of a SARS-CoV-2 variant vaccine (mRNA-1273.351) in naïve and previously vaccinated adults.

Country-US

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

1. ARM 1A: 50 µg 1273.35,
2. ARM 1B: 25 µg 1273+25 µg 1273.351,
3. ARM 2A: 100 µg 1273/100 µg 1273/50 µg 1273.351,
4. ARM 2B:50 µg 1273/50 µg 1273/50 µg 1273.351,
5. ARM 2C: 100 µg 1273.351/100 µg 1273.351,
6. ARM 2D: 50 µg 1273.351/50 µg 1273.351,
7. ARM 2E: 100 µg 1273/100 µg 1273.351,
8. ARM 2F:50 µg 1273/50 µg 1273.351,
9. ARM 2G:50 µg 1273 + 50 µg 1273.351/50 µg 1273 + 50 µg 1273.351,
10. ARM 2H:25 µg 1273 + 25 µg 1273.351/25 µg 1273 + 25 µg 1273.351.

Summary: Planned enrolment was 210 subjects and actual subjects exposed to mRNA-1273 was 135. Start date for this study was 29 Mar 2020 and end date was in Apr 2023. The estimated completion date

for the CSR is late 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.

Protocol or Study Number: mRNA-1273-P101/20-0003/NCT04283461

A Phase 1, open-label, dose-ranging study to access the safety and immunogenicity of 2019-nCov Vaccine (mRNA-1273) in Healthy Adults.

Country-US

Dosing details: In this study doses were divided into below mentioned groups and all groups had option of booster dose 100 µg.

1. Cohort 1 ages 18-55 25 µg mRNA-1273
2. Cohort 2 ages 18-55 100 µg mRNA-1273
3. Cohort 3 ages 18-55 250 µg mRNA-1273
4. Cohort 4 ages 56-70 25 µg mRNA-1273
5. Cohort 5 ages 56-70 100 µg mRNA-1273
6. Cohort 6 ages 56-70 250 µg mRNA-1273
7. Cohort 7 ages ≥71 25 µg mRNA-1273
8. Cohort 8 ages ≥71 100 µg mRNA-1273
9. Cohort 9 ages ≥71 250 µg mRNA-1273
10. Cohort 10 ages 18-55 50 µg mRNA-1273
11. Cohort 11 ages 56-70 50 µg mRNA-1273
12. Cohort 12 ages ≥71 50 µg mRNA-1273

Summary: Planned enrolment was 140 subjects and actual subjects exposed to mRNA-1273 was 120. Start date for this study was 16 Mar 2020 and end date was 26 Apr 2023. The estimated completion date for the CSR is Oct 2023. No safety concerns were reported. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. Dose of 250 µg was not well tolerated (previously reported). Immunogenicity data was submitted to FDA and published. ModernaTx, Inc. has all the immunogenicity data and papers generated. Preliminary CSR was published in Feb 2021.
Follow-up for booster is still ongoing.

Protocol or Study Number: 21-0012
A Phase 1/2 study of delayed heterologous SARS-CoV-2 vaccine dosing (Boost) after receipt of EUA vaccines.

Country-US

Dosing details: mRNA-1273 - 100 µg; mRNA-1273-50 µg, 1273-211-100 µg.

Summary: Planned enrolment was 433 subjects and actual subjects exposed to mRNA-1273 were 423. Start date for this study was 28 May 2021 and projected end date is 14 Dec 2023. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. ModernaTx, Inc. has all the immunogenicity data and papers generated. Immunogenicity reports have been submitted to the FDA. This study has additional manufacturers to ModernaTx, Inc.; for this reason, total enrolment exceeds that noted here.

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

Phase 2 Clinical Trial to Optimize Immune Coverage of SARS-CoV-2 Existing and Emerging Variants-COVID-19 Variant Immunologic Landscape Trial (COVAIL Trial).

Country-US

Dosing details: In this study, dosing was conducted in 6 different arms as follows:

1. Arm 1: 1 Dose Prototype mRNA-1273, = (99);
2. Arm 2: 1 Dose Beta (B.1.351) + Omicron (B.1.1.529) = (100);
3. Arm 3: 2 Dose Beta (B.1.351) + Omicron (B.1.529) = (102);
4. Arm 4: 1 Dose Delta (B.1.1529) = (101);
5. Arm 5: 1 Dose Omicron (B.1.1.529) = (100);
6. Arm 6: 1 Dose Omicron (B.1.1.529) + Prototype 1273 = (100).

Summary: Planned enrolment was 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. One hundred ninety-four breakthrough infections to date, sequencing of the variants is ongoing, as well as correlates of protection study being conducted. Manuscript reporting on serological data through day 91, for stages 1-3, being prepared.

Sponsored by National Cancer Institute (NCI):

Study or Protocol Number 000115

A Trial of the Safety and Immunogenicity of the COVID-19 Vaccine (mRNA-1273) in Participants with Hematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumors on PD1/PDL1 Inhibitor Therapy, Including Booster Doses of Vaccine.

Country: US

Dosing details: The vaccine is administered in 2 doses, 28 days apart. Participants receive an IM injection (0.5 mL) of mRNA-1273 on Day 1 and Day 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394).

Summary: Up to 120 participants will be enrolled, 1) 60 participants with solid tumour malignancies who have initiated programmed cell death 1(PD1)/programmed cell death ligand 1 (PDL1) inhibitor therapy as part of standard of care and are deemed to have a stable regimen without the need for any immunosuppressive therapy or corticosteroids; 2) Sixty participants with leukaemia, lymphoma, multiple myeloma and participants post-allogeneic stem cell transplant will be enrolled based on their perceived risk of immunosuppression. As of 17 Jun 2023, 17 subjects were exposed to mRNA-1273. Start date for this study was 27 Apr 2021 and estimated study completion date is 25 Feb 2024. No significant safety findings in this ongoing CT have been identified during the reporting period.

Sponsored by the University of California, Los Angeles (UCLA):

Study or Protocol Number: COVID-19 Version 2.0

Phase I/II, Open-label Dose-Escalation Trial of High Dose mRNA-1273 Booster for Lung Transplant Recipients.

Country: US

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

Summary: Planned enrolment was 60 subjects and number of subjects enrolled and exposed to mRNA-1273 were 19. Start date for this study was in Mar 2022, enrolment has been completed, and the end date was 27 Feb 2023. Data analysis is currently ongoing. No safety concerns were reported. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons.

Sponsored by South Africa Medical Research Council (SAMRC):

Study or Protocol Number: Sisonke 4 (SHERPA)/mRNA-1273-P508

Sisonke Heterologous mRNA-1273 boost after prime with Ad26.COV2.S (SHERPA study).
Open-label, phase 3 study to evaluate the effectiveness of heterologous mRNA-1273 boosting of the single or two dose Ad26.COV2.S COVID-19 vaccine among health-care workers in South Africa.

Country: South Africa

Dosing details: 50 ug.

Summary: Planned enrolment was 15,000 subjects and number of subjects enrolled and exposed to RNA-1273 was 12,340 subjects. Actual recruitment end date was 12 Nov 2022 and last subject visit was on 09 May 2023. One hundred and six AEs have been reported, of which 18 were Grade 1 Related Adverse events and 4 were Grade 2 Related Adverse events. Fifteen SAEs have been reported, all of which were not Related to the study product. Eight AESIs have been reported, 4 of which were Related to study product. Five hundred and eighty-two cases of Reactogenicity have been reported, none of which were Grade 3 or higher. Forty-six breakthrough infections have been reported, 1 of which resulted in death. The remaining breakthrough infections were mild or asymptomatic infections. There are no safety concerns, new efficacy/effectiveness information or regulatory actions taken for safety reasons.

Sponsored by Merck, Sharp and Dohme (MSD):

Study or Protocol Number: V110-911-00

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a Booster Dose of SARS-CoV-2 mRNA Vaccine in Healthy Adults 50 Years of Age or Older.

Country: US, including Puerto Rico

Dosing details: Participants enrolled in the concomitant groups will receive either 23-Valent Pneumococcal Polysaccharide Vaccine (V110) or 15-Valent Pneumococcal Conjugate Vaccine (V114) (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive placebo (blinded) in the left arm 30 days later at Visit 3 (Day 30). Participants enrolled in the non-concomitant groups will receive placebo (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive V110 or V114 (blinded) in the left arm 30 days later at Visit 3 (Day 30).

Summary: Planned enrolment was 850 subjects and total subjects enrolled were 850 subjects and all 850 subjects enrolled were exposed to mRNA-1273. Start date for this study was 12 Jan 2022 and last participant last visit was on 21 Feb 2023. Database lock is targeted for Oct 2023. The CSR is targeted for finalization in Jan 2024. No safety concerns were reported. No new efficacy or effectiveness information has been obtained. No regulatory actions were taken for safety reasons.

Study or Protocol Number: V503-076-00

A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9v Human papillomavirus and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age.

Country: US

Dosing details: 50 µg primary series (2 doses of 50 µg 28 days apart).

Summary: Planned enrolment was 160 subjects and total number of subjects enrolled were 165 and out of which 162 subjects were exposed to mRNA-1273. Start date for this study was 28 Mar 2022 and projected end date is 14 Jun 2024. No new safety concerns, and no regulatory actions taken for safety reasons during the reporting period. There is no information that would affect the safety profile of the product through the reporting period. There is no new efficacy, effectiveness, or immunogenicity information.

Sponsored by the University of Southampton (CoV Boost):

Study or Protocol Number: RHM MED1781

A randomized, phase II UK multicenter study to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2.

Country: UK

Dosing details: mRNA-1273.529 50 µg and mRNA-1273.214 50 µg

Summary: For mRNA-1273.529 50 µg, planned enrolment is 205 subjects and the number of subjects enrolled and exposed to mRNA-1273 were 209. Start date for this study was 18 Feb 2022 and projected end date is 30 Nov 2023. No SAEs have been reported to ModernaTx, Inc. Interim analysis is not yet complete for efficacy and effectiveness information. No regulatory actions have been taken for safety reasons.

For mRNA-1273.214 50 µg, planned enrolment is 100 subjects and number of subjects enrolled and exposed to mRNA-1273 were 96. Start date for this study was 25 Jul 2022 and project end date is 31 Mar

2024. No SAEs are reported to ModernaTx, Inc. Interim analysis is not yet complete for efficacy and effectiveness information. No regulatory actions have been taken for safety reasons.

Rapporteur assessment comment:

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

The information provided is acknowledged.

1.3.5.3.2. Medication errors

Table 9.1 Medication errors

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 0 ○ 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. European Union legislation requires information on medication errors to be collected and reported through national pharmacovigilance systems.
Methods	The ModernaTx, Inc. GSDB was searched using the SMQ *Medication errors*, with a broad scope. The results were reviewed to exclude cases describing scenarios of off-label use and intentional product use issues.
Results	Refer to Appendix 9.g for additional information. **Medication Errors Involving Elasomeran** During this review period, the MAH received 2,745 cases (8,995 events) of Medication

	errors with 402 serious cases (1,164 serious events), and 11 cases with a fatal outcome. There were 2,512 medically confirmed cases involving elasomeran. The most frequently reported PTs were "Expired product administered" (1163; 12.9%), followed by "Interchange of vaccine product" (565; 6.3%), and "COVID-19 Immunization" (454; 5.0%). It should be noted that the PT "No adverse event" (1665; 18.5%) had the highest number of events. During the review period, there were 798 cases (3,183 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (258;8.1%), followed by "Headache" (78; 2.5%) and "Vaccination site pain" (70; 2.2%). The number of case reports are listed below by age group exposed: • **<6 months of age:** 6 cases (9 events) of medication errors were reported. None of the medication error reports noted an associated AE. • **Infants and toddlers (6 months to 23 months):** 86 cases (130 events) of medication errors were reported. 5 cases (5 non-serious events; 1 serious event) reported AEs. • **Children (2 years to 5 years):** 117 cases (173 events) of medication error were reported. 4 cases (4 non-serious events) reported AEs. • **Children (6 years to 11 years):** 47 cases (53 events) of medication error were reported. 3 cases (6 non-serious events) reported AEs • **Adolescents (12 to 17 years):**31 cases (36 events) of medication error were reported. 4 cases (3 non-serious events; 1 serious event) reported AEs. **<u>Medication Errors Involving Elasomeran/Imelasomeran</u>** During the review period, the MAH received 349 cases (474 events) of Medication errors with 28 serious cases (25 serious events), and no cases with a fatal outcome. There were 308 medically confirmed cases involving elasomeran/imelasomeran. The most frequently reported PTs were Expired product administered" (192; 40.5%), followed by "Underdose" (70; 14.8%), and "Product storage error" (48; 10.1%). During the review period, there were 88 cases (216 events) of medication error reported with an associated AE. The most frequent AE reported were "Adverse drug reaction" (21; 9.7%), followed by "Pain in extremity" (13; 6.0%), and "Headache" (10; 4.6%). **<u>Medication Errors Involving Elasomeran/Davesomeran</u>** During the review period, the MAH received 2,742 cases (3,897 events) of Medication errors with 5 serious cases (1 serious event), and no cases with a fatal outcome. There were 2,728 medically confirmed cases involving elasomeran/davesomeran. The most frequently reported PTs were "Expired product administered" (1,405; 36.1%), followed by "Product storage error" (715, 18.3%), and "Underdose" (386; 9.9%). During the review period, there were 113 cases (261 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (17; 6.5%), followed by "Pyrexia" (16; 6.1%), "Myalgia" (10; 3.8%) and "Pain" (10; 3.8%).
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 elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccine beyond the primary series or any interchange of other COVID-19 vaccine products. There seemed no difference for the nature of reported

	medication errors and importantly associated AEs among the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in general. AEs associated with reported medication errors were usually known to the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran safety profile, and no events were associated with significant harm to the patient due to the medication error. There were no significant changes in the frequencies and types of medication error events in general from this review period and the last review period.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest medication errors associated with administrations of elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran impact the benefit--risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The benefit-risk evaluation remains positive. Medication errors reported to ModernaTx, Inc. will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

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 from elasomeran/imelasomeran did not reveal any patterns or other safety information relevant to the benefit-risk assessment for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

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

Endorsed.

1.3.5.4. Non-clinical data

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

Rapporteur assessment comment:

Endorsed.

1.3.5.5. Literature

A global literature search and analysis were performed utilizing Embase, Medline and PubMed databases for abstracts for the reporting period 18 Dec 2022 to 17 Jun 2023. The literature search was performed for the publications related to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran 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). Find the complete global literature search strategy used for Medline and Embase search under [PSUR] Appendix 13.1 and search strategy used for PubMed under [PSUR] 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. Please find the journal list under [PSUR] Appendix 13.3. Literature search strategy for medical topics can be found under [PSUR] Appendix 13.4.

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

Response: The MAH has implemented a series of improvements to the literature retrieval process. While routine global literature reviews were previously conducted weekly using Medline and Embase in screenings elasomeran-related literature articles. The MAH recognizing vast literature on Covid-19, expanded its literature screening to the comprehensive PubMed database (rather a part covered through Medline). Consequently, PubMed is now searched at the product level without specific AE filters. This strategic addition has introduced an additional 30,000 articles/hits for retrospective review since IBD compared to the previous methodology. This upgraded literature screening process involved retrospective identification of previously missed articles that were then assessed for Individual Case Safety Reports (ICSRs), signal detection and aggregate reporting and submitted accordingly. Thus, MAH is confident in the thoroughness of the literature retrieval process, ensuring minimal likelihood of overlooking pertinent articles, as evidenced by MAHs comprehensive representation in the PBRERs.

During the reporting period, there were a total of 71,091 abstracts retrieved and upon removal of duplicates 23,574 abstracts were reviewed from the global search. There were 7,745 local journal searches performed and 236 abstracts were reviewed. From all the searches performed, two articles were identified with new safety relevant information and are summarized below. For more detailed information and full text articles please refer to [PSUR] Appendix 13.5.

Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study [13].

Ljung et al. performed a nationwide, register based cohort study from Swedish national and regional registers RECOVAC and SCIFI-PEARL to check the risks of any menstrual disturbance and bleeding following first, second and third dose of SARS-CoV-2 vaccination (BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19) in premenopausal or postmenopausal women. A total of 2,946,448 Swedish women aged 12-74 years were included in the vaccination analyses. Pregnant women, women living in nursing homes, and women with history of any menstruation or bleeding disorders, breast cancer, cancer of female genital organs, or who underwent a hysterectomy between 01 Jan 2015 and 26 Dec 2020 were excluded. The following observations were made from the study: The highest risks for bleeding in women who were postmenopausal were observed after the third dose in one to seven days risk window (hazard ratio 1.28 [95% CI=1.01 to 1.62]) and in the 8-90 days risk window (1.25 [1.04 to 1.50]). The impact of adjustment for covariates was modest. An increased risk of postmenopausal bleeding suggested 23 to 33 percent after 8-90 days window with BNT162b2 and mRNA-1273 after the third dose, but the association with ChAdOx1 nCoV-19 was less clear. During the analyses for menstrual disturbance or bleeding in women who were premenopausal, an adjustment for covariates almost completely removed the weak associations noted in the crude analyses. The premenopausal bleeding estimates were more imprecise

compared with the other outcomes because of the fewer observed events. The strongest associations observed in premenopausal bleeding after vaccination were not significant and noted a 14% increased risk during one to seven days window after the first dose (1.14 [0.86 to 1.50]) and the third dose (1.14 [0.77 to 1.70]). There was no increased risk observed after the second dose (0.96 [0.71 to 1.30]) in the corresponding risk window. The authors observed a weak and inconsistent associations between SARS-CoV-2 vaccination and healthcare contacts for bleeding in women who are postmenopausal, and even less evidence was recorded of an association for menstrual disturbance or bleeding in women who were premenopausal. The study findings did not provide substantial support for a causal association between SARS-CoV-2 vaccination and healthcare contacts related to menstrual or bleeding disorders.

Morphologic and molecular analysis of liver injury after SARS-CoV-2 vaccination reveals distinct characteristics [14].

The article by Uzun et al, 2023, is presented in [PSUR] Section 11, as this event of Vaccine Induced Liver Injury (VILI) was reported for the first time during the PBRER#5 review period and after thorough medical review of such cases and the article, do not provide sufficient information to establish a causal relationship with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The following article by Uzun et al, describes six (6) Swiss elasomeran patients with reported VILI and nine (9) with the initial diagnosis of Autoimmune Hepatitis. Formalin fixed liver biopsies for both were examined using immunofluorescence, immune repertoire histomorphology, whole -transcriptome and spatial transcriptome sequencing. The article had no information on the PMH, family history or medication for the subjects with Autoimmune Hepatitis, except 4 had stage 1 fibrosis. For the subjects with presumed VILI the age ranged from 21-85 years and the medical histories of the patients are limited except for one patient, a 21-year-old female is said to have "polymyalgia" and antibodies to thyroid peroxidase; another, a 78 y/o male with significant HBP and a third, a 63 y/o male with Type 2 Diabetes Mellitus and elevated lipids. Only 3/6 Antinuclear Antibody+, both SMA and anti-Liver Abs Negative, Immunoglobulin G (IgG) levels normal in 4/6. Two females/4 males, time to onset (TTO) 2 to 28 days. There is no information on any previous liver issues or on the medications received by these for the other subject. For the presumed VILI subjects, one was untreated and the other 5 given steroids with all achieving drug free remission for the 12 to 18 months of follow-up.

The results of the extensive histomorphology studies were similar for both the presumed VILI and autoimmune hepatitis (AIH) cohorts. However, for the subjects with presumed VILI, the gene expressions profiling showed that mitochondrial metabolism and oxidative stress-related pathways were more and interferon response pathways less enriched. In addition, in these subjects, the multiplex analysis revealed that inflammation was dominated by CD8+ effector T-cells. In contrast, for the Autoimmune Hepatitis subjects, there was a predominance of CD4+ effector T--cells and CD79a+ B and plasma cells. T-cell receptor (TCR) and B-cell receptor sequencing demonstrated- the T- and B-cell clones were more dominant in the presumed VILI than the Autoimmune Hepatitis subjects. In addition, many T-cell clones detected in the liver were also found in the blood. Finally, analysis of TCR beta chain and Ig heavy chain variable-joining gene usage showed that TRBV6-1, TRBV5-1, TRBV7-6 and IgHV1-24 genes were used differently in the presumed VILI than Autoimmune Hepatitis subjects.

The authors concluded that the liver injury in the presumed VILI subjects is related to AIH but demonstrated distinct differences in histomorphology, pathway activation, cellular immune infiltrates, and TCR usage. They further note that these 6 patients appear more closely like drug-induced autoimmune-like hepatitis. The extensive data presented in this article is based upon a selected cohort of subjects who developed liver injury within 30 days of the first (3) or second (3) vaccination with elasomeran in comparison to cohort of initial Autoimmune Hepatitis. Both cohorts have limited medical histories which are important in assessing the etiology of liver injury in patients. The presumed VILI subjects either required no treatment (1) or a limited course of steroids with continued remission for 12-18 months. The

article presents an interesting concept which at this point is a diagnostic concept based upon an extensive assessment of a limited group of patients with liver injury post elasomeran vaccination out of over 80 cases reported in the literature. Using the Simplified Criteria for Autoimmune Hepatitis, 2 met Definite, 2 Probable and 2 did not meet Simplified Criteria for Autoimmune Hepatitis. Similar to the conclusions of assessment of Autoimmune Hepatitis, the reports in this article are rare, confounded, lack a clinically well-characterized representative comparison group and do not provide sufficient information to establish a causal relationship with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

Rapporteur assessment comment:

MAH's literature retrieval process

In the previous PSUSA procedure (EMEA/H/C/PSUSA/00010897/202212) as an "issue to be addressed in the next PSUR", the MAH was requested to review its literature retrieval process to ensure that publications published prior to the reporting interval but missed in previous literature searches are also included in relevant reviews in the current PSUR.

The MAH states that it has implemented improvements to its literature retrieval process and that the new methodology has resulted in an additional 30,000 articles for retrospective review since IBD. Furthermore, the MAH reports that its updated literature screening process involved retrospective identification of previously missed articles.

MAH's clarification of its updated literature retrieval process is endorsed.

Presented literature

The MAH identified two articles with new safety relevant information.

Ljung et al.: In this study, the risks of menstrual disturbances and bleeding following SARS-CoV-2 vaccination in premenopausal and postmenopausal women were investigated. The authors conclude that: "Weak and inconsistent associations were observed between SARS-CoV-2 vaccination and healthcare contacts for bleeding in women who are postmenopausal, and even less evidence was recorded of an association for menstrual disturbance or bleeding in women who were premenopausal."

The Rapporteur noted that for the topics "menstrual disturbance" and "premenopausal bleeding" almost all of the adjusted hazard ratios reported in the study were not statistically significant. Based on the presented information on the topics "menstrual disturbance" and "premenopausal bleeding", the Rapporteur did not identify new and significant safety information which warrants further action.

The study also investigates the topic "postmenopausal bleeding" and the results from the study are included together with other new data on this topic in the signal validation for a signal of "postmenopausal haemorrhage" with COVID-19 mRNA vaccine exposure that has recently been triggered (EPITT no: 19989). Please note that this signal has recently been confirmed by the PRAC for further evaluation in a 60-day signal procedure, and which is scheduled to be presented to the PRAC in March 2024. Therefore, the topic will not be evaluated further in this PSUSA procedure.

Uzun et al.: In this study, the authors compared liver biopsies from 6 patients with reportedly COVID-19 vaccine-induced liver injury to liver biopsies from 9 patients with autoimmune hepatitis with focus on differences in histomorphology and gene expression. The MAH notes that only few details of these patients' medical histories are presented and the Rapporteur acknowledges this. However, the Rapporteur deems that enough key case details are presented to assess causality. The following case details are available: Time-to-onset (2 to 28 days), concomitant medication (including time-to-onset for these), negative test for hepatitis A, B, C, D, and E, information on autoimmune diseases (only 1 patient), and no history of liver disease or alcohol abuse in any of the cases. Several important laboratory values are also reported (AST, ALT, GGT, bilirubin, IgG and relevant auto-antibodies). However, it is acknowledged that

some potential causes of hepatitis have not been accounted for including e.g. viral hepatitis due to cytomegalovirus or Epstein-Barr virus infection. Even so, in at least 5 out of 6 cases, the Rapporteur has not identified obvious alternative explanations for the observed adverse event. Furthermore, the authors have presented a list of published case reports and observational studies (see PSUR page 7558); some of which appear to have been published after the topic "autoimmune hepatis" was evaluated in PSUSA no. 3 with a cumulative review covering the period from 18 Dec 2020 to 18 Jun 2022.

The Rapporteur notes that the observed liver injury in the suspected cases of COVID-19 vaccine-induced liver injury is similar to the pattern seen in autoimmune hepatitis. On this, the authors state: *"In summary, histological analysis revealed a diagnosis of likely AIH [autoimmune hepatitis] in five out of six VILI [COVID-19 vaccine-induced liver injury] patients and a diagnosis of possible AIH in one patient according to the most recent recommendations. Moreover, 3 out of 5 VILI patients had a probable/definite AIH score according to the simplified AIH criteria."*

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

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

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

[...]

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

If the MAH considers an update of the product information warranted, a wording and frequency for inclusion in the SmPC and package leaflet should be proposed with presentation of the used method for calculation of frequency.

The Rapporteur deems that it is appropriate to evaluate this issue in the next PSUSA procedure instead of within this procedure for the following reasons:

- The clinical course of the patients observed in Uzun et al. was relatively benign ("[…] *all VILI patients responded well to steroid therapy and remained in remission to date*").

- The current PSUR submission frequency is 6 months.

- The topic was evaluated in PSUSA no. 3.

- Evaluation in the next PSUSA procedure enables a more thorough evaluation compared to evaluation within this procedure.

Ljung R, Xu Y, Sundström A, Leach S, Hallberg E, Bygdell M, et al. Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study. Bmj 2023;381:e074778.

Uzun S, Zinner CP, Beenen AC, Alborelli I, Bartoszek EM, Yeung J, et al. Morphologic and molecular analysis of liver injury after SARS-CoV-2 vaccination reveals distinct characteristics. J Hepatol 2023.

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 16.1 provides the Summary of Safety Concerns as per RMP v6.3 approved on 15 Dec 2022 in place at the beginning of the reporting period.

Table 16.1 Summary of Safety Concerns valid at the beginning of the reporting period (as per RMP v6.3 approved 15 Dec 2022)

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

During the reporting period, the Spikevax RMP v6.3 was updated to v6.4 (not approved) to include the proposed indication for the US vaccine elasomeran for individuals 12 years of age and older and updated studies mRNA-1273-P903, mRNA-1273-P904, mRNA-1273-P911 and mRNA-1273-P910 as per Part III with no changes to the list of safety concerns.

Further v6.3 was updated to v6.5 (approved on 26 May 2023) to include the proposed indication and posology for Spikevax bivalent BA.4-5 for individuals 6 years of age and older. Risk Management Plan v6.5 was updated to v6.7 (endorsed on 20 Jul 2023) with no additional changes to the list of safety concerns. Additionally, v6.3 was updated to v7.0 (endorsed by PRAC after the DLP of this PBRER, on 06 July 2023) to update the list of safety concerns by removing VAED including Vaccine-Associated Enhanced Respiratory Disease (VAERD) as an important potential risk, and use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities

(e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns, as missing information. Also, v7.0 was updated to include mRNA-1273-P910 for pericarditis and study details for mRNA-1273-P901, mRNA-1273-P910 and mRNA-1273-P919 in Part II.C.2 as per Part III update. Of note, a consolidated Spikevax EU RMP v7.1 including all versions endorsed/approved by PRAC/CHMP (v6.5, 6.7 and 7.0) received positive opinion by CHMP on 21 Jul 2023 and the opinion was adopted within procedure EMEA/H/C/005791/II/0104/G by European Commission on 11 Aug 2023 after the DLP of this PBRER.

Table 16.2 Summary of Safety Concerns valid at the end of the reporting period (as per RMP v6.5 approved 26 May 2023)

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

Rapporteur assessment comment:

The MAH presented the RMP Summary of safety concerns at baseline and at the end of the reporting period. Furthermore, the MAH reported on changes to the RMP during and after DLP. This is acknowledged. The MAH did not include the PSUR summary of safety concerns in the overview tables, which gives the reader an incomplete picture of the safety specification.

2.2. Signal evaluation

- Tabular overview of signals: new, ongoing or closed during the reporting interval 18.12.2022 to 17.06.2023.

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Tabular overview of signals: new, ongoing or closed during the reporting interval 18.12.2022 to 17.06.2023.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Amenorrhea (reevaluation)	Jun/2022	Closed	Jan/2023	Health Authority Request	[Re-evaluation signal was triggered internally by Moderna following PRAC request to provide an updated analysis in PBRER#4, as an outcome of closed EPITT 19781.] A signal of amenorrhea was evaluated as a refuted signal in Mar 2022 (EPITT No 19781). A new signal for amenorrhea was opened based on PRAC Signal AR (dated 13 Jun 2022) where PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present and agreed that the MAH of COVD-19 mRNA vaccine (nucleoside-modified) elasomeran, should provide an updated cumulative review of amenorrhea events post-vaccination in the PBRER with the DLP of 18 Dec 2022. FIGO definition of primary amenorrhea is absence of menarche by age 15 years. Following MAH re-evaluation based on the review of all available sources, no mRNA-1273-related effects or changes in mating and fertility and ovarian/uterine examinations were found in non-clinical data. In the CT setting, no cases of amenorrhea were reported in the mRNA- 1273 arm P301 Part A (controlled cohort) versus 1 case in the placebo arm; 3 additional cases of amenorrhoea (all confounded by age or hormonal	PBRER/PSUR /MSSR RTQ	Routine Pharmacovigilance. Other (5 NIH funded studies on amenorrhoea and vaccination)

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					therapy) were reported in the uncontrolled cohort, however results were difficult to interpret without baseline menstrual characteristics. In post-marketing surveillance, a total of 2,948 cases with PT Amenorrhea (13.8% (408) serious, 10.6% (311) medically confirmed) were retrieved from the Company GSDB. 62.8% of the serious events of amenorrhea (242 cases) met FIGO definition, of which 2.1% had no reported confounders. In amenorrhoea cases reporting multiple doses (681), 0.8% reported recurrence of amenorrhoea with subsequent vaccination. Observed reporting rates for post-marketing data was below background IR. Published data did not support an association between amenorrhea and elasomeran vaccination. In conclusion MAH considered amenorrhea in association with elasomeran as a refuted signal, due to the lack of evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. Amenorrhea will continue to be monitored through routine pharmacovigila ncesurveillance and in the 5 NIH funded studies evaluating amenorrhoea and vaccination. Updates on topic following signal closure: In PRAC updated assessment report for PBRER#4 (22 Jun 2023) PRAC Rapporteur considers that available evidence is currently insufficient to establish a causal association between amenorrhea and elasomeran. The MAH is requested to continue monitoring the topic via routine pharmacovigilance and actively report in the literature section when new information from e.g. the NIHfunded studies emerges.		
Diarrhea (re-evaluation)	Oct/2022	Closed	May/2023	EudraVigilance/	[Signal was triggered internally by Moderna]	Signal Evaluation	Routine Pharmacovigil

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
				EVDAS Spontaneous Reports Routine Signal Detection	Diarrhea was evaluated as a refuted signal in Apr 2021, but included in several local labels, as part of regional variations. A re-evaluation of diarrhea was performed as the post-marketing data accrued. Based on assessment of two more years of accumulated data no additional evidence of a potential causal association was found between the occurrence of diarrhea and the administration of elasomeran, at any dose. No plausible mechanism of action was identified for elasomeran to cause diarrhea; nonclinical studies demonstrated that mRNA-1273 is safe and well- tolerated, with no information relative to diarrhea; no imbalance was observed in availa ble CTS data (subjects > 6 months age); no new information from spontaneous reports of diarrhea was found that would impact the benefit/risk balance of elasomeran. MAH considered diarrhea in association with elasomeran as a refuted signal. MAH did not plan changes in CT conduct, labeling, other reference safety information or the risk management plan. Diarrhea will continue to be monitored through routine pharmacovigilance surveillance.	Report	ance
Pemphigus and pemphigoid	Dec/2022	Closed	Jan/2023	Health Authority Request EudraVigilance/EVDAS Literature Article	MAH considered pemphigus and pemphigoid as a validated signal following receipt of PRAC's signal assessment report (EPITT No. 19860) requesting MAH for elasomeran (Moderna Biotech Spain S.L.) to perform a cumulative review of all reported cases of pemphigus/bullous pemphigoid (first search criteria) and cases associated with 'blisters' (second search criteria), including a separate discussion on new onset cases and cases reporting flare-up and/or aggravation. Following MAH assessment based on the review of all available sources, no imbalance was noted in any of the mRNA-1273 clinical studies, with overall 6 reports of Blister on mRNA-1273 group versus 5 reports on the placebo group. In the GSDB, a total of 152 cases were identified cumulatively for pemphigus/BP or related events. These	Signal Evaluation Report RTQ	Close Monitoring Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					included: 124 cases (PTs of BP [93 cases]; Pemphigus [31 cases]), retrieved as part of the first search and another 28 case reports from the second search containing various other relevant terms (Blister 6 cases, dermatitis bullous 2 cases, linear IgA disease 1 case; autoimmune disorders 19 cases- *see also Responses to Spikevax- Signal Pemphigus and pemphigoid/EPITT ref.no.19860- preliminary PRAC AR 15 March 2023)*. Off these, 78 cases that fulfilled the established case definition for pemphigus/BP, showed no specific reporting pattern by gender; 45 cases (58%) reported in patients above 65 years of age, cases that were assessed as at least possible (WHO-UMC causality) and deemed newonset - 32 cases (41%), flare- up- 9 cases (12%). The WHO-UMC causality was assessed by the MAH as probable in a total of 2 cases of pemphigoid and as possible in 39 cases (containing a number of potential contributory/pre-disposing risk factors including relevant medical history/comorbidities or concomitant medications having close associations with pemphigus/BP). No specific patterns identified from a review of fatal cases. The events appeared to be generally manageable in clinic with appropriate treatment given. Literature search results were not suggestive of a potential MoA and any evidence of causal association between mRNA vaccines or mRNA-1273 and Pemphigus/BP. In conclusion MAH considered Pemphigus in association with elasomeran as a refuted signal, due to insufficient evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. Pemphigus and pemphigoid will however be closely monitored as part of signal detection for further characterization.		

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					Updates on topic following signal closure: Within the signal procedure (EPITT No 19860) MAH replied to a list of questions from PRAC; summary of data above was updated to reflect the updated analyses (09 Feb 2023). PRAC requested MAH should continue to monitor "Pemphigus" and "Pemphigoid" in PBRERs. (Final PRAC signal assessment report, dated 14 Apr 2023).		
Idiopathic inflammatory myopathy/Myositis	Jan/2023	Closed	Mar/2023	Health Authority Request	MAH considered idiopathic inflammatory myopathy (IIM)/ Myositis as a validated signal following receipt of PRAC's signal assessment report (EPITT No. 19884) requesting MAH for elasomeran (Moderna Biotech Spain S.L.) to perform a cumulative review of all cases of IIM/myositis with considerations on whether the cases of IIM/myositis are considered "new onset" or "flare". Following MAH assessment based on the review of all available sources, only one participant who received placebo reported IIM in any of the mRNA-1273 clinical studies. A total of 295 IIM/Myosistis cases were retrieved from the Company safety database, including 4 cases with a TTO prior to elasomeran and 9 flares. For the new onset cases (282 cases), using the EULAR/ACR classification criteria for IIM/Myositis, majority cases were either Unassessable (241) or Not a case (33); 8 cases met the EULAR/ACR classification as probable IIM (4) or definite IIM (4) [WHO causality: Probable (1), Possible (6) and Unlikely (1)]. No specific reporting pattern was identified by gender; mean age was 51.5Y (SD 17); most cases were reported from EEA (55.9%) followed by US (26.8%); vast majority of cases had either extremely limited information (56.6%) or at least one confounder (34.5%, e.g. age, concurrent infections or autoimmune disease, diabetes, rhabdomyolysis, co-suspected drug such as lipid-lowering drugs, alcohol, immune checkpoint inhibitors, glucocorticoids, anti-malaria drug, antiretroviral drug, chemotherapy); 9 cases were	Signal Evaluation Report RTQ	Close Monitoring Routine Pharmacovigilance

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
					identified as flare; most events were reported after Dose 1 (32.2%), with a cluster of TTO within the first 2 days after vaccination. The O/E analysis using a 7-day risk window showed observed reporting rates (RR) above the background incidence rate for females aged 25-49Y. However, when taking into account only those cases that met the EULAR/ACR classification, the observed RRs were below background IR for all age and gender groups. Literature search results did not provide evidence of causal association between mRNA-1273 and IIM/Myositis; also, IIM/Myositis pathogenesis is poorly understood and no clear biological plausibility between IIM/Myositis and elasomeran was found. In conclusion MAH considered IIM/Myositis in association with elasomeran as a refuted signal, due to insufficient evidence across data sources reviewed. MAH did not plan to update the product information and/or risk management plan, including relevant risk minimization measures. Idiopathic Inflammatory Myopathy/Myositis will however be closely monitored as part of signa l detection for further characterization. Updates on topic following signal closure: PRAC requested that MAH should continue to monitor IIM/myositis and their flares through routine pharmacovigilance in the upcoming PBRERs. And MAH should include and follow-up on IIM/myositis in the final study report of EU PASS study mRNA-1273-P904 to be submitted in Dec 2023 (Final PRAC signal assessment report (12 May 2023).		
IgA nephropathy flare-up*	Apr/2023	Ongoing	NA	Health Authority Request Literature	MAH considered IgA nephropathy flare-ups as a validated signal following receipt of a signal letter from Swissmedic, triggered by the publication Canney et al: A Population-Based Analysis of the Risk of Glomerular Disease Relapse after Covid-19 Vaccination. JASN 33.	Signal Evaluation Report RTQ	Evaluation Ongoing

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
				Article	2247- 2257,2022. (https.//dio.org/10.1681/ASN.202203025). The MAH was requested to comment on the signal, taking into account the following aspects and questions: -Current figures on a flare-up of glomerular disease associated with mRNA vaccination, both nationally and internationally. -Presentation and discussion of relevant case reports of a flare-up of glomerular disease from internal and external databases, e.g., from WHO database. -Presentation and discussion of the scientific literature -Any previous signal evaluations on the same topic And submit a signal evaluation report, including the signal outcome and whether any risk minimizations measures are required, by 01 Jun 2023		
Sensorineural hearing loss**		Ongoing	NA	Health Authority Request Spoontaneous Reports	MAH considered Sensorineural hearing loss (SNHL) as a validated signal following receipt of a request from TGA, triggered by disproportionate reporting of hearing loss with elasomeran in TGA's Adverse Event Management System (AEMS). The MAH was requested to provide an updated signal analysis on hearing loss cases including age stratified and age specific observed versus expected analyses in the next PBRER to enable further evaluation of this signal by TGA.	Signal Evaluation Report RTQ	Evaluation Ongoing

*IgA nephropathy was ongoing till the DLP and was considered closed and refuted by MAH after the DLP i.e., on 22 Jun 2023.

**Sensorineural hearing loss was ongoing till the DLP and was considered closed and refuted by MAH after the DLP i.e., on 14 Aug 2023.

Rapporteur assessment comment:

The MAH reported on six signals; 4 closed (Amenorrhea (re-evaluation), Diarrhea (re-evaluation), Pemphigus and pemphigoid, and Idiopathic

inflammatory myopathy/Myositis) and 2 ongoing (IgA nephropathy flare-up and Sensorineural hearing loss).

For the closed signals, signal evaluation reports and responses to requests for additional information is presented and evaluated by the MAH. Please see below.

IgA nephropathy is categorised as an Important potential risk in the PSUR only (and not in the RMP). The important potential risks are assessed in AR section 2.3.1.2. However, the aspect of IgA nephropathy flare up was reported by the MAH to be an ongoing signal procedure triggered by the Swissmedic. The MAH considered the signal closed and refuted after the DLP, and the final signal evaluation report is expected with the next PSUR.

The ongoing signal Sensonrineural hearing loss was closed and refuted by the MAH after DLP of the PSUR. However, a signal evaluation report was included in the present PSUR and assessed in AR section 2.2.5.

Request from previous PSUSA AR (no 4) ITEM 9: Safety signals

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

MAH Response:

The MAH acknowledges the PRAC's request and will present in the next PBRERs, including PBRER #5, only those signals that pertain to the reporting period under review and will add a clear statement for those signals in case re-opened.

Rapporteur assessment comment:

The MAH clarifies that it wil only present those signals that pertain to the reporting period under review and will add a clear statement for those signals in case re-opened.

No further action is needed.

2.2.1. Amenorrhea (re-evaluation)

The topic of "Amenorrhea" was evaluated by the MAH as two signals. The first signal ("Amenorrhea") was triggered by Pharmacovigilance Risk Assessment Committee (PRAC) Signal EPITT 19781 and closed on 30 Mar 2022. The second signal ("Amenorrhea [Re-evaluation]") was triggered by the PRAC's request to provide an updated analysis of Amenorrhea in PBRER#4, which the MAH considered a validated signal. This signal was closed by the MAH on 25 Jan 2023, during the reporting period of this PBRER, hence included here again for completeness. Please find below a tabular summary to clarify when these two signals were presented in PBRERs.

Table 16.3 Amenorrhea (re-evaluation)

Signal	Date Detected	Date Closed By MAH	PRAC Signal Details	Presented in PBRER#
Amenorrhea	14 Feb 2022	30 Mar 2022	EPITT 19781 Trigger for MAH signa l (PRAC Meeting 07-10 Feb 2022) EPITT 19781 signal was closed by PRAC in Jun 2022 (PRAC Meeting 07-10 Jun 2022)	**PBRER#3** (signal closed by MAH, presented in Section 16 of PBRER#3, signal evaluation report appended to PBRER#3).
Amenorrhea (Re-eva luation)	13 Jun 2022	25 Jan 2023	Not a signal for PRAC. As an outcome of closed EPITT 19781, PRAC requested MAH to provide an updated analysis in PBRER#4. This was the trigger for MAH to open a "re-evaluation" signal.	**PBRER#4** (signal ongoing by MAH, signal not presented in Section 16.2 of PBRER#4, signa l evaluation report not appended to PBRER#4. The updated analysis requested by PRAC was submitted to PRAC separately) **PBRER#5** (signal closed by MAH, presented in PSUR section 16.2.1, signal evaluation report appended to PBRER#5 [same content as the updated analysis submitted separately to PRAC]).

Rapporteur assessment comment:

The signal "amenorrhea" was evaluated in the previous PSUSA procedure (EMEA/H/C/PSUSA/00010897/202212). The conclusion as documented in section 2 of the PRAC AR was: "*The PRAC considers that the data presented is insufficient to establish causal association between elasomeran and amenorrhea. No further actions beyond routine PV are considered warranted at this*

stage".

In the current PSUR, the MAH states that the updated analysis on "amenorrhea" requested by PRAC was not appended to PSUR no. 4 but submitted to PRAC separately. The MAH states that the signal evaluation report on "amenorrhea" appended to this PSUR has the same content as the updated analysis submitted separately to PRAC.

As the signal evaluation report for "amenorrhea" has already been evaluated in the previous PSUSA procedure, no further action is considered necessary at this stage.

2.2.2. Diarrhea (re-evaluation)

Table 16.5 Diarrhea (re-evaluation)

Signal evaluation criteria	Summary
Source	a) Diarrhea was evaluated as a signal and refuted by Moderna in Apr 2021; however, it was listed as a labeled event in the EEA, UK and Swiss local labels (Section 4.8 Undesirable effects, ARs Table) as per health authority request. b) As post-marketing data continued to accrue, the SMT reviewed the topic of diarrhea on 10 Feb 2023 and validated the signal to perform a re-evaluation of the topic.
Background	Although diarrhea is typically self-limiting, it can be severe and can lead to profound dehydration, which can lead to abnormally hypovolemic shock with end organ damage. Acute diarrhoea remains a major cause of infant mortality around the world. Over 2 million deaths are attributed to acute diarrhea each year world-wide, most of them in the developing world. Children and the elderly are particularly prone to dehydration secondary to diarrhea. Diarrhea has been reported as an AEs following immunization for various vaccines administered to adolescents and adults, including: • Herpes zoster vaccine (reporting rate of 1.8 cases per 100,000 doses distributed [58]. • Influenza vaccine (0.15 cases per person per week • Polio vaccine (9.9% of vaccine recipients in Kinshasa, DRC with median age of 16.8 [59]. • Comirnaty (The frequency is listed as >1/10; "Very common" in Section 4.8 Undesirable effects; Table 1; Gastrointestinal disorders of the SmPC).
Methodology	The MAH's clinical database and the GSDB were queried for valid case reports of Diarrhea received from HCP, HA, consumer, and literature sources, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) as of 17 Mar 2023, using the MedDRA PTs "Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Diarrhoea neonatal, Post procedural diarrhoea". Due to inherent differences in CTs and pharmacovigilance operations, MedDRA version 23.0 was utilized to query the CTs database, and MedDRA version 25.1 was used for querying the GSDB. There was no impact to the search due to the differences in the dictionary versions utilized. • Clinical Trial Data: Data from three Moderna sponsored clinical studies (mRNA-1273-P203, mRNA-1273-P204 and mRNA-1273-P301) were queried as part of this signal evaluation. • External Databases: VAERS and EVDAS were reviewed for reported PTs "Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Diarrhoea neonatal, Post procedural diarrhoea. • Review of the Pharmacovigilance Database: The MAH GSDB was queried for valid case reports of Diarrhoea received from HCP, HA, consumers, and literature sources, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) as of 17 Mar 2023, using the MedDRA v25.1 PTs "Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Diarrhoea neonatal, Post procedural diarrhoea". • Literature search review: A focused literature search and review was performed using

Signal evaluation criteria	Summary
	PubMed since the IBD of elasomeran through 17 Mar 2023. Multiple search strategies were used to identify articles related to Diarrhea and Moderna COVID-19 vaccines.
Results	Clinical Trial Data: *mRNA-1273-P203 Study (Cutoff date: 27 Jan 2022):* There were a total of 21 (0.6%) participants (16 [0.6%] on mRNA-1273 and 5 [0.4%] on Placebo) were identified who reported the treatment-emergent AEs of Diarrhea via unsolicited reporting. *mRNA-1273-P204 Study (Cutoff date: 21 Feb 2022):* There were 172 reports of diarrhea with mRNA-1273 and 52 reports of Diarrhea with Placebo. *mRNA-1273-P301 Study (Cutoff date: 04 May 2021):* There were 317 (1.3%) participants (157 [1.3%] on mRNA-1273 and 160 [1.3%] on Placebo) who reported the treatment-emergent AEs of diarrhea via unsolicited reporting. Overall, the review of relevant CT data did not show any meaningful imbalance in events of diarrhea reported between patients vaccinated with mRNA-1273 and placebo. External Databases: • Overall, there was no disproportion observed in VAERS. • There was a minor disproportion observed in EVDAS with North America which did not reveal any significance in overall Diarrhea-related EB05 scores. Review of the Pharmacovigilance Database: Cumulatively, through 17 Mar 2023, there were 18,259 (18,956 events) reported cases of diarrhea with elasomeran, of which 4,136 cases (3,016 serious events) were considered serious. Of the 18,259 cases reported after elasomeran, 8,205 (44.9%) cases were medically confirmed and 86 had a fatal outcome. The outcome in the majority of the reports was reported as recovered or recovering 9,481 (50.0%) followed by not recovered 4,981 (26.3%) and unknown 4,408 (23.3%). Of the 18,259 reports, 73.2% (13,358) involved males and 24.5% (4,465) involved females; gender infomation was missing for 2.4% (436) cases. The mean age was 51.2 years (SD: 17.7), and the median age was 51.0 years (range 0 to 120). Age distribution is shown below with no unusual pattern identified. Cumulatively, 14,157 (77.5%) reports were from regulatory authorities, 4,076 (22.3%) were spontaneously reported to the MAH, and 22 (0.1%) were literature reports. Most of the cases were received from the United States (8,016; 43.9%) and the EEA (7,229; 39.6%). Of the 18,956 reported events, 4,981 events (26.3%) had an outcome of "Not Recovered/Not Resolved", with 9,481 events (50.0%) having an outcome of "Recovered or Recovering" and 4,408 (23.3%) having unknown outcome. There were 86 (0.5%) cases with a fatal outcome, of which 2 cases have reports of "Diarrhoea" as the only event. The remaining 84 cases included diarrhea along with other co-occurring event(s). When dose number and TTO could be determined, most of the events were reported following Dose 1 and Dose 2, however most events (35.6%) were missing dosage information. Most events had an onset of less than 7 days from the time of vaccination (2,438; 65.6%), inclusive of 1,680 (8.9%) events following a third/booster dose, with a significant proportion occurring within 3 days of vaccination which reflects expected vaccine reactogenicity, consistent with the safety profile. Most cases lacked important information for proper assessment including details of

Signal evaluation criteria	Summary
	medical history, concomitant medications, clinical course and workup. Furthermore, a significant proportion of reports were received from health authorities and in such cases, follow-up is not possible due to privacy restrictions. **Diarrhoea Reports with Booster elasomeran/imelasomeran and elasomeran/davesomeran**: Cumulatively, through 17 Mar 2023, there were 462 (464 events) cases, of which 243 cases (231 serious events) were serious with diarrhea-related events for patients receiving a dose of bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran. Of the 462 cases reported after administration of Bivalent vaccines, 63 (13.6%) cases were medically confirmed and 1 had a fatal outcome. The outcome in the majority of cases was reported as recovered or recovering 296 (63.8%) followed by not recovered 144 (31.0%) and unknown 23 (5.0%). Of the 462 reports, 66.7% (308) involved males and 28.6% (132) were females; gender information was missing for 4.8% (22) cases. The mean patient age was 61.0 years (SD: 15.4), and the median age was 64.0 years (range 6 to 92). No unusual pattern was identified based on age and gender. Following review of reports pattern of occurrence of diarrhea-related events, no meaningful differences were noted in the reported cases of diarrhea after administration of bivalent vaccines. Literature search review: The search retrieved 141 articles and upon review, 121 were excluded since they pertained to topics not germane to this review such as COVID-19 disease or its impact on diarrhea, effect of the pandemic on diarrhea, therapeutic approaches for treatment of diarrhea, case reports/series, review articles and studies that did not include elasomeran. A critical analysis of the remaining 20 articles was performed, identifying 16 articles elasomeran and diarrhea and 4 articles describing non-Moderna COVID-19 vaccination. There were articles describing diarrhoea as predominantly non-life-threatening and transient events following administration of mRNA vaccine against COVID-19. While these articles described diarrhea following vaccine administration (predominantly following Dose 1 and Dose 2, as expected due to the prevalence the doses), no compelling causal association between diarrhea and elasomeran vaccine administration could be established.
Discussion	Evaluation of CTs data does not show any difference in the pattern of diarrhea-related event compared when with the prior previous signal evaluation with no imbalance observed in evaluable subjects > 6 months age. Review of the post-marketing data similarly do not reveal evidence of a change in the observed pattern of diarrhea when compared to the prior evaluation with no identifiable causal association between elasomeran and events diarrhea. Most cases lacked important information for proper assessment including details of medical history, concomitant medications, clinical course, and workup. Furthermore, a significant proportion of reports were received from health authorities and in such cases, follow-up is not possible due to privacy restrictions. Nonclinical studies demonstrated that mRNA-1273 vaccines are safe and well-tolerated. Overall, there is no conclusive plausible mechanism of action for elasomeran to cause diarrhea. The observed to expected analyses within 7-day risk window, using background incidence from Sweden and the UK showed that the reporting rates for diarrhea were snbstantially below expectation. Based on the analysis of all the safety data available as of 17 Mar 2023, the MAH considers that the nearly two more years of data accumulated since last evaluation in Apr 2021 do not reveal new information that would impact the benefit/risk balance of elasomeran. The

Signal evaluation criteria	Summary
	MAH considers that the currently core labeling adequately reflects the known safety profile of elasomeran and will continue to monitor diarrhea-related events through its routine post-marketing safety surveillance.
Conclusion	Overall, based on the analysis of all available safety data as of 17 Mar 2023, the MAH considers that there is insufficient information at this time to establish a causal relationship between the administration of elasomeran or elasomeran/imelasomeran and elasomeran/davesomeran and the development of Diarrhea. The MAH considers that this validated signal is refuted and no change to the reference safety information is required. The benefit-risk profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran continues to be positive.

Rapporteur assessment comment:

The MAH states that: *"Diarrhea was evaluated as a signal and refuted by Moderna in Apr 2021; however, it was listed as a labelled event in the EEA; UK and Swiss local labels (Section 4.8 Undesirable effects, ARs Table) as per health authority request."* Based on the amount of post-marketing case reports the MAH considers "diarrhoea" a new validated signal. The MAH refutes the signal and deems that no change to the reference safety information is required. Based on the presented data, the PRAC Rapporteur agrees. The PRAC Rapporteur notes that "diarrhoea" is listed in section 4.8 of the SmPC with the frequency "common", and the data presented do not suggest increased severity or otherwise new aspects of "diarrhoea". The MAH states that it will continue to monitor diarrhoea-related events through routine post-marketing safety surveillance. This is endorsed.

2.2.3. Pemphigus and pemphigoid

Table 16.4 Pemphigus and pemphigoid

Signal evaluation criteria	Summary
Source	On 01 Dec 2022, the MAH received a request from the PRAC for a signal assessment

Signal evaluation criteria	Summary
	(EPITT No. 19860) including a cumulative review of all evidence concerning the association between pemphigus and pemphigoid and vaccination with Spikevax (Moderna Biotech Spain S.L.): • *Review from information from post-marketing cases reporting pemphigus or pemphigoid, CTs and relevant scientific literature.* • *Perform a causality assessment of all cases of pemphigus and pemphigoid using the WHO-UMC causality assessment criteria, including a clear breakdown of all cases identified. Justification of causality category should be given for each case. A discussion of cases assessed as WHO Possible, Probable or Certain should be presented.* • *MAH responses to a list of questions (e.g., WHO-UMC causality assessment; potential reporting patterns (gender, age, TTO), risk factors, seriousness, treatment of ADR and outcome; tabular presentation of cases; literature review regarding plausibility and Mechanism of action overview of PT Dermatitis bullous and other related terms within HLT Bullous conditions for identification of pemphigus/pemphigoid cases; O/E analyses with a risk window of 28 days).* • *In addition, to account for all possible cases of blistering conditions, the MAH should provide an overview of the HLT Bullous conditions including cases of various blisters especially outside of administration site and the Important medical event PT dermatitis bullous. Case reports likely describing pemphigus/pemphigoid should be presented with the same level of details as mentioned above.* • *Including the need for potential amendment to the product information and/or risk management plan should be provided by 09 Feb 2023.*
Background	Pemphigus/ pemphigoid represents a group of autoimmune blistering/bullous disease of skin and/or mucous membranes; antibodies (mainly IgG) are formed against adhesion molecules (desmoglien) on the cell surface of keratinocytes; Clinically presents as erosions on mucosal surfaces (blisters), generalized; acantholysis (loss of intercellular connections/integrity); Treatment for the condition usually includes Rituximab, corticosteroids, adjuvant corticosteroid-sparing immunosuppressants (azathioprine, cyclosporine, mycophenolate mofetil, etc.). **Main types:** Pemphigus Foliaceus (PF)–Mostly limited to skin; Pemphigus vulgaris (PV) – Mucosal erosions, appearing as flaccid blisters on the skin; other types e.g., Bullous Pemphigoids, which represent a more chronic presentation of cutaneous signs/symptoms); Prognosis/Outcomes: PF more favorable than PV (Infectious complications septicemia, pneumonia, etc.). **COVID-19 and Pemphigus:** Clinical evidence of COVID-19 infestation itself can trigger Pemphigus (or related events) is still evolving; the data are very limited and sometimes conflicting at present. There is emerging published data / case reports suggestive of PV/ Bullous Pemphigoids reported in patients with a COVID-19 infection [53] [54].
Methodology	The assessment of Pemphigus and Pemphigoid in association with the use of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analysed data sources is described below: • Clinical Trial Data: The topic of Pemphigus and Pemphigoid was cumulatively reviewed in the CT datasets, within the following studies: mRNA-1273-P301 study

Signal evaluation criteria	Summary
	(ages ≥18 years; DLP: 04 May 2021), mRNA-1273-P203 study (ages 12-17 Years; DLP: 27 Jan 2022) and mRNA-1273-P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022). The following PT were used according to MedDRA dictionary (version was 23.0 and 24.0). Blister; Dermatitis bullous; Pemphigoid; Pemphigus; Blister rupture; Generalized bullous fixed drug eruption; Linear IgA disease; Mucous membrane pemphigoid; Oedema blister; Acquired epidermolysis bullosa; Autoimmune blistering disease; Autoimmune dermatitis; Autoimmune disorder; Immune-mediated adverse reaction; Immune-mediated dermatitis; Benign familial pemphigus; Paraneoplastic pemphigus; Ocular pemphigoid; Pemphigus disease area index. • External Databases: VAERS and EVDAS were reviewed for the PT of Pemphigus and Pemphigoid and neither of these databases showed disproportionality of EB05 or ROR. • Review of the Pharmacovigilance Database: Given that this request from the PRAC included two different evaluations of reports associated with pemphigus or bullous pemphigoid, and cases associated with "blister", the MAH conducted two separate searches by querying the GSDB, cumulatively to 17 Dec 2022 for valid case reports received from HCP, HA, consumers, and literature worldwide reported for elasomeran (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). The first search was conducted using the PTs of "Pemphigus" and "Bullous pemphigoid". This search retrieved 124 cases. The second search conducted for the purpose of identifying "blisters" cases that may potentially be cases of pemphigus/bullous pemphigoid, was conducted using a customized MedDRA SMQ created using: the MedDRA SMQs Narrow (Severe cutaneous ARs, Drug reaction with eosinophilia and systemic symptoms syndrome and Immune-mediated/autoimmune disorders), the MedDRA HLT (Bullous conditions) as well as the list of PTs included in the PRAC's report. Given the broad search criteria, a large volume of cases were retrieved (1870 cases; 1938 events). The 124 cases (that were retrieved as part of the first search) were removed to avoid duplication of cases. The remaining 1746 cases were reviewed further by the MAH using the specific 'key terms' in each of these cases that could be associated with the identification of a "case" according to the established case definition, these included: *'Immunofluorescence; Autoantibodies; IgG; Immunoglobulin G; ELISA; Acantholysis; Desmoglein; Complement deposits; Keratinocytes cell surface; Transmembrane glycoproteins; Nikolsky; C3; Complement factor'*. • Literature search review: A focused literature search and review was performed using PubMed cumulative till 17 Dec 2022. Multiple search strategies were used to identify articles related to Pemphigus and Moderna COVID-19 vaccines.
Results	Clinical Trial Data: *mRNA-1273- P301 Study:* In mRNA-1273-P301 the following PTs were reported (n=30,000): • Blister: mRNA-1273 (3) vs Placebo (3) • Dermatitis bullous: mRNA-1273 (0) vs Placebo (2) No imbalance was noted in mRNA-1273-P301. *mRNA-1273-P203 Study:*

Signal evaluation criteria	Summary
	There were no reports observed with the MedDRA search terms mentioned above. *mRNA-1273-P204 Study:* There were 3 reports received under the above mentioned MedDRA customized query for "Pemphigus" for participants of P204 in the mRNA vaccination arm. Overall, very few cases were reported in all three mRNA studies with no imbalance noted between the vaccine-treated subjects compared to the subjects in the placebo arms. There was no imbalance noted in any of the Moderna sponsored CTs, and all the reported events in the mRNA-1273 arm were reported as not related by the investigators. External Databases: • VAERS: No Disproportionate Reporting of Events Using EB05 > 2 (mRNA-1273 versus All vaccines) in VAERS as of 31 Dec 2022; Pemphigus (EB05: 0.88; N=89) and Pemphigoid (EB05: 0.82; N=34). • EVDAS: The PT of Pemphigus and Pemphigoid did not show Disproportionality as the ROR was <1. The observed ROR for Pemphigus (N=30; ROR=0.13) and Pemphigoid (N=90; ROR=0.35). Review of the Pharmacovigilance Database: A total of 152 case reports of pemphigus/ bullous pemphigoid or related events were retrieved from the 2 searches, including: • 124 cases (Bullous Pemphigoid [93 cases]; Pemphigus [31 cases]), retrieved as part of the first search conducted using the PTs of "Pemphigus" and "Bullous pemphigoid". • 28 case reports from the second search, after applying "key terms" (PTs: Blister 6 cases, dermatitis bullous 2 cases, linear IgA disease 1 case; Autoimmune disorders 19 cases) (*see also Responses to Spikevax-Signal Pemphigus and pemphigoid/EPITT ref.no.19860-preliminary PRAC AR 15 Mar 2023*). **First Search Results- Summary of Bullous pemphigoid (93 cases); Pemphigus (31 cases) [total 124 cases]** Cumulatively, a total 124 cases (124 events) with 116 serious cases (115 serious events) with PTs of Pemphigus and/or bullous pemphigoid PTs were identified for elasomeran. There were 3 cases reporting a fatal outcome (see below). There were 91 cases medically confirmed. There have not been reports of pemphigus and/or bullous pemphigoid terms after vaccination with any of the two bivalent vaccines. There were no important differences between reports involving females (65; 52.4%) compared to males (59; 47.6 %). The largest proportion of the reports were in individuals ≥50 years of age (92; 74.2%) The median age of reported cases was 70.0 years (min 24/ max 96 years) with a mean age of 66.5 years. When dose number and TTO information was provided, most of the events were reported after Dose 1 (21; 16.9%) and Dose 2 (25; 20.2%), and within 7 days after vaccination (33; 26.6%) regardless of dose number. Most

Signal evaluation criteria	Summary
	of the events (56; 45.2%) did no provide dose or TTO information. Overall, review of the 124 cases reporting pemphigus or bullous pemphigoid identified 22 cases as confirmed cases, 1 as probable case, 53 as possible cases, 3 as not a case, and there were 45 cases that were unassessable due to the lack of information including clinical presentation as well as supportive diagnostic laboratory data for confirmation of the cases. Further, using the WHO causality assessment, out of the 76 cases (which were classified as either confirmed, probable or possible), 38 cases were assessed as possible, 1 case as probable, 32 cases as unassessable, and 5 were considered unlikely related to the vaccine due to very prolonged TTO of more than 128 days to 397 days, as well as associated comorbidities that may provide a more plausible explanation for the occurrence of the reported events. **Second search results- Summary of cases under the customized MedDRA SMQ (28 cases):** A total of 28 relevant case reports were identified. These included cases/PTs of: Blister (6 cases), dermatitis bullous (2 cases), linear IgA disease (1 case); Autoimmune disorders (19 cases). Off these, 20 cases (72%) were reported in females; 8 in males, where the age is known, 11 (40%) of these cases were reported in patients aged >60 years. According to the established case definition for pemphigus or pemphigoid, there was 1 confirmed case (after Dose 1; onset day 11), 1 possible case (after Dose 3; day 13), 22 unassessable cases, and 4 cases classified as 'not a case'. The two cases that met the case definition criteria (1 confirmed; 1 possible) were further assessed for causality using the WHO-UMC criteria as: probable in one case and possible in the other. Out of those 1,746 cases (1,790 events), there were 621 serious cases (544 serious events) with 8 cases with a fatal outcome reported. There were 979 (52.4%) cases medically confirmed. There were more reports involving females (1,260; 72.2%) compared to males (448; 25.7%), and 38 (2.2%) cases did not specify gender. The largest proportion of the reports were in individuals ≥50 years of age (1,068; 61.2%) The median age of reported cases was 56.0 years (min 0.1/ max 121.0 years) with a mean age of 54.4 years. Overall, following the evaluation of the total 152 cases retrieved, 78 reports were identified that fulfill the established case definition criteria for pemphigus or bullous pemphigoid: 23 cases classified as confirmed cases, 1 as probable case, and 54 as possible cases. Of the remaining 74 cases: 67 were deemed 'unassessable' as contained insufficient clinical and/or diagnostic information for assessment in the context of pemphigus/pemphigoid and 7 cases were assessed as 'not a case' (alternative/ unconfirmed diagnosis, negative specific laboratory findings for pemphigus/pemphigoid). Further, using the WHO-UMC causality assessment, the evaluation of 78 cases which fulfilled the established case definition criteria, 2 cases were assessed as probable,

Signal evaluation criteria	Summary
	39 assessed as possible, 32 cases as unassessable, and 5 were considered unlikely related to the vaccine due to very prolonged TTO of more than 128 days to 397 days, as well as associated comorbidities that may provide a more plausible explanation for the occurrence of the reported events. Overall, following the evaluation of the total 152 cases retrieved, 78 reports were identified that fulfill the established case definition criteria for pemphigus or bullous pemphigoid: 23 cases classified as confirmed cases, 1 as probable case, and 54 as possible cases. Of the remaining 74 cases: 67 were deemed 'unassessable' as contained insufficient clinical and/or diagnostic infomation for assessment in the context of pemphigus/pemphigoid and 7 cases were assessed as 'not a case' (alternative/ unconfirmed diagnosis, negative specific laboratory findings for pemphigus/ pemphigoid). Further, using the WHO-UMC causality assessment, out of the 78 cases which fulfilled the established case definition criteria, 2 cases were assessed as probable, 39 assessed as possible, 32 cases as unassessable, and 5 were considered unlikely related to the vaccine due to very prolonged TTO of more than 128 days to 397 days, as well as associated comorbidities that may provide a more plausible explanation for the occurrence of the reported events. **Review of Fatal Cases**: Off the total 152 cases, there were 8 cases with a reported fatal outcome, of which 7 cases were from regulatory authority and 1 was spontaneous case. All the patients reporting a fatal event were ≥66 years of age and majority of they were female (6) compared to males (2). Review of these 8 fatal cases with case definition, identifies most of them as Unassessable (6 cases), followed by Unlikely (1 case) and Possible (1 case). **Cases that Qualified for Pemphigus and Pemphigoid Review After Receiving Booster Dose with elasomeran/imelasomeran (Cumulatively through 17 Dec 2022)**: Cumulatively, there were no reports that qualified for Pemphigus and Pemphigoid review in patients vaccinated in elasomeran/imelasomeran. **Cases that Qualified for Pemphigus and Pemphigoid After Receiving Booster Dose with elasomeran/davesomeran (Cumulatively till 17 Dec 2022):** Cumulatively, there was one report that qualified for Pemphigus and Pemphigoid review in patients vaccinated with elasomeran/davesomeran. <u>Literature search review: There</u> are few articles that describe Pemphigus in COVID-19 and in association with COVID-19 vaccination. But none of these articles were indicative or suggestive of a potential for a causal association or a potential MoA. • The following article by Martora F et al [55] with limited evidence and sample size, describes 32 patients with PV at the Dermatology Center of the University of Naples Federico II. All subjects received three COVID-19 vaccine doses (mRNA-BNT162b2 and mRNA-1273 were the vaccines administered). The

Signal evaluation criteria	Summary
	authors reported that 21.9% (n = 7) of patients with history of PV, experienced disease worsening after new lesions development, usually within 5–11 days after vaccination. These relapses were usually easily managed by increasing oral corticosteroid dosage, and all patients completed the vaccination cycle. According to the authors most PV patients (80%) showed no changes on the disease and the remaining were managed increasing corticosteroid dosage without significant complications. • Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. Immunol Res. 2018;66(2):255-270. doi:10.1007/s12026-018-8986-7. This review provides a brief overview about the different subtypes of pemphigus: pemphigus vulgaris, PF, paraneoplastic pemphigus, pemphigus herpetiformis, and IgA pemphigus. In addition, it summarizes the most recent understanding of the epidemiology, mortality data, and comorbidities of this group of organ-specific autoimmune diseases [24]. • According to a systematic review by Avallone, et al, 2022 [56] the introduction of large-scale vaccination programs, patients should be monitored for cutaneous manifestations following vaccine administration, and dermatological evaluation should be offered, when needed. However, if compared to the high number of vaccine doses already administered worldwide, cutaneous ARs seem to be rather infrequent and not life-threatening/severe, albeit heterogeneous and worth being studied. Being largely based on case reports and case series to date, our knowledge of SARS-CoV-2 vaccine-related dermatological manifestations should be further developed, and the underlying mechanisms should be clarified. Conclusion: Literature search results did not provide evidence of a potential mechanism of action or for a causal association between mRNA vaccines and Pemphigus/Pemphigoid (or related events).
Discussion	In the MAH's sponsored CTs, no imbalance was noted with 6 reports of Blisters identified on mRNA-1273 arm compared to 5 reports on the placebo arm (n=~20,000) group. No cases in the vaccination arms were considered related by the investigator. Cumulatively, in the MAHs GSDB, utilizing two different searches requested by the PRAC, a total of 152 cases were identified for pemphigus and/or bullous pemphigoid or related events. These included: 124 cases (PTs of BP [93 cases]; Pemphigus [31 cases]), retrieved as part of the first search and another 28 case reports from the second search containing various other relevant terms (Blister 6 cases, dermatitis bullous 2 cases, linear IgA disease 1 case; autoimmune disorders 19 cases). These cases were received via a Regulatory Authority (94 cases; 62%), spontaneous reporting (32 cases; 21%) and in published literature (26 cases; 17%). A review of the cases that fulfilled the established case definition (total 78 cases) showed

Signal evaluation criteria	Summary
	no specific reporting pattern by gender (40 female (51%); 38 male (49%)); 45 cases (58%) occurred in patients aged above 65 years (old age is a risk factor). Where the relevant information was available and the WHO-UMC causality was assessed as at least 'possible' by the MAH, a total of 32 cases (31 possible; 1 probable – see case below) were assessed as new onset (41%); and 9 cases (all assessed as 'possible') reported a flare-up (12%). Most cases were reported after Dose 1 and 2 (41%; 32 cases) while the Dose number was unknown in 40 cases (51%). The TTO following Dose 1 was ≤ 1 week in 5 out of 15 cases (33%) and 7 out of 17 cases (41%) following Dose 2. The event outcomes were recovered/ recovering/resolving/resolved/ resolved with sequelae in 29 out of 78 cases (37%), not recovered/ not resolved at the time of reporting in 24 cases (31%), unknown in 23 cases (29%) and fatal in 2 cases (3%). Overall, the WHO-UMC causality was assessed by the MAH as probable in 2 cases, both involved the event of pemphigoid: a possible re-challenge was reported in one case; the second case described an atypical bullous pemphigoid in terms of clinical manifestations and development in a patient with known eczema and it was postulated that the vaccination may have unmasked subclinical disease, defined by the presence of antibodies before clinical symptoms through the immunostimulatory process of the vaccine. In the other 39 cases for which the WHO-UMC causality was assessed as possible by the MAH, a number of potential contributory/pre-disposing risk factors were noted, for example, relevant medical history/comorbidities or concomitant medications having close associations with pemphigus/pemphigoid (e.g. autoimmune disorder(s), SLE, myasthenia gravis, multisystem inflammatory syndrome, psoriasis, dementia, nasopharyngeal cancer, dermatitis, eczema, depression, anxiety, hypothyroidism, skin cancer, pemphigus/pemphigoid and diabetes, etc.), and use of medication e.g. anti-hypertensives (such as lisinopril, ramipril, etc.), NSAIDs, aspirin, etc. Confirmatory diagnostic laboratory data for pemphigus or pemphigoid were not reported in some of these cases. Where the information was available, the events appeared to be generally manageable in clinic with appropriate treatment given. No specific patterns were identified from a review of cases with a reported fatal outcome, all these cases were reported in elderly patients >65 years of age. With a total of 152 cases reported in the GSDB containing the reported PTs of pemphigus/pemphigoid (or related events) following elasomeran vaccination among an estimated 772,908,958 million doses administered, this represents a reporting rate of 0.19 cases of pemphigus/pemphigoid per million doses of elasomeran administered. A review of the published literature did not provide evidence suggestive of a potential for a causal association between mRNA vaccines or mRNA-1273 and Pemphigus/Pemphigoid. A small study by Tomayko MM et al [57], have opined that the association of whether the mRNA-based vaccines may have a role in BP activation may simply be coincidental given the variable incidence of BP worldwide and the mass

Signal evaluation criteria	Summary
	vaccinations that have been carried out. It is possible that the individuals harbored subclinical forms of BP that were unmasked following the vaccination. Additional investigations/studies will need to be undertaken to study any off-target side effects of these medications. Similarly, a major review by Avallone et al [56], noted that the similar cutaneous manifestations were generally manageable in clinical practice with appropriate treatment. The overall reporting rates are still infrequent (in relation to the large-scale vaccinations globally) and opined that further studies need to be undertaken to allow better understanding of the cutaneous manifestations following the COVID-19 vaccination including that of the underlying mechanisms of action.
Conclusion	Cumulative analysis of the data as of 17 Dec 2022, for elasomeran, presented in this report showed that no specific patterns or concerns were identified. The reports of pemphigus/bullous pemphigoid are rare, and reports associated with the term "blister" did not identify any different pattern of reports than those that include the pemphigus and bullous pemphigoid terms. The CCDS (version 15.0) is considered to adequately reflect the safety profile of elasomeran. ModernaTx, Inc. concludes that no further action is warranted at this time and will continue to monitor events of pemphigus and bullous pemphigoid using routine surveillance. The benefit-risk evaluation remains positive. The PRAC final assessment report received on 14 Apr 2023, provided the following adopted PRAC recommendations: Having considered the available evidence from EudraVigilance, literature, the data submitted by the MAH and the analysis by EMA of real-world data, the PRAC has concluded that the current evidence is insufficient to establish a causal relationship between Spikevax and pemphigus or pemphigoid. The MAH for COVID-19 mRNA vaccine Spikevax (Moderna Biotech Spain, S.L.) should continue to monitor these topics in PBRERs. In the next PBRER (DLP 17 Jun 2023), the MAH should perform a review all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid (separately) after exposure to Spikevax, including data from CTs, post-marketing exposure and new scientific literature. The MAH should perform the assessment of causality, an O/E analysis and provide all case narratives within this review. The MAH is requested to clearly state if cases identified using the MedDRA HLT "bullous conditions" fulfil the definitions of bullous pemphigoid or pemphigus, and group them accordingly.

Rapporteur assessment comment:

Signal evaluation regarding pemphigus and pemphigoid

The information in the section is from the previous signal evaluation comprising data from the MAH's databases for clinical trial data and the global safety database as well as data from VAERS and EVDAS, and additionally a focused literature search. The signal evaluation did not give rise to concern regarding causality between administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and development of pemphigus or pemphigoid. The provided summary of the signal evaluation is acknowledged. As requested in the signal recommendation all new data from the same sources, DLP 17

June 2023, are submitted, presented, and assessed below.

Response to RSI

Table 15.4 Pemphigus and Pemphigoid

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: PSUR Appendix 13.4 ○ Retrieved: 27 ○ New and Significant Safety Information: None (0)
Background	During the review period covered by this report, the MAH received a request from a Regulatory Authority followed by Responses to Queries (RTQ) to the preliminary Health Authority Assessment Report for this safety topic (EPITT ref. no. 19860). The Health Authority subsequently concluded that '*…the current evidenceis insufficient to establish a causal relationship between Spikevax and pemphigus or pemphigoid*'. Further, it noted: • *The MAH for COVID-19 mRNA vaccine Spikevax (Moderna Biotech Spain, S.L.) should continue to monitor these topics in PSURs.* • *In the next PSUR (DLP 17 Jun 2023), the MAH should perform a review all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid (separately) after exposure to Spikevax, including data from clinical trials, post-marketing exposure and new scientific literature. The MAH should perform the assessment of causality, an O/E analysis and provide all case narratives within this review.* • *The MAH is requested to clearly state if cases identified using the MedDRA High level term (HLT) "bullous conditions" fulfil the definitions of bullous pemphigoid or pemphigus, and group them accordingly.*
Methods of Evaluation	Moderna GSDB was searched for all new cases reported from 18 Dec 2022 to 17 Jun 2023 for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran using the previously established customized MedDRA SMQ (as detailed in PBRER#4). This also included the MedDRA HLT 'Bullous conditions.' There is no universal case definition for Pemphigus or pemphigoid, therefore MAH developed a working case definition (see Appendix 12.10). The Company causality assessment is provided utilizing the WHO-UMC causality assessment.

Results:

Results for pemphigus and pemphigoid reports are summarized below. Refer to PSUR Appendix 12.10 for additional information, including summary of cases and events, case evaluations, and additional analyses.

During the review period, the MAH retrieved a total of 118 new cases (120 events) included in the HLT of 'Bullous conditions'; 95 cases were reported for elasomeran, 14 cases for elasomeran/imelasomeran and 10 cases for elasomeran/davesomeran (Note: there is overlap of one report, as the following case#MOD-2023-713419 was reported after elasomeran and elasomeran/imelasomeran), with 74 serious cases (74 serious events), and no cases with a fatal outcome. There were 44 medically confirmed cases. The majority of cases involved females (76 cases, 64.4%) than males (35 cases, 29.7%); 7 cases did not include gender information. The mean age was 52.2 years (SD: 18.1) and median age was 53.0 years

(range: 19 to 94 years). For events associated with a known dose number (34 events), 17 (50%) had an onset of < 7 days (other than events on Dose-4, reported events > 7 days) from the time of vaccination on any dose. Of note, a total of 85 (70.8%) events were reported with insufficient information to determine dose number.

All the 118 cases (120 events) were medically reviewed to identify potential cases of Pemphigus or pemphigoid and to differentiate them. There were 58 events reported as Blister, 42 events as Autoimmune disorder, 13 events as Pemphigoid, 3 events as Pemphigus, 2 events as Dermatitis bullous, one event as Immune-mediated adverse reaction, and one event as Acquired epidermolysis bullosa.

Summary of cases identified for Pemphigus:

A total of 3 cases with the reported PT of pemphigus were identified during the reporting period. The WHO causality was assessed as unlikely in two cases: A long latency (6 months or more) following the vaccination with elasomeran was noted in two cases. In one other case, insufficient clinical and laboratory details were provided for a detailed causality assessment (see Appendix 12.10).

Review of the cases from HLT of Bullous Conditions did not identify any other relevant cases that fulfil the definitions of pemphigus.

Summary of cases identified for Pemphigoid:

A total of 13 new cases (13 events) with the reported PT of Pemphigoid were identified during the reporting period. Of these, 11 cases were reported for elasomeran and 2 cases for elasomeran/imelasomeran. There were no pemphigoid cases reported for elasomeran/davesomeran during the interval period. There have been no cases with a fatal outcome. There were 8 medically confirmed cases. Most cases involved males (6 cases, 46.2 %) compared to females (5 cases, 38.5%); 2 (15.4%) cases did not include gender information. The mean age was 68.8 years (SD: 15.2) and median age was 69.0 years (range: 44 to 94 years). Of the 13 cases, 9 cases had a missing TTO and rest of the 5 cases, no specific pattern was observed on TTO. Similarly, majority of cases had unknown dose (11 cases, 11 events) and two cases with known dose were reported one each on Dose-2 and Dose-4.

All 13 cases were medically reviewed using the MAH case definition criteria and were accordingly classified as: 'confirmed' for 2 cases; and 'possible' for 6 cases; 'unassessable' for 4 cases as these cases were lacking in sufficient clinical information details and supportive laboratory diagnostic information for pemphigoid. One another case was assessed as 'not a case' since the event reported as a pemphigoid occurred >3 months after vaccination, the laboratory findings for immune serology returned negative. Refer to Appendix 12.10.

Out of the 13 cases reported during the reporting period:

Summary of Reports on Elasomeran (11 cases):

• There were 4 cases that were considered new onset cases based on the information provided. The WHO-causality in two (2) of these cases were considered as possible: Alternative etiology is suspected in this case as the concurrent medical history of chronic urticaria which could be suggestive of a potential underlying autoimmune disorder (predisposing risk factor); the second case with limited diagnostic confirmatory data for pemphigoid described event onset >1 month in an 87-year-old (risk factor) patient who was receiving polypharmacy (bullous dermatitis is listed for Cordarone). The WHO-causality in one other literature case was deemed unlikely as the event of pemphigoid (onset >3 months post vaccination) was attributed to a preceding COVID-19 infection and not vaccine related by the authors. One case was assessed as not a case (described above).

• Three cases described a flare-up of pre-existing pemphigoids. The WHO-causality was assessed as unlikely in two cases: the TTO in one case was >3 months after vaccination and in the other 140 days

post vaccination, and unassessable in one case where the latency information was unavailable for a complete case assessment.

• In 4 other cases, the status of pemphigoid was unclear from the available information. The WHO-causality in one case was assessed as possible in a 94-year-old patient (advanced age is a risk factor) while the complete information regarding the patient's medical history, co-morbidities including COVID-19 status and concomitant medications were unavailable, limiting the causality assessment. The second case was deemed unlikely related as the event onset was >6 months after vaccination. Two other cases were unassessable due to insufficient case information.

Summary of Reports on Elasomeran/Imelasomeran (2 cases):

• There was 1 case which was considered new onset case based on the information provided. The WHO-causality in this case was considered as possible which described blisters affecting the soles of the feet (atypical presentation) in a 72-year-old patient with concurrent asthma (risk factor) and who concomitantly received spironolactone (risk factor; severe skin reactions including Stevens–Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms listed). No confirmatory diagnostic laboratory data (biopsy/Direct Immunofluorescence/serology) for pemphigoid were provided.

• The WHO-causality assessment in one (1) other case was unassessable due to lack of sufficient clinical or diagnostic laboratory details confirming diagnosis of pemphigoid, including information on medical history/comorbidities, concomitant medications were reported.

There were no other relevant cases identified from the medical review of cases from the MedDRA HLT bullous conditions that fulfilled the definition of pemphigoid (see Appendix 12.10).

Discussion

The MAH conducted a review of cases for pemphigus and pemphigoid in the GSDB, CTs data and in literature for the interval period covered by this PBRER (18 Dec 2022 to 17 Jun 2023) for elasomeran, elasomeran/ imelasomeran and elasomeran/ davesomeran.

For the review period, a total of 3 cases (3 events) contained the reported PTs of pemphigus. The WHO-causality was unlikely in 2 cases with onset of events >6 months following vaccination with elasomeran. One other case contained insufficient details for causality assessment. There were no cases with a reported fatal outcome.

Overall, the observed post-marketing safety data from the cases containing relevant PTs of pemphigus revealed no new significant safety information. The events were generally manageable in clinic with appropriate treatment.

For the review period, a total of 13 cases (13 events) containing the reported PTs of Pemphigoid were retrieved: 11 cases for elasomeran (4 new onset; 3 flare-ups, where the relevant information was available) and 2 for elasomeran/imelasomeran (1 new onset).

Overall, in four cases (3 cases for elasomeran; 1 elasomeran/imelasomeran), the WHO-causality was assessed as possible. In these cases, alternative etiologies provided a more likely explanation of the reported pemphigoid event such as involving concomitant usage of medications for which pemphigoid or a related dermatological event are listed (e.g. spironolactone, Cordarone, etc), having known pre-disposing risk factors including a history of allergy (e.g. bronchial asthma, having potential association with pemphigoid [24], underlying chronic autoimmune condition) or involving patients of advanced ages (>70 years old). In two of these cases, the confirmatory laboratory diagnostic information for pemphigoid were not provided.

Overall, the observed post-marketing safety data from the cases containing relevant PTs of Pemphigoid revealed no new significant safety information. There were no cases with a reported fatal outcome.

No new significant safety information of relevance for this topic became available from the ongoing CTs for elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during the period of this report.

The clinical presentation of events in this reporting period was similar to that reported in the previous PBRER. Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported pemphigus or pemphigoid, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Conclusion

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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of pemphigus/ pemphigoid reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor for events of pemphigus and pemphigoid using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Pemphigus and pemphigoid

According to request the MAH has presented a review for the period 18 December 2022 to 17 June 2023 presenting all new cases for pemphigus and pemphigoid registered in their clinical trial database, global safety database, and from the literature. The MAH has included the HLT "bullous conditions" in the search of cases, and has met the request about defining them, this by using a working case definition developed by the MAH; cases are presented by group as pemphigus or pemphigoid. Causality assessment is done according to the WHO-UMC criteria. Information on case definitions and narratives is thoroughly reported (PSUR appendix 12.10a-12.10e). Observed/expected analyses are presented too.

Results

A total of 118 cases (120 events) were retrieved from the latest period. By vaccine, 95 cases (80.5%) were reported for elasomeran. The gender distribution was 76 females (64.4%), 35 males (29.7%), 7 (5.9%) of unknown gender. The age range was 19 to 94 years of age, median age 53.0 years. Only for 34/120 (28.3%) events dose number was known.

All 120 events were reviewed and grouped diagnostically; only 16 met the case definition for pemphigus or pemphigoid, hereof 3 events as pemphigus and 13 as pemphigoid.

Pemphigus: Causality assessment of the 3 cases (3 events) of pemphigus was "unlikely" in two cases, and "unassessable" in one.

Pemphigoid: Causality assessment of the 13 cases (13 events) was "possible" in 3 cases of new onset

and in 1 diagnostically uncertain. It was "unlikely" in 1 case of new onset, in 2 cases of flare-up of pre-existing pemphigoid, and in 1 of diagnostically uncertainty. And it was "unassessable" in 1 case of new onset, in 1 case of flare-up of pre-existing pemphigoid, and in 3 of diagnostically uncertainty.

O/E analyses: Cumulative O/E analyses through 17 December 2022 demonstrated observed numbers much below expected, for both overall numbers and for numbers by gender and age groups. The rates and the corresponding confidence intervals are all < 0.2.

Literature: A new literature search has been performed. Despite that 27 papers were retrieved, the MAH did not find any new and significant information in these.

Conclusion

The MAH has provided a review for the latest period and has met all requests. The clinical presentation of cases, of which none fatal, and the low O/E rates and corresponding confidence intervals do not raise concern. In accordance with the recent signal evaluation, the presented data do not indicate a causal association between pemphigus/pemphigoid and elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran.

2.2.4. Idiopathic inflammatory myopathy/Myositis

Table 16.6 Idiopathic inflammatory myopathy/Myositis

Signal evaluation criteria	Summary
Source	On 12 Jan 2023, Moderna received a Health Authority request to perform for Spikevax (Moderna Biotech Spain S.L.): o *A cumulative review of all cases of IIM/myositis from all sources including, but not limited to, available data from CTs, scientific literature andpost-marketing exposure.* o *Search strategy should include, but not be limited to the following PTs: Anti- melanoma differentiation associated protein 5 antibody positive, Anti-signal recognition particle (SRP) antibody positive, Anti-synthetase syndrome (ASS), Autoimmunemyositis, Dermatomyositis, Focalmyositis, Idiopathic inflammatory myopathy, Immune mediated myositis, Inclusion body myositis, Juvenile polymyositis, Lupus myositis, Myositis, Necrotizing myositis, Orbital myositis, Overlap syndrome, Polymyositis. The discussion should include considerations on whether the identified cases of IIM/myositis are considered "new onset" or "flare". The MAH should use a DLP as recent as possible.*
Background	Idiopathic inflammatory myopathies, also referred to as (autoimmune) myositis or autoimmune myopathies, are a group of autoimmune disorders with a heterogenous and specific spectrum of muscular and extra-muscular involvement. Idiopathic inflammatory myopathies classifications vary but the main subtypes include dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy and inclusion body myositis (IBM). Forms of IIM that share features with other connective tissue diseases are referred to as overlap myositis. These include Anti-synthetase syndrome. Idiopathic inflammatory myopathies are rare conditions (DM/PM annual incidence 0.4-4 cases per 100,000 patients) more common in women and people of Black ethnicity. The usual onset age of PM is between 45-60 years while DM shows a bimodal age distribution (5-15 and 45-60 years). Patients with IIM typically present with progressive symmetric proximal weakness that may manifest as difficulty rising from cha irs, climbing sta irs, or combing one's ha ir. Patients with DM also show typical skin lesions (heliotrope rash, shawl sign, Gottron papules, mechanic's hands) while those with ASS experience a variable combination of myositis, arthritis, Raynaud phenomenon, mechanic's hands, and interstitial lung disease. Diagnosis of IIMs is ba sed on muscle biopsy (gold standard), clinical signs, serology (autoantibodies), laboratory parameters (e.g., creatine kinase), electromyography

	(EMG) and/or magnetic resonance imaging (MRI). Therapeutic management is based on immunomodulating and immunosuppressive agents: corticosteroids, methotrexate, mycophenolate, tacrolimus, azathioprine, rituximab, Vig. About 50% of treated patientsexperience long-term remission. The 5-year survival rate is around 75%, with causes of death linked to generalized weakness, dysphagia/undernutrition, respiratory failure, or infections. IIMs are associated with both genetic factors (certain HLA subtypes) and environmental triggers such as drugs, infections, UV light, vitamin D deficiency, smoking and cancer. SARS-CoV-2 infection has been linked to a viral myositis attributable to direct myocyte invasion or induction of autoimmunity. COVID-19-induced myositis may vary in presentation, from typical dermatomyositis to rhabdomyolysis, and a paraspinal affliction with back pain. The pathophysiology of IIM is complex with various pathways: DM isa complement-mediated microangiopathy leading to destruction of capillaries, distal hypoperfusion and inflammatory cell stress on the perifascicular regions, while PM is characterized by cytotoxic CDS-positive T-cells which clonally expand in situ and invade muscle fibresexpressing the major histocompatibility complex (MHC)-1. An autoimmune response to nuclear and cytoplasmic autoantigens is detected in 60-80% of patients with PM/DM. The autoantibodies involved in IIM are divided into myositis-specific autoantibodies (MSA), which are found primarily in patients with IIM, and myositis-associated autoantibodies (MAA), which are shared with other connective tissue diseases. Target antigens of MSA include the nuclear antigens Mi-2a, Mi-213, SAEl, NXP2, MDA5, cN-lA and TIFly and the cytoplasmic antigens Jo-1 PL-7, PL-12, EJ, OJ, SRP, and further tRNA synthetases. Target antigens of MAA are the nuclear antigens Ku, PM-Scl75, PM-SclIO0 and the cytoplasmic antigen Ro-52. These antibodies are important markers of dia gnosis and prognosis a nd guide therapeutic management of IIM. For instance, anti-MDA5 antibodies are associated with a form of DM with a poor prognosis, while anti-Jal antibodies are found in ASS.
Methodology	The MAH's clinical database and the GSDB were queried for valid case reports of IIM/myositis received from HCP, HA, consumers, and literature, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) using the following below criteria: o Clinical Trial Data: Three Moderna sponsored clinical studies (mRNA-1273-P203, mRNA-1273-P204 and mRNA-1273-P301) were queried as part of the response to the agency's request for information. For study mRNA-1273-P203, the data cutoff was 27 Jan 2022; for mRNA-1273-P204, the data cutoff date was 21 Feb 2022, and for mRNA-1273-P301, the data cutoff date was 04 May 2021. o External Databases: VAERS and EVDAS were reviewed for the list of PTs: Anti- melanoma differentiation associated protein 5 antibody positive, Anti-SRP antibody positive, Anti-synthetase syndrome, Autoimmune myositis, Dermatomyositis, Focal myositis, Idiopathic inflammatory myopathy, Immune-mediated myositis, IBM, Juvenile polymyositis, Lupus myositis, Myositis, Necrotizing myositis, Orbital myositis, Overlap syndrome and Polymyositis. o Review of the Pharmacovigilance Database: The MAH GSDB was queried for valid P, HA, consumers, and litera ture, worldwide, for elasomeran, and for both bivalent vaccines(elasomeran/imelasomeran and elasomeran/davesomeran) as of 17 Dec 2022, using the following PTs: "Anti- mela noma differentiation associated protein 5 antibody positive, Anti-SRP antibody positive, ASS, Autoimmune myositis, Dermatomyositis, Focal myositis, Idiopathic inflammatory myopathy, Immune mediated myositis, IBM, Juvenile polymyositis, Lupus myositis, Myositis, Necrotizing myositis, Orbital myositis, Overlap syndrome, Polymyositis". o Literature search review: A focused literature search and review was performed using PubMed cumulative till 17 Dec 2022. Multiple search strategies were used to identify to Pemphigus and Moderna COVID-19 vaccines.

Results	Clinical Trial Data: *mRNA-1273-P203 Study (Cutoff date: 27 Jan 2022):* No participants were identified who reported the treatment-emergent AEs of Myositis related terms via unsolicited reporting. *mRNA-1273-P204 Study (Cutoff date: 21 Feb 2022):* No participants were identified who reported the treatment-emergent AEs of IIM/Myositis-specific terms. *mRNA-1273-P301 Study (Cutoff date: 04 May 2021):* Only one participant [redacted] who received placebo wasidentified who reported the treatment-emergent adverse event of IIM/Myositis-specific terms via unsolicited reporting. She is a 55-year-old female who received placebo and reported the event of "Myositis" (right shoulder muscle inflammation) 27 days after the first placebo dose and 1 day prior to second placebo dose. It was a mild non-serious event that lasted for 76 days, it was deemed not related and the participant recovered. External Databases: o VAERS: Overall, there is no disproportion observed in VAERS. There was minor disproportion observed in EVDAS with Focal myositis (1.15) and Autoimmune myositis (1.03) which did not trigger any significance in overall Myositis related EB05 scores. Review of the Pharmacovigilance Database: Cumulatively, through 17 Feb 2023, there were 295 (306 events) reported cases, of which 164 cases (149 serious events) were considered serious with IIM/Myositis related events after receipt of elasomeran. There were two cases with two non-serious events reported after elasomeran/imelasomeran and no cases reported after the elasomeran/davesomeran. Of the 295 cases reported after elasomeran, 151 (51.2%) cases were medically confirmed and three had a fatal outcome (one case [redacted] was identified as a fatal case during medical review. The reported outcome for the event of "dermatomyositis" was "unknown" and the reported cause of death was "gastrointestinal hemorrhage and anti- MDA-5 antibody positive interstitial pneumonia" 9 months after vaccination). Of the 295 reports, 62.0% (183) were females and 36.6% (108) were males; gender information was missing for 1.4% (4) cases. The mean age was 51.5 years (SD: 17.0), and the median age was 51.0 years (range 17.0 to 91.0). The reporting of these events is consistent with the known natural history of IIM/ Myositis events with more cases reported in women and in the older age groups with 51.5% of cases in individuals >50 years of age. According to epidemiological studies conducted on these rare and diverse events, there is a female preponderance for IMM/Myositis (specifically for dermatomyositis and polymyositis) and a higher prevalence among older age group. There was only one (0.3%) case report among adolescents 12-17 years of age. No unusual pattern was identified based on age and gender. **Confounders for IIM/Myositis:** Cumulatively, of the 291 cases, 35.4%(103) had at least one confounder, 57.0% (166) had extremely limited information and so the lack or presence of a confounder could not be determined, and 7.6% (22) cases did not report a medical condition or concomitant medication that were confounders. Most of the non- literature cases were missing critical information such as diagnostic evaluation, treatment, and clinical course needed to make an informed case classification and WHO causality assessment. Given that IIM has many causes, the list of confounders was extensive and included:

	1) age 2) infections including EBV, hepatitis, SARS-CoV-2; 3) autoimmune disease such as giant cell arteritis, Sjogren, mixed connective tissue disease, scleroderma, myosclerosis, Crohn's, ulcerative colitis, multiple sclerosis (MS), polymyalgia, fibromyalgia, (and specifically for just cutaneous findings, lupus erythematosus, 17 psoriasis); 4) rhabdomyolysis; 5) medications such as lipid-lowering drugs (statins, ezetimibe), alcohol (long standing use), immune checkpoint inhibitors, glucocorticoids, anti-malarial drug (hydroxychloroquine), antiretroviral drugs, chemotherapy; 6) endocrine: hypothyroid and diabetes and 7) others: malignancy, neuropathy. **EULAR/ACR classification criteria and WHO-UMC Causality**: Overall, there were 8 fatal cases of which 7 cases were from regulatory authority and 1 was spontaneous case. All the patients reported a fatal event were ≥66 years of age and majority of them were female (6) compared to males (2). Review of these 8 fatal cases with case definition, identifies most of them as Unassessable (6), followed by Unlikely (1) and Possible (1). Evaluation of the 291 cases with at least one IIM/myositis-specific event after elasomeran cumulatively through 17 Feb 2023 was conducted using the EULAR/ACR classification criteria . Evaluation of the spontaneous reports, particularly, the non-literature cases, was challenging because most of them had limited available data; information regarding the characteristics of the events e.g., "myositis", clinical examination to assess muscle weakness and skin manifestation, results (including the value) of la boratory measurements (e.g., muscle, liver enzymes and myositis antibody panel), whether a biopsy was performed and results if done were not available. Additionally, the reports also lacked medical history, concomitant medications, detailed evaluation including tests to exclude other etiologies (e.g., infections, malignancy workup), treatment and clinical course. Review of the 295 cases, also revealed that PT of "Myositis" was applied to a heterogenous group of symptoms that were unrelated to IIM, such as expected reactogenicity, aswe l as vaccination-rela ted events like injection site pa in and swelling, possibly extensive limb swelling, COVID-19 arm etc. The EULAR/ACR classification wasnot applied to the nine case reportsthat noted a flare after elasomeran of their prior diagnosis of IIM, as they were already considered casesof IIM/Myositis. There were also 4 reports that were excluded from the case evaluation as the TTO of the events were reported before administration elasomeran. Of the remaining 282 cases, four case report were classified as "definite" IIM, five cases as "probable", 34 cases as "Not a case", and 239 cases as "Unassessable". As mentioned above, the vast majority of the reports lacked critical information needed to evaluated cases according to the established IIM case classification, as well as to establish causality according to the WHO causality assessment. Information regarding the clinical course of the event of "myositis", clinical examination to assessmuscle weakness and skin manifestation, results (including the value) of laboratory measurements including muscle, liver enzymes and myositis antibody panel, and whether a biopsy was performed, and results were not provided. Of the nine cases that noted experiencing a flare of IIM/myositis after elasomeran, causality was assessed as "Possible" for three cases because there was limited data regarding their baseline status of IIM, whether they were on treatment and whether they stopped treatment before vaccination as well as the lack of clinical evaluation including la bs to establish the diagnosis of a flare. Three cases were assessed as "Unassessable" due to very limited available data including dose number and TTO, important to establish a temporal association to ela someran vaccination. The reports are also missing information to accurately assess causality such as baseline status of condition, concomitant medications, dia gnostic evaluation, treatment, and clinical course. One case was assessed as "Unlikely" because he also reported COVID-19 pneumonia around the time of reported IIM/myositis events and there are reports that infectionsincluding SARS-CoV-2 can cause IIM/myositis and two cases were deemed as "Not a case" of IIM/myositis flare. **Cases Who Received a Booster with elasomeran/imelasomeran**: Cumulatively, through 17 Feb 2023, two non-serious cases were reported after receipt of a booster with elasomeran/imelasomeran with only two non-serious IIM/myositis events. Only one case had enough data reported to assess the dose

	and TTO, the event was reported five days after Dose 5. Both cases had very limited available data and lacked the critical information needed to perform an informed IIM case classification and causality assessment. Information regarding the quality of the reported "myositis", clinical examination toassess muscle weakness and skin manifestation, results (including the value) of laboratory measurements including muscle, liver enzymes and myositis antibody panel, whether a biopsy was performed and results if done as well as detailed evaluation including tests to exclude other etiologies (e.g., infections, malignancy workup), medical history, and concomitant medications are not provided. Both cases were deemed "Unassessable" by the modified EULAR/ACR classification criteria and causality was also "Unassessable" by WHO-UMC causa lity criteria. Literature search review: Five hundred and twenty articles were identified. The title and abstracts were reviewed and after exclusion of articles that discussed COVID-19 disease or its impa ct on IIM/myositis, effect of the pandemic on IIM/myositis, therapeutic approaches for treatment of IIM/myositis, case reports/series, review articles and studies that did not include elasomeran, 34 articles underwent an in-depth full length text review. A critica l analysis of the 34 articles was performed, identifying only 16 articles rega rding ela someran and IIM/myositis and 5 articles describing COVID-19 vaccination (other than Moderna vaccine). The other 13 articles were general articles describing COVID-19 associated myopathy. The 16 articles with elasomeran and IIM/Myositis were case reports/series describing 19 cases with IIM/myositis-specific events. These case reports have important limitations including lack of a comparison group, lack of ability to genera lize, no possibility to establish cause-effect relationship, possibility of over- interpretation, selection bias, and recall bias. Evaluation of those published literature reports do not support a causal relationship between IIM and elasomeran. **Conclusion**: Overall, the published data currently does not support an association between Myositis and elasomeran or elasomeran/imelasomeran and elasomeran/davesomeran.
Discussion	To date, there is no definitive evidence to demonstrate association between receipt of elasomeran and IIM as there is no clear biological plausibility. Idiopathic inflammatory myopathies like all autoimmune diseases, is a complex disorder and, most likely, multiple factors including genetic, immunological, and environmental ones in combination all play a role in its development. Although much is known about the pathologic processes present in this group of disease and that the clinical and histopathologic distinctions between these conditions suggest that different processes underline each of the inflammatory myopathies, the pathogenesis is poorly understood, and the precise cause of IIMs remains unknown. Additionally, although there have been case reports of IIM occurring after other vaccines including those against viruses (hepatitis B, influenza, smallpox, mumps, rubella, and poliomyelitis) or bacteria (Mycobacterium tuberculosis, Clostridium tetani, Corynebacterium diphtheria and Bordetella pertussis), mostly, any connection between the immunization and autoimmune reaction was temporal and the exact pathogenesis still unknown [60] [61] [62] [63]. Overall, the observed to expected rate ratios for IIM using post-marketing data and expected incidence from Sweden, reported no increase in the rate ratios. However, the age and gender stratified analyses, using 7-day risk window reported an increased rate ratio in females 25-49 years. As the background incidence was based on cases identified as IIM compared to the observed cases identified using PTs not restricted to IIM, there is possible overestimation of the rate ratio. Hence, the results of the observed to expected analyses should be interpreted with caution. In the P203, P204 and P301 CTs, no participants who received mRNA-1273 reported an IIM/myositis-specific event. Post-marketing data showed a geographic disproportion in the origin of reports of IIM/myositis-specific events with majority of reports originating from EEA (55.9%). The distribution of reports by age and gender is consistent with limited available data on the epidemiology of IIM; there were no unusual patterns identified based on age, gender, doses administered and medical history. The most frequently reported

	coreported PTs by cases with IIM/myositis-specific PTs were consistent with reactogenicity events. Medical review of the cases revealed that PT of "Myositis" was applied to a heterogenous group of symptoms that were unrelated to IIM, such as expected reactogenicity, as well as vaccination-related events like injection site pain and swelling, possibly extensive limb swelling, COVID-19 arm etc. A focused literature review identified literature articles that only described case reports/case series of IIM/myositis after COVID-19 vaccination. Case reports and case series are limited for many reasons including lack of a comparison group, lack of ability to generalize, no possibility to establish cause-effect relationship, danger of overinterpretation, publication bias, recall bias and retrospective design. These studies cannot establish a causal relationship and support the need for well-designed prospective and longitudinal studies to study. Additionally, the pathogenesis of IIM is complicated and not well-defined and the exact pathogenesis of reports of IIM occurring after vaccines is still unknown. The total number of reports of IIM/myositis related events included in the MAH GSDB can be considered very low in relation to the number of people who have received COVID-19 vaccines to date (as of 17 Feb 2023, 1,347,109,306 elasomeran doses have been distributed with 791,426,717 doses elasomeran administered). The reporting rate of IIM/Myositis related events elasomeran is 0.4 events per 1 million doses administered. Based on the analysis of all available safety data as of 17 Feb 2023, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran and the development of IIM/ myositis. No new or emerging safety concern was identified.
Conclusion	Overall, based on the analysis of all available safety data as of 17 Feb 2023, the MAH considers that there is insufficient information at this time to establish a causal relationship between the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and the development of IIM/Myositis. The observed to expected analyses within 7-day risk window, using background incidence from Sweden and the UK showed an increased rate ratio in females 25-49 years old. However, there was no increase in rate ratio using the background incidence from Spain. As mentioned, myositis cases as reported in the GSDB lack medical history, concomitant medications and other clinically relevant information to assess the validity of the case, thus limiting the interpretation of the observed to expected analyses. The MAH considers that this health authority validated signal is refuted and no change to the reference safety information, labeling or risk management plan is required. The benefit-risk profile of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran continues to be positive. Given the increased report of IIM/myositis-specific events among females aged 25-49 years of age, the MAH will monitor IIM/myositis related events closely through enhanced signal detection activities. Idiopathic inflammatory myopathies /Myositis will be included as a topic of interest in the MAH' Signal Management Process. Additionaly, given the conflicting results and limitations of the observed to expected analyses, the MAH will assess myositis in an ongoing PASS study using US claims data (mRNA-1273-P903). The evaluation in the PASS study, will enable the MAH to mitigate the concerns of case definition by using the same case definition for observed and expected cases, also it will minimize the confounding factors using self-controlled risk analysis. The results of systematic evaluation of myositis in the ongoing PASS study will be submitted with the final study report in Jun 2023. Please refer to PSUR Section 8 for results from the PASS study. The PRAC final assessment report received on 12 May 2023, provided the following adopted recommendations: Having considered the available evidence, including from the cumulative review performed by the MAH, the PRAC has agreed that a causal association between COVID- 19 mRNA vaccine (nucleoside-modified) elasomeran and

	myositis cannot be concluded at present. No update to the product information and/or the risk management plan is warranted. The PRAC has agreed that the MAH of COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should continue to monitor IIM/myositis and their flares through routine pharmacovigilance in the upcoming PBRERs. Any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms should be presented. The MAH should include and follow-up on IIM/myositis in the final study report of EU PASS study mRNA-1273-P904 to be submitted in Dec 2023.

Rapporteur assessment comment:

A signal evaluation comprising data from the MAH's databases (clinical trial database and global safety database) with DLP 17 February 2023, data from VAERS and a focused literature search was performed. The signal evaluation did not give rise to concern regarding causality between administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran and development of IIM/myositis. The provided summary of the signal evaluation is acknowledged. Data submitted as requested in the signal recommendation is presented and assessed below.

Response to RSI

PSUR table 15.3 Idiopathic Inflammatory Myopathies (IIM)/Myositis

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: PSUR Appendix 13.4 ○ Retrieved: 48 ○ New and Significant Safety Information: None (0)
Background	In response to a request from a Health Authority on 12 Jan 2023, the MAH performed a signal evaluation for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran regarding IIM/myositis. The Health Authority agreed with the MAH's assessment that a causal association between Modern COVID-19 mRNA vaccine and myositis could not be concluded. The following were further requested by the Health Authority: • *The MAH should continue to monitor IIM/myositis and their flares through routine pharmacovigilance in the upcoming PSURs. Any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms should be presented.* • *The MAH should include and follow-up on IIM/myositis in the final Study report of EU Post authorization safety study (PASS) mRNA-1273-P904 to be submitted in Dec 2023.*

Methods of Evaluation	In 2017, European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) developed and validated classification criteria for IIMs and their major subgroups. The EULAR/ACR criteria employ easily accessible and operationally defined elements including age, muscle weakness, skin/other clinical manifestations, laboratory measurements, and muscle biopsy features for the classification of "definite", "probable", and "possible" IIM. The MAH adopted the EULAR/ACR criteria for classification of IIMs, and given the nature of spontaneous reports, added two categories: • "Unassessable" for case reports lacking critical information needed to complete IIM case classification (e.g., lack of data on objective signs of weakness, skin manifestations, myositis antibody panel, liver or muscle enzymes, muscle, or skin biopsy results); and • "Not a case" for case reports that do not meet the EULAR/ACR "definite," "probable," or "possible" classification and clearly have an alternate diagnosis for the reported events. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

Results:

Results for IIM/myositis are summarized below. Refer to PSUR Appendix 12.9 for additional information, including summary tables of cases and events, case evaluations, and additional analyses

The MAH performed an updated review of reports received after 17 Feb 2023, the DLP of the signal evaluation, to cover the period 18 Feb 2023 through 17 Jun 2023, the DLP of PBRER #5. During this period, the MAH received 17 cases (16 serious) of IIM/myositis. No cases had a fatal outcome. There were 7 medically confirmed cases. (Note: Medically confirmed case reports are reports provided by a medically qualified patient, friend, relative or caregiver of the patient. In the same way, where one or more suspected ARs initially reported by a consumer are subsequently confirmed by a healthcare professional, the ICSR should be considered medically confirmed.) The majority of cases involved females (11 cases, 64.7 %) compared to males (6 cases, 35.3%). The mean patient age was 54.6 years (SD: 11.9) and median age was 57.0 years (range: 31.0 to 71.0 years). The reporting of events is consistent with the natural history of IIM/myositis which occurs more commonly in women and in the older age groups.

Of the total 17 cases, 14 cases (13 serious) with 15 events (11 serious) were reported for elasomeran and 3 serious cases (3 serious events) were reported for elasomeran/imelasomeran. There were no cases reported for elasomeran/davesomeran. [redacted], and [redacted] are serious cases with elasomeran with non-serious IIM events reported.

Most reports were from regulatory authorities (13, 76.5%), followed by spontaneous reports (3, 17.6%) with one (5.9%) report originating from the literature (non-study report). Most of the cases were received from the EEA (9 cases, 52.9%), followed by the United Kingdom and United States (3 cases, 17.6% from each).

Dose number and TTO could not be determined for 12 of the 18 events and given the low case/event counts, no meaningful pattern in dose number or TTO was appreciable.

Out of the 17 cases identified in the reporting period, 9 were unassessable, 4 were unlikely, 3 were not cases of IIM (note however, [redacted] indicated potential rechallenge), and 1 case [redacted] was a possible case of IIM according to the modified EULAR/ACR criteria adopted by the MAH.

The MAH considers [redacted] and [redacted] as relevant new cases (including those reporting re-challenge information) to present as requested by the Health Authority.

[redacted] (WW Identifier [redacted]) is a literature non-study

case concerning a 71-year-old female reported to have no significant medical history, who started having gradual onset of proximal lower extremity weakness 2 weeks after the second dose of mRNA-1273 COVID-19 vaccine. Over the next 9 months, she reported persistent weakness and leg pain. Blood work revealed aspartate aminotransferase 126 unit/L, normal alanine transaminase, creatinine kinase level 541 IU/dL, and a positive Antinuclear Antibody test. The patient was evaluated by outpatient rheumatology and found to have objective proximal muscle weakness. Electromyography and nerve conduction study reportedly showed evidence of myopathic disease. She was admitted for inpatient workup and found to have proximal muscle weakness with preservation in distal muscle groups. A routine myositis antibody panel was negative. Brain, cervical, and thoracic Magnetic Resonance Imaging (MRI) showed findings that were chronic and not compatible with her symptoms. Muscle biopsy revealed frequent necrotic muscle fibres undergoing myophagocytosis and patchy endomysial macrophage, which supported the diagnosis of immune-mediated necrotizing myopathy. Given the high association of immune-mediated necrotizing myopathy to underlying malignancy, computed tomography of the chest, abdomen and pelvis was performed which did not show malignancy or metastatic disease but did show a mildly thickened endometrium. Endometrial biopsy could not be performed due to cervical stenosis, and the patient declined colonoscopy for colon cancer screening. She had persistent muscle weakness despite being on high-dose prednisone for a month. Intravenous immune globulin (IVIG) and rituximab were added as steroid-sparing agents, and the patient continued to be monitored closely. According to the authors malignancy was not completely excluded given the patient's refusal to undergo further colonoscopy and endometrium biopsy.

MAH Comment: Based on the temporal association, clinical presentation, high Creatinine Kinase, positive Antinuclear Antibody (presumably anti-Jo-1), and muscle biopsy results, this is assessed as a possible case of IIM. Based on the confounding possibility of associated malignancy, this case is considered possible according to WHO causality assessment.

[redacted] (WW Identifier [redacted]) is a regulatory authority case from a consumer of a 56-year-old male, with diabetes and asthma, and COVID-19 (SARS-CoV-2) infection 54 days after receiving the second dose of the CHADOX1/NCOV-19 vaccine, who experienced first episode myositis 44 days after dose 1 CHADOX1/NCOV-19, and a second episode of myositis 72 days after elasomeran as third vaccination. The patient experienced sharp pain in the muscle of the upper arms for which he went for physiotherapy and after about 6 weeks was recommended to have steroid injection. Patient had loss of strength in both arms. No further information regarding risk factors, relevant medical history, concurrent conditions, investigations, and additional treatment received were provided. The outcome of myositis was reported as not recovered.

MAH Comment: While the events were reported as myositis, the clinical presentation is inconsistent with myositis, likely representing reactogenicity events occurring after vaccine interchange. Additionally, this report is heavily confounded by the reporting of the first episode after dose 1 of the CHADOX1/NCOV-19 vaccine, as well as the reported COVID-19 (SARS-CoV-2 infection) 54 days after dose 2 of the CHADOX1/NCOV-19 vaccine. This is not considered a case of IIM.

Discussion

In this reporting period, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported IIM, no consistent or independent risk factors were identified in any of the cases that would support a causal association with administration of elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran.

A focused literature review did not identify articles that provided any new information on possible pathogenic mechanisms on the occurrence of IIM.

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 elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of IIM/myositis reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events for IIM/myositis using routine surveillance and present new relevant cases in PBRERs. The benefit-risk evaluation remains positive.

As per request from a health authority, the MAH will include myositis as an AESI for the final study report for the EU PASS study mRNA-1273-P904 to be submitted in Dec 2023.

Rapporteur assessment comment:

According to request, the MAH has presented information on new cases regarding IIM/myositis for the latest period 18 February 2023 through 17 June 2023 with data from the MAH's global safety database; previous data on IIM/myositis were presented in the recent signal evaluation with DLP 17 February 2023. Furthermore, a new literature search has been performed. Despite that 48 papers were retrieved, the MAH did not find any new and significant information in these.

The MAH has categorized cases as diagnostically "definite", "probable", or "possible" according to the EULAR/ACR classification criteria for IIM and their major subgroups. The MAH has, though, added "unassessable" and "not a case" as two extra categories. Causality assessment is done according to the WHO-UMC standardized case causality assessment.

Results

In the period 18 Feb to 17 Jun 2023 there were 17 cases of IIM/myositis. Of these 16 were serious, no fatal outcome. The gender distribution was 11 females (64.7 %) to 6 males (35.3%). The median age was 57.0 years, and the age range was 31.0 to 71.0 years. Of the 17 cases, 14 were reported for Elasomeran, 3 for elasomeran/imelasomeran, 0 for elasomeran/davesomeran.

Categorised according to EULAR/ACR only 1 of the 17 cases (5.9%) was defined a possible case, the rest comprised 9 unassessable, 4 unlikely, 3 not cases of IIM and hence overall a poor diagnostic certainty. Likewise, there is no indication of a certain pattern regarding dose number and TTO, as this information was unknown for 66.7% of the events.

Conclusion

The total of 17 cases of IIM/myosotis in the latest reporting period were reported to occur more commonly in women and more in patients > 50 years of age. This matches the natural history of IIM/myositis. Some of the cases had a plausible temporal relationship from vaccination to reported IIM, nevertheless only a single case was found of possible diagnostic certainty and WHO-UMC possible.

The findings from the global safety database do not raise new concerns. Furthermore, the MAH's literature review did not identify new information on possible pathogenic mechanisms on the occurrence of IIM, or other aspects that would raise concern. On basis of the present information IIM/myositis should be monitored by routine surveillance.

2.2.5. Sensorineural hearing loss (ongoing)

Table 16.7 Sensorineural hearing loss

Signal evaluation criteria	Summary
Source	There have been multiple evaluations conducted on the medical topic of sensorineural hearing loss (SNHL) due to requests from health authorities, as well as internal evaluation through the signal detection process for hearing loss since Jun 2021.

Signal evaluation criteria	Summary
	• **01 Jun 2021**: The signal "Deafness" was evaluated and subsequently refuted. • **06 Jul 2021**: PRAC agreed with this decision in the Assessment Report of MSSR5 mentioning the following: *"Overall, PRAC Rapporteur agrees on the MAH's conclusion that available evidence is currently insufficient to establish a causal association between the risk of hearing loss and COVID-19 vaccine Moderna. The closure of the signal is accepted, and the MAH should continue to monitor cases reporting hearing loss as part of their routine pharmacovigilance practices."* • **28 Mar 2022**: Sudden hearing loss was reviewed internally as a safety topic triggered by EVDAS results of DLP 28 Feb 2022. • **27 Apr 2022**: Closed with the following conclusion: *"Based on review of available data, there is insufficient evidence to consider Hearing Loss as a potential signal. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities".* • **31 May 2022:** Triggered by a RTQ from Health Canada, the topics "Tinnitus, vertigo, and hearing losses" were addressed in the RTQ response to the agency. • **14 Sep 2022**: Hearing loss and Tinnitus were internally re-assessed as a safety topic review triggered by publication of the French Healthcare Authority (ANSM) on its website. • **19 Sep 2022**: Closed with following conclusion: *"Based on the analysis of the cumulative data, the MAH considers that there remains insufficient evidence for an increased risk for tinnitus, vertigo and hearing loss after vaccination with SPIKEVAX. The MAH will continue to evaluate these events using routine surveillance."* • **On 22 Dec 2022:** PRAC requested the MAH to address the topic "Hearing loss" in the next PBRER4. This topic was addressed with following conclusions: *"Based on the cumulative review of available data as of 17 Dec 2022, the MAH considers there is insufficient evidence to consider Hearing Loss as a safety concern. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities. No changes to the product information are required at this time."* • **11 May 2023**: PRAC confirmed that there is not sufficient evidence to establish a causal association between elasomeran and sudden hearing loss mentioning the following: *"Overall, the evidence presented by the MAH is not sufficient to establish a causal association between elasomeran and sudden hearing loss. However, given that the MAH did not provide any information on the causality of the cumulative cases and did not state whether any of the 2,116 reports could be classified as 'index cases', the assessor cannot form an opinion about the strength of the evidence available in the cumulative case reports. Thus, further information is needed. Within the current PSUSA, the MAH is requested to present in detail (including case narratives and MAH's causality assessment) all reports that fulfil level 1-3 BC case definition of sudden hearing loss AND that can be considered as 'index cases'*."* • **22 Jun 2023**: PRAC mentioned the following:

Signal evaluation criteria	Summary
	"Following review of additional data submitted by the MAH in response to RSI, the PRAC Rapporteur considers that a causal association between hearing loss and Spikevax cannot currently be established. No further actions beyond routine PV pharmacovigilance are required. " • **TGA RTQ Request for Review of Signal SNHL**: TGA's Medicines and Vaccines Investigation and Surveillance Section reviewed signal of SNHL with elasomeran. Signal detected in Nov-Dec 2022 Disproportionality Analysis Report. Thirty-four reports of hearing loss associated with elasomeran (including one report associated with Spikevax Bivalent Original/Omicron) in the TGA's Adverse Event Management System). Requests sponsor to provide *"updated signal analysis on hearing loss cases including age stratified and age specific observed versus expected analyses in the next PSUR to enable further evaluation of this signal. Please confirm your agreement with this request by 23 Jun 2023.* **On 09 Aug 2023, the validated signal** of SNHL was evaluated at the SRMT Meeting. Results from this meeting and SER will be submitted with PBRER #5 (PSUR). The SRMT decision was to refute the signal of SNHL. There were no changes to the product information or RMP. Additionally, the following actions were recommended: • Routine PV monitoring Sensorineural hearing loss will be included as an ad-hoc adverse event to study mRNA-1273-P920 (Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States).
Background	Hearing loss is defined as a person who is not able to hear as well as someone with normal hearing–hearing thresholds of 20 dB or better in both ears–is said to have hearing loss. Sensorineural hearing loss is estimated to be the most common type of hearing loss and affects between 5-27 per 100,000 people each year, with approximately 66,000 new annual cases in the US. Incidence estimates of sudden sensorineural hearing loss after COVID-19 vaccination ranged from 0.3 to 4.1 per 100 000 per year. New onset is investigated by a full audiometric evaluation by a multidisciplinary team (e.g., otolaryngologist, audiologist, radiologist, and speech/language therapist). There are two types of hearing loss: conductive and SNHL. Sensorineural hearing loss results from pathology of the cochlea, auditory nerve, cranial nerve VIII or central nervous system. Conductive hearing loss is secondary to lesions affecting the external auditory canal or middle ear. Two types of hearing loss: conductive and SNHL 1. SNHL: results from pathology of the cochlea, auditory nerve, cranial nerve VIII or central nervous system. 2. Conductive: secondary to lesions affecting the external auditory canal or middle ear. Sensorineural hearing loss is more common in women than men and can be diagnosed in all ages; however, diagnosis is most common in older adults aged 50-64 years old and elderly with bilateral HL in patients aged >70+ years at time of diagnosis. In sudden onset

Signal evaluation criteria	Summary
	SSNHL, the exact pathophysiology is still unknown; however, it is most likely caused by a viral infection. Confounders for SNHL include the following: • **Infections:** Viral cochleitis associated with herpesviruses, parainfluenza virus, influenza, mumps, measles, rubella or HIV; bacterial meningitis; Mycoplasma pneumoniae infection; Lyme Disease; tuberculosis, syphilis or fungal infection • **Ototoxic Drugs:** Aminoglycosides, vancomycin, erythromycin, loop diuretics, antimalarials, cisplatin, sildenafil, cocaine • **Endocrine:** Diabetic vasculopathy, hypothyroidism • **Neoplasms:** Acoustic neurinoma meningeal carcinomatosis; lymphoma, leukemia, or plasma cell dyscrasia. • **Trauma:** Head injury, barotraumas; exposure to loud noise or music • **Autoimmune Disease**: Autoimmune inner ear disease, Cogan's syndrome, Susac syndrome, systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, Sjogren's syndrome, Kawasaki disease, Wegener's granulomatosis, temporal arteritis of primary central nervous system vasculitis. • **Vascular Disorders**: Vertebrocerebellar cerebral vascular accident or transient ischemic accident, cerebellar infarction, inner ear hemorrhage. • **Other Causes:** Meniere's disease, osteosclerosis, Paget's disease, multiple sclerosis, age, idiopathic. Treatment includes steroids to improve the prognosis. Also, decrease exposure to loud music or sounds in cases due to noise-induced hearing loss observed in young adults is recommended. Autoimmune related causes are rare clinical entity in which progressive fluctuating bilateral asymmetric SNHL that develop over several weeks to months. Vestibular symptoms, tinnitus and aural fullness are present in up to 50% of patients.
Methodology	The assessment of SNHL in association with the use of mRNA-1273 in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources is described below • <u>Clinical Trial Data:</u> The company clinical database was queried cumulative from 18 Dec 2020 to 17 Jun 2023. Safety data from six clinical trials in different age groups (adults, adolescents, and children) and in one clinical trial in immunosuppressed adults was reviewed to identify unsolicited events (serious and non-serious) reported using the MedDRA (version 23.0) PTs 'Deafness neurosensory', 'Hypoacusis' and 'Tinnitus'. The topic of SNHL was cumulatively reviewed in the clinical trial datasets, within the following studies: o mRNA-1273-P301, data as of 04 May 2021 o mRNA-1273-P203 Part 1A and Part 1B, data as of 31 Jan 2022 o mRNA-1273-P204 Part 1 and Part 2, data as of 21 Feb 2022 o mRNA-1273-P306 Part 1 and Part 2, data as of 05 Dec 2022 o mRNA-1273-P205:

Signal evaluation criteria	Summary
	➢ Day 91 Interim Clinical Study Report, Part G (mRNA-1273.214), data as of 08 Sep 2022 ➢ Day 29 Interim Clinical Study Report, Part H (mRNA-1273.222), data as of 31 Oct 2022 ○ Immunocompromised Adults: mRNA-1273-P304, data as of 01 Sep 2022 • Epidemiological studies: A total of 1,664,690,323 doses of elasomeran have been distributed as of 17 Jun 2023. Elasomeran was distributed in 91 countries, elasomeran/imelasomeran in 42 countries, and elasomeran/davesomeran in 41 countries. The estimated administered doses were used to calculate the denominator for the observed to expected analyses. Person-years were estimated by assigning 21 days after each dose including all products elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). The assumed age and gender distribution was based on CDC data as of 11 May 2023. • <u>External Databases:</u> Disproportionality was performed for external safety databases. • <u>Review of the Pharmacovigilance Database:</u> A cumulative search in the GSDB, through 17 Jun 2023 for reports under the MedDRA HLT of "Hearing losses" was performed. An additional search string of the narrative and PTs using an algorithm was applied to avoid any missing cases. Cumulative analysis of HLT of hearing loss cases focused on PTs of hypoacusis, and any combination of sensorineural hearing loss/deafness including: MedDRA Version 26.0 PTs: 'Deafness neurosensory', Neurosensori hypoacusis', 'Hypoacusis', 'Neurosensory Deafness'. All case reports identified from the above search (whether or not the PT SNHL was coded) were medically reviewed for evidence of SNHL based on Brighton Collaboration (BC) case definition which included evidence of physical examination (e.g., ENT) to rule out conductive hearing loss, and for specific diagnostics to determine index cases of SNHL (e.g., audiometry, MRI, tuning fork exams), medical diagnosis of SNHL or reported diagnosis of hypoacusis. • <u>Literature search review:</u> A targeted literature search was performed from 18 Dec 2022 to 17 Jun 2023 using PubMed.
Results	<u>Clinical Trial Data:</u> No imbalance was observed between the placebo arm and mRNA-1273 vaccination arm for PTs "Deafness neurosensory", "Hypoacusis" or "Tinnitus" in any of the studies were reports for the evaluated PTs were reported (P301 and P204). No cases associated with the PTs "Deafness neurosensory", "Hypoacusis" or "Tinnitus" were reported in: • mRNA-1273-P205 • mRNA-1273-P304 • mRNA-1273-P203 • mRNA-1273-P306 There was no imbalance or change to the benefit risk safety profile. Epidemiological studies: In data from a US, administrative claims-based study of sudden sensorineural hearing loss identified an incidence of 27 cases per 100,000 person-years [64]. Increases by age were consistent for men and women. The literature-based estimates varied widely: • Taiwan: 10.2/100,000 person-years [65]

Signal evaluation criteria	Summary
	• Japan: 27.5/100,000 person-years [66] • Germany: 160/100,000 person-years [67] External Databases: • VAERS: No Disproportionate Reporting of Events using EB05 > 2 (mRNA-1273 versus All vaccines in adults) in VAERS as of 10 May 2023. • EVDAS: Disproportionality was observed in EVDAS (27 May 2023, to 09 Jun 2023). PTs for HLT of hearing loss including SNHL, deafness neurosensory, and hypoacusis showed Disproportionality as the ROR was >1. There was higher disproportionality in North America compared to other regions. Deafness neurosensory (ROR=738) was disproportionate in general population and in geriatric population and increased overall (All ROR: 2.03; N=170, ROR>1). While disproportionality is not uncommon in EVDAS, results should be taken with caution given the limitations in EVDAS and based on low case counts. For bivalents, regional disproportionality was seen in elasomeran/imelasomeran (deafness in EU and hypoacusis in Asia). For elasomeran/davesomeran, disproportionality was reported in North America only; deafness neurosensory was reported in general population Review of the Pharmacovigilance Database: Two analyses were performed. A cumulative review was submitted as part of a health authority request (EMA/PRAC) for PBRER4 (cumulatively from 18 Dec 2020 through 17 Dec 2022) and an updated analysis of cases reported during the reporting period for PBRER#5 (17 Dec 2022 to 17 Jun 2023) based on a request received from another health authority (TGA). **Summary of Cumulative HLT Hearing Loss Cases (18 Dec 2022 to 17 Dec 2022):** Of the 2,327 cases (2,589 events) identified, 25.2% (586) of cases were reported as non-serious and 74.8% (1,741) were reported as serious, of which 3 were fatal cases. There were 1,254 (53.9%) medically confirmed cases. Gender distribution was highest among women (57.5%) with 40.4 % in men and 2.1% of unknown gender. The mean age was 52.0 years (SD: 17.0) and the median age was 52.0 years (range: 0.3 to 101.0 years, noting that the cases in very young children were found to have age coding discrepancies which are being corrected). The highest proportion of cases occurred in the 50–64-year-old age group (28.5%) followed by the elderly 65 years and older (24.4%), and the 25-39-year-old age group (18.3%). There were 16 cases (0.6%) in the pediatric age group. The majority of these cases originated from the United States (51.6%), followed by EEA countries (35.5%) and the United Kingdom (5.8%). The highest events were for the PTs of hypoacusis (33.3%) followed by deafness (25.9%). When time to onset (TTO) was reported, most events occurred after Dose 1 (30.1%), with Dose 2 (28.9%), and Dose 3 (7.6%) with TTO not reported in 32.9% of the events. The time to onset of all doses was on average 13.7 days (SD: 33.9) with a median of 3.0 days (range of -217 to 379 days). Almost 60% of the 2,589 events (59.6%; 1,544) were not resolved, 14.4% (372 events) resolved, and 8.6% (224) were either resolving or resolved with sequelae. Note: Not resolved outcomes must be interpreted with caution as most reports do not have follow-up. Serious events represented 65.3% (1,220) of the "not resolved" outcomes; 44.9% (324) of the "not resolved" events were non-serious. Most cases were confounded by extensive medical history and/or concomitant medication use. The MAH conducted a detailed evaluation of the cases of SNHL by searching both the narratives and filtering for the MedDRA PTs which contained verbatim combinations of

Signal evaluation criteria	Summary
	SNHL or hypoacusis. Using the results from the MAH SAS algorithm of the 2,327 cases, there were 994 cases of SNHL/hypoacusis and 1,333 cases of 'Other hearing loss (HL)' identified. Of the 994 cases, gender distribution was highest among women (599; 60.3%) with 380 (38.2%) in men and 15 (1.5%) of unknown gender. There were 689 cases (69.3%) in the adult age group, 254 cases (25.6%) in the elderly 65 years and older population, and 51 cases (5.1%) in the pediatric age group with a mean age of 49.6 years and median age of 50 years. Of the 994 cases, over 76% of the cases reported treatment with steroids, antibiotics or other medications; the remaining cases had (237) missing/unknown treatment information. There were 242 cases, which had confounders of either medical history, concurrent illnesses, or concomitant medications. However, 432 cases had missing or unknown medical history. A total of 785 cases did not report diagnostic studies (e.g., audiogram/acoustic test, magnetic resonance image [MRI], computerized tomography) information. The remaining 209 cases were identified with diagnostic studies and underwent medical review and assessment (BC case definitions for acute neurosensory hearing loss and WHO causality). Of these 209 diagnostics cases, 64% met the Level 3 criteria. Overall, there were no index cases for SNHL identified; there were 6 cases classified as Level 2 and 129 cases as Level 3. Among the 6 Level 2 cases, all cases were in adult age range 38 to 67 years. No cases had relevant medical history of hearing disorders. However, 2 cases had a history of high cholesterol, 4 had histories of other vaccines (Shingles), severe hypersensitivity reactions and allergies/respiratory problems. All cases had documented abnormal audiograms of >30 db-71db. Of the 4 cases that reported treatment, 2 cases did not resolve, and 2 cases were resolving/resolved after receiving therapy for the event. All cases were assessed as possible except for one case assessed as probable, which did not resolve with treatment. All Level 3 cases (129) had diagnostics studies (e.g., audiogram, MRI, etc.). In the 129 cases, the ages ranged from 27 to 90 years in 39 females and 24 males. Overall, although the majority of cases presented with a plausible temporal association; however, there were 63 cases that had confounders (medical history and/or concomitant medications). The outcomes reported in these cases were "not resolved" (111 cases), "resolved" (10), and "resolving" (8). In 49 cases, the patients received steroid treatment (either oral steroids and/or intra-tympanic steroid injections) in which 42 were not recovered/resolved and 7 resolved or resolving after treatment. **Summary of HLT Hearing Loss Cases during the PBRER 5 reporting period (18 Dec 2022 to 17 Jun 2023)** During the reporting period of this PBRER (18 Dec 2022 to17 Jun 2023), a total of 152 cases were identified using the same search strategy as before, with the HLT of "Hearing losses". After application of the same SAS algorithm, a total of 82 cases of SNHL were identified (70 for elasomeran; 8 for elasomeran/ imelasomeran, and 4 for elasomeran/ davesomeran), of which, 18 cases provided information in order to evaluated cases for SNHL. Given that the number of reported cases during this RP was small, all cases in the RP were medically reviewed and evaluated using the Brighton Collaboration and WHO causality assessment. **Overview of Reporting Interval Hearing Loss Cases**: As part of this analysis, a comparison of SNHL cases reported for PBRER 4 (2,327 cases) vs those reported for PBRER 5 (152 cases) was performed and is presented below. No differences were observed between the two reports regarding gender, age and time to onset (TTO). There

Signal evaluation criteria	Summary
	were 3 cases reporting a fatal outcome during the PBRER 4; no fatal outcomes were reported during this RP. The demographic presentation was similar across both PBRERs with more cases reported for females compared to men, and higher proportion of reports in the 50-60 years old age group with a mean age of 56.87 years; time to onset was similar for both analysis (<3 days). Young adults (18-49 years old) had similar proportion of cases compared to elderly. There was significant number of missing data during the RP, which impacted the assessment. No cases were reported in children during this reporting period. When dose number was known, events occurred more often after dose 1 and dose 2, and time to onset was similar for both analysis (<3 days), regardless of dose number. Among the 152 new cases (168 events) of the SNHL HLT, the most commonly reported PT was hypoacusis (48; 12.5%), followed by deafness neurosensory (35; 9.1%). Overall, most of the cases did not report relevant medical history or concomitant medications and for those that provided that information most cases were confounded including use of ototoxic medications (loop diuretics) or relevant medical history (other vaccines, cardiovascular history or viral infections). Out of the 152 cases included in PBRER#5 RP, 82 Cases (383 events) were identified as SNHL using the described algorithm, of which 18 cases met diagnostic criteria. There were 55 serious cases and none with fatal outcomes. Most cases were medically confirmed (50; 61.0%). Most of the cases were reported after vaccination with elasomeran (70 cases); there were 12 cases after vaccination with the bivalent vaccines (8 for elasomeran/imelasomeran and 4 for elasomeran/davesomeran). Literature search review: From the search result 104 unique articles captured, 5 articles were related to SNHL and mRNA vaccination. Of the 5 relevant articles, 2 discussed the Moderna vaccine and SNHL and 3 discussed the Pfizer vaccine and SNHL. 99 articles were not relevant and consisted of 2 articles discussing SNHL/HL in COVID-19 infection, 3 editorials on SNHL studies in COVID-19 vaccine, and 43 about the Moderna vaccine with no SNHL. One article discussed a hypothetical mechanism of action and etiology of SNHL and mRNA vaccines [68]. Of note, hearing loss is associated with other medications and vaccines in the literature (Rabies, tetanus-diphtheria and meningococcal, MMR, Influenza, HBV, and oral poliomyelitis). Thai-Van H, Valnet-Rabier MB, Anciaux M, et al [69]: This is a nationwide retrospective study aimed to assess the relationship between SSNHL and exposure to mRNA COVID-19 vaccines and to estimate the reporting rate of SSNHL after mRNA vaccination per 1 million doses (primary outcome) in France between Jan 2021 and Feb 2022. This is a review of all suspected cases of SSNHL after mRNA COVID-19 vaccination spontaneously reported based on a comprehensive medical evaluation, including the evaluation of patient medical history, side and range of hearing loss, and hearing recovery outcomes after a minimum period of 3 months. Demographics included a median age of 51 years (range: 13-83 years old) and 59.2% female and 40.8% male. The two comparator groups were tozinameran and elasomeran. The median time to onset (TTO) for SNHL in <21 days in the tozinameran arm (n=108, 76.1%) was 4 (2-9) days, the TTO for SNHL in >21 days in the tozinameran arm (n=34, 23.9%) was 41 days (25-67). In the elasomeran arm, the median TTO for SNHL in <21 days (n=26, 86.7%) was 8 (1-21) days, and the median TTO for SNHL in >21 days (n=3, 10.3%) was 50 (26-144) days. Autoimmune, cardiovascular, or audio vestibular risk factors were present in approximately 29.8% (51/171) of the cases. Eligible SSNHL cases were selected using the MedDRA hierarchy, with preferred term selected from the narrow Standardized Medical

Signal evaluation criteria	Summary
	Queries "Hearing impairment." All data analyzed according to the American Academy of Otolaryngology-Head and Neck Surgery Foundation guidelines; patients were categorized according to a grading system modified from the Siegel criteria. No mechanism of action was listed in the article. Steroids were administered orally in 47.2% of cases. There were 8 positive rechallenges. Limitations include a large population-based pharmacovigilance studies or a case-control study appropriate for rare events is needed to further define the role of mRNA COVID-19 vaccination in the occurrence of SSNHL. Nationwide post-marketing surveillance did not include any control group, thus preventing the consideration of potentially important variables such as age or SSNHL time to onset. In conclusion, SSNHL after COVID-19 mRNA vaccines are very rare adverse events that do not call into question the benefits of mRNA vaccines but deserves to be known given the potentially disabling impact of sudden deafness. Therefore, it is essential to properly characterize post injection SSNHL, especially in the case of a positive rechallenge, to provide appropriate individualized recommendations. The lack of available data for the general population precluded comparisons with historical incidence or incidence in the unvaccinated population. Further studies are needed to establish the correlation between SSNHL and mRNA vaccination. Leong S, Teh BM, Kim AH. [70]: This was a cross-sectional study of patients seen in the otology clinic at an academic center. Patients completed a questionnaire on the development of new otologic symptoms within 4 weeks of COVID-19 vaccination. Demographics included a median age of 56.6 years (range: 16-101 years), and 59.4% female and 40.2% male. All mRNA vaccines were studied. No TTO or risk factors were provided. Diagnostic and audiometric data were obtained via retrospective chart review and may not have been reflective of the full workup that patients received. No mechanism of action provided. Cochlear implant and steroids (intratympanic dexamethasone or oral prednisone) were used as corrective treatment. No mention of rechallenge or dechallenge. Limitations included no specified diagnostic criteria were used for the collected data. Retrospective chart review may be reflective of the full workup the patients received. Otologic symptoms following COVID-19 vaccine are likely over-represented and thus cannot be generalized. Patients self-reported otologic symptoms. Patients were screened from otologic clinics only. Small sample size of 500 otology patients. In conclusion, patients reporting otologic symptoms following COVID-19 vaccination received various diagnoses of uncertain etiology. The incidence of SSNHL in these patients is comparable to the general otology patient population. Additional studies are required to determine the incidence of specific diagnoses following vaccination. Otologic symptoms following COVID-19 vaccination do not appear to have mechanistic associations with these specific vaccines. This study further affirmed that the benefits of COVID-19 vaccination significantly outweigh the risk. Cohen Michael S, Tamir SO, O'Rourke N, Marom T [71]: This was a retrospective study that compared SSNHL incidence rates over the COVID-19 outbreak and the COVID-19 vaccination campaign periods to pre-COVID-19 periods. Patients >12 years with auditory-confirmed SSNHL were enrolled. COVID-19 status and BNT162 inoculation records ≤28 days before SSNHL diagnosis were retrieved. Patients were categorized according to their date of presentation over four equal periods. Demographics included in the pre-pandemic Period 1 (07/2018–04/2019) (N = 22), the median age was 52 years (23–81), 6 (27.3%) females, and 16 (72.7%) males. In the pre-pandemic Period 2 (05/2019–02/2020) (N = 21), the median age was 47.5 years (20–75), 10 (47.6%) females, and 11 (52.4%) males. In the post-pandemic Period 3 (03/2020–12/2020) (N = 23), the median age was 51 years (20–82), 11 (47.8%) females, and 12

Signal evaluation criteria	Summary
	(52.2%) males. In the post-pandemic Period 4 (01/2021–10/2021) (N = 34), the median age was 49.5 years (17–82), 15 (44.1%) females, and 19 (55.9%) males. The BNT162b2 vaccine was studied. Eight out of 127,543 patients presented with SNHL on the median 13th day after vaccination. No risk factors were included. Patients with clinical history and audiometry supported an SNHL with other ICD-9 codes were determined to have SNHL. No mechanism of action discussed. Oral steroids, intratympanic steroids, and hyperbaric oxygen treatment were used as corrective treatment. Limitations included due to the pandemic, hearing tests were not routinely conducted, and confirmed COVID-19 patients were even less likely to be sent to undergo audiometric studies. At-home and mobile SSNHL tests have been developed and seem to be reliable but could not eventually replace an objective audiometry. Small sample size, no comparator. No mention of Moderna vaccine. No specified diagnostic criteria were used for the collected data. Large-scale audiometrically confirmed research is required. In conclusion, despite the increase in SSNHL cases during the period when vaccination with BNT162b2 had taken place, there was no increase in audiometrically confirmed SSNHL cases among these vaccine recipients. The association between COVID-19 disease and its vaccination warrants further large-scale, audiometrically confirmed research conducted over many years post-pandemic. Fisher R, Tarnovsky Y, Hirshoren N, Kaufman M, Stern Shavit S [72]: This was a retrospective chart review of all patients diagnosed with idiopathic sudden sensorineural hearing loss (ISSNHL) during 2021 was conducted and compared to patients who presented in 2018-2020. Patients collected in 2018 (n = 41) had a mean age of 51 (± 17.5) years, and 15 (37%) females. In 2019 (n = 38), the mean age was 49 (± 17.07) years, and 17 (45%) females. In 2020 (n = 31), the mean age was 49 (± 20.3) years, and 19 (63%) females. In 2021 (n = 51), the mean age was 48 (± 18.4) years, and 25 (50%) females. In 2021 of the nonvaccinated population (n = 38), the mean age was 47 (±20) years, and 16 (43%) females. In 2021 of the vaccinated population (n = 13), the mean age was 52 (± 18.55) years, and 9 (70%) females. The 2018–2019 group was used as a control group before the SARS-CoV-2 pandemic and vaccination era. The 2020 group was used for the period in the presence of the pandemic and before the vaccination era. Comparisons were made between patients diagnosed in 2021 with previous years and between the vaccinated and nonvaccinated. The time to onset was 14.9 ± 9.87 days. No risk factors were included. All medical records of patients diagnosed and treated with ISSNHL at a tertiary medical center between Jan 2018 and Dec 2021. Patients were excluded if (1) their diagnosis did not meet ISSNHL criteria, (2) they had Meniere's disease, (3) were later diagnosed with vestibular Schwannoma per MRI, (4) had a progressive or bilateral loss, or (5) lacked information regarding their diagnosis, treatment, or vaccination status. The vaccinated group consisted only of vaccinated patients who received a vaccine dose in the 30 days preceding the ISSNHL presentation. No mechanism of action was discussed. Systemic prednisone for 7 days and intratympanic dexamethasone injection were used for corrective treatment. No rechallenge or dechallenge discussed. Limitations included this was a retrospective, relatively small cohort from a single center. As such, it was exposed to selection bias and may not accurately represent other medical centers, even though we found a similar incline as the Israeli large-scale population-based study. No statistically significant difference was found between different years or between the vaccinated and nonvaccinated groups. This study evaluated a population vaccinated with the Pfizer COVID-19 vaccine almost exclusively. No risk factors documented. In conclusion, a marked incline in ISSNHL incidence was seen in 2021, of which 25% of patients reported experiencing symptoms within a month post-anti-COVID-19 vaccination. While other

Signal evaluation criteria	Summary
	causative factors could be sought, an association with the vaccine cannot be ruled out, and further large-scale research is needed. Nevertheless, the benefits of the anti-COVID-19 vaccine immensely outweigh any potential otologic adverse effects. Ekobena P, Rothuizen LE, Bedussi F, et al [68]: This was four case studies with only 1 case of SNHL in a 61-year-old female vaccinated with Pfizer-BioNTech. Time to onset was 10 days. No risk factors were discussed. Patient received a pure tone audiogram, bilateral otoscopy, and video head impulse test as diagnostic tests. Prednisone 5 days after and vestibular physiotherapy was initiated as corrective treatment. The patient declined the second vaccine. Limitations included this was an isolated case report with Pfizer-BioNTech vaccine. In conclusion, the occurrence of audio-vestibular manifestations following mRNA-based vaccines needs ENT monitoring to support their causality in such rare vaccine-related adverse events. Audio-vestibular disorders appeared of transitory nature, including hearing loss, and should not deter further efforts in large-scale vaccination campaigns against SARS-CoV-2. The benefits of the COVID-19 vaccination appear to outweigh the risks of audio-vestibular disorders, since reported cases are mostly transient with favorable outcome. Conclusion: In conclusion, the literature is consistent with findings from the GSDB. Overall, the literature search results did not provide evidence of causal association between mRNA vaccines or mRNA-1273 and SNHL.
Discussion	The MAH conducted an extensive evaluation of a validated signal of SNHL due to a request from a health authority (TGA) received on 22 Jun 2023. The signal evaluation included a cumulative review (18 Dec 2020 to 17 Jun 2023) of clinical trial data as well as post-marketing information from the GSDB and the literature for reports included in the HLT of "Hearing Losses". SNHL is the most common type of hearing loss estimated at 5-27/100,000 per year with higher reported rates in men and elderly populations. In sudden onset sensorineural hearing loss (SSNHL), the exact pathophysiology is still unknown; however, it is most likely caused by a viral infection. According to the National Institute on Deafness and other Communication Disorders, men are twice as likely to experience hearing loss, but are less likely than women to seek help. There is evidence in the literature that sex and gender may influence the development of SNHL. The prevalence of hearing impairment is higher among older men than older women. However, the GSDB cases showed the highest cases were seen in the 50–64-year-old age group and higher proportion seen in women compared to men. Potential triggers include infections and ototoxic medications, as well as other immune activation events resulting in inflammation to the ear as postulated in the literature. The exact etiology and pathophysiology of SNHL remain unknown. New-onset hearing loss should be investigated and undergo full audiometric evaluation by a multidisciplinary team (e.g., otolaryngologist, audiologist, radiologist, and speech/language therapist). There was no imbalance reported from clinical trials for events within the terms included in the MedDRA HLT "Hearing Losses", as well as for the specific PT of Hypoacusis, Tinnitus, and information from the GSDB as well as the literature supports the recommendations received from the PRAC from the review of PBRER#4 (Procedure EMEA/H/C/PSUSA/00010897/202212), that stated: "The data presented above does not change the PRAC Rapporteur's opinion that the available evidence is insufficient to establish causal association between 'hearing loss' and Spikevax. No further actions beyond routine PV are thus considered warranted at this stage."

Signal evaluation criteria	Summary
	A review of cases identified during the reporting period did not show any prominent clinical pattern of occurrence of SNHL outside of what would be expected in a large, vaccinated population. Many of the reports were heavily confounded by historical conditions, concurrent illnesses, and concomitant medications. The observed reporting rates of SNHL are well below background incidence rates. Overall, 18 SNHL reports in 978,005,565 doses administered, shows an approximate reporting rate of 0.02 per 1 million doses administered.
Conclusion	A cumulative review, including an updated review conducted during the reporting period of PBRER 5, of the GSDB for reports under the HLT of "Hearing losses" received after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran was conducted, as per request received from a HA. Cumulative, as of 17 Jun 2023, the MAH identified 2,479 cases (2,757 events), including reports from the PBRER#5 RP, for individuals between the ages of 5 to 101 years old. The review of cases identified showed that most of the cases were heavily confounded by known risk factors associated with acute sensorineural hearing loss. There were five cases associated with herpes zoster reactivation. In general, it is difficult to adequately analyze post-authorization data due to inherent limitations in spontaneous reporting. Evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Based on the literature review of the mechanisms of action postulated including direct viral invasion of the middle ear and vascular injury to the terminal vessels of the middle ear and the three epidemiological studies that aimed to assess the relationship between COVID 19 vaccination and hearing loss do not provide convincing evidence to show an association with vaccination; moreover, a pathophysiologic process to explain such an association has not been shown. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Based on the cumulative review of available data as of 17 Jun 2023, the MAH considers there is insufficient evidence to consider Hearing Loss as a safety concern as this signal is considered refuted. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities, and the topic of SNHL will be added as an ad-hoc adverse event to study mRNA-1273-P920 (Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States). No changes to the product information or inclusion in to the RMP are required at this time.

Rapporteur assessment comment:

Introduction

The MAH presents the signal "sensorineural hearing loss" (SNHL). The signal is listed as ongoing, as the signal was closed and refuted on 14th August 2023 (after the DLP of this PSUR).

In the previous PSUSA procedure (EMEA/H/C/PSUSA/00010897/202212), the MAH presented a cumulative review of "hearing loss" as requested by the PRAC. The conclusion as documented in section 2 of the PRAC AR was: "*Following review of additional data submitted by the MAH in response to the RSI, the PRAC considers that a causal association between hearing loss and Spikevax cannot currently be established. No further actions beyond routine pharmacovigilance are required.*"

The MAH states that the signal evaluation presented in the current PSUR was conducted due to a request from a health authority (TGA) received on 22 June 2023.

Safety database

The data presented in this signal evaluation overlap somewhat with the data presented in the previous PSUSA procedure. With regard to new data compared with the previous evaluation, the MAH has retrieved 152 cases with the HLT "hearing losses" from its safety database from this PSUR period. The MAH reports that: *"Overall, most of the cases did not report relevant medical history or concomitant medications and for those that provided that information most cases were confounded including use of ototoxic medications (loop diuretics) or relevant medical history (other vaccines, cardiovascular history or viral infections)."*

Literature

For this PSUR period, the MAH retrieved the following literature articles related to sensorineural hearing loss:

Thai-Van et al.: In this case series study, the authors identified 29 medically documented cases of SNHL with elasomeran exposure from the French Pharmacovigilance Database including 3 cases demonstrating positive re-challenge. The authors excluded cases with insufficient information and alternative explanations for the adverse event. The authors reported that 9 out of 29 patients "had a medical history" - 4 of which were "otoneurological". However, it is not explained whether these medical histories provide more likely explanations for the observed adverse events. Furthermore, too few details are presented of the 29 cases to assess causality. The authors also found that the reporting rate of mRNA COVID-19 vaccine–induced sudden sensorineural hearing loss (SSNHL) cases remained below the estimated incidence of SSNHL cases in the general population. For these reasons the Rapporteur did not identify new and significant safety information from this study.

Leong et al.: In this cross-sectional study conducted in an otology clinic, the patients completed a questionnaire on the development of new otologic symptoms within 4 weeks of COVID-19 vaccination. The study presents 3 cases of idiopathic sudden sensorineural hearing loss after exposure to Moderna's COVID-19 vaccine. However, as no details of these cases are provided, causality cannot be assessed and therefore, the Rapporteur did not identify new and significant safety information from this study.

Cohen et al.: As this study investigates sudden sensorineural hearing loss among recipients of the BNT162b2 COVID-vaccine and not elasomeran, this study will not be commented further upon.

Fisher et al.: This study reports that 13 patients experienced idiopathic sudden sensorineural hearing loss within 30 days after COVID-19 vaccination. As no details of these cases are presented (including if any of the patients received elasomeran specifically), causality cannot be assessed. The Rapporteur did not identify new and significant safety information from this study.

Ekobena et al.: This study presents a case of diplacusis and right-sided hearing loss, along with flu-like symptoms (myalgia and malaise) and eventually vertigo after vaccination with elasomeran. The patient is described as healthy, but it is unclear whether the patient had risk factors for hearing loss. Similarly, it is not reported whether the hearing loss was sensorineural. Therefore, causality cannot be assessed. The main contribution of this study is the citation of other studies that present hypothetical mechanisms of action. One proposed mechanism of action is autoimmune processes involving autoreactive T-lymphocytes and a transient break of peripheral immune tolerance mediated through vaccine antigen molecular mimicry that could enhance isolated inflammation of the vestibulocochlear or facial nerve. Another assumption includes reactivation of latent viruses following immunisation.

With regard to the retrieved literature, the MAH concludes: *"Overall, the literature search results did not provide evidence of causal association between mRNA vaccines or mRNA-1273 and SNHL."*

Conclusion

The MAH concludes: *"Based on the cumulative review of available data as of 17 Jun 2023, the MAH*

considers there is insufficient evidence to consider Hearing Loss as a safety concern as this signal is considered refuted. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities, and the topic of SNHL will be added as an ad-hoc adverse event to study mRNA-1273-P920 (Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States). No changes to the product information or inclusion in to the RMP are required at this time."

The article by Ekobena et al. presents hypothetical mechanisms of action in which COVID-19 vaccination might result in otologic disorders such as sensorineural hearing loss – including autoreactive T-lymphocytes or reactivation of latent viruses. The PRAC Rapporteur cannot dismiss these hypotheses entirely, however, the data accumulated in this PSUR period in the form of spontaneous reports and literature articles are not deemed robust enough to support the existence of a causal association between sensorineural hearing loss and elasomeran exposure. The new data do not change the conclusion of the previous PSUSA procedure on this topic. No further actions beyond routine pharmacovigilance are considered warranted at present.

As this signal was closed and refuted by the MAH after the DLP of this PSUR, the MAH is reminded to present the signal as closed and refuted in the next PSUR in compliance with GVP module VII. However, further evaluation of the signal in the next PSUR is not necessary unless new and significant data emerge that trigger a new signal.

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Evaluation of risks

2.3.1.1. Important identified risks

2.3.1.1.1. Anaphylaxis (Safety concern in PBRER only)

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

Rapporteur assessment comment:

The MAH did not identify any new and significant safety information changing the characterisation of Anaphylaxis (safety concern in PSUR only), and no further action is considered warranted at this stage.

2.3.1.1.2. Myocarditis and Pericarditis

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

Table 16.8 Myocarditis and Pericarditis

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 240 ○ New and Significant Safety Information: None (0).
Background	An association between myocarditis and pericarditis and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events, particularly among adolescent and young-adult males within 7 days after Dose 2.
Methods	Cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [73] [74], and the CDC working case definition [75] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	*Myocarditis and Pericarditis Cases Involving Elasomeran* During the review period, the MAH received 263 cases (271 events) of myocarditis and pericarditis with all cases considered serious cases. There were 13 cases reporting a fatal outcome (See Appendix 12.17). There were 147 medically confirmed cases involving elasomeran. A total of 162 (61.6%) cases involved males and 94 cases (35.7%) involved females; 7 cases (2.7%) were missing gender information. The mean age of the patients was 42.1 (SD: 17.5), with a median 40.0 years (range 3.0 to 90.0 years); 44 cases were missing age data. Most events were reported after Dose 2 (89; 33.8%), followed by Dose 3 (74; 28.1%). There were 51 (19.4%) reports with an unknown dose number. Of the 212 cases with a known dose number, 65 cases (30.7%) were within 7 days of vaccination. During the reporting period, 101 events (38.4%) were reported as "Recovered/ Resolved/ 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

	in patients ≥18 years of age, 28 cases met Level 1; 19 cases met Level 2; 9 cases met Level 3; 185 cases met Level 4, and 12 cases met Level 5. Also, there was one report where the event of myocarditis was reported after Dose 2 with Comirnaty, hence case classification and causality assessment were not conducted. (See Appendix 12.17). According to the CDC working definition [75], 22 cases were classified as "Confirmed"; 34 cases were classified as "Probable"; 184 cases were classified as "Unassessable"; one case was classified as "Acute Pericarditis", and 13 cases were considered "Not a case" of myocarditis or pericarditis. (See Appendix 12.17). According to the WHO causality assessment, there were 3 cases considered "Probable"; 40 cases considered "Possible"; 166 cases considered "Unassessable", and 32 cases considered "Unlikely" related to the vaccine. Thirteen case reports were not assessed given that they were not considered cases of myocarditis or pericarditis, including the case that reported the events after dose 2 with another mRNA COVID-19 vaccine. (See Appendix 12.17). For the 13 cases reporting a fatal outcome, six were the same literature report from Korea, and they were all considered "Unassessable" according to the WHO causality assessment given that important information is missing from these reports including concomitant and treatment medications, medical histories, additional test conducted, among others. This study has several limitations that are included in Section 11. For the other seven fatal reports four were considered unassessable due to the lack of information, and 3 were considered unlikely related to the vaccine based on associated comorbidities that provide a more plausible explanation for the occurrence of the reported events. (See Appendix 12.17). *Subpopulation Analyses for cases involving elasomeran* • **Children (2 years to 5 years):** During this reporting period, 2 cases (2 events) were reported. Both reports were from Taiwan. Both were classified as Level 3 according to the Brighton Collaboration case definition, as Probable according to the CDC case definition, and as Possible according to the WHO causality assessment evaluation. One case [redacted] reported the events two days after Dose 1; and the second case [redacted] was two days after Dose 2 (See Appendix 12.17). • **Children (6 years to 11 years):** During this reporting period, there were no cases reported in this age group. • **Adolescents (12 years to 17 years):** During this reporting period, 7 cases (7 events) were reported. One case [redacted] was reported three days after Dose 1. Five reports were after Dose 2 with one case reporting a fatal outcome ([redacted]). The reported cause of death was liver transplant, sepsis and endocarditis. There was one case reported after Dose 3 [redacted]. See Appendix 12.17 for more information.

Myocarditis and Pericarditis Cases Involving elasomeran/imelasomeran

During the review period, the MAH received 49 cases (49 events) of myocarditis and pericarditis involving elasomeran/imelasomeran. All cases were considered serious, and 18 cases were medically confirmed. There were 2 cases with a fatal outcome. There were no gender differences in the number of cases reported involving males (24; 49.0%) compared to cases involving females (24; 49.0%); 1 case (2.0 %) was missing gender information. The mean age of the patients was 59.4 (SD: 18.9), with a median 64.5 years (range 24.0 to 95.0 years); 9 cases were missing age data.

During this reporting period, most events were reported after an unknown dose number (24; 49.0%). Of the 24 events with a known dose number, 14 events (56.0%) were within 7 days of dosing. There were 27 cases (55.1%) reporting an outcome of "Recovered/Resolved/ Recovering."

During the reporting period, there were no reports of myocarditis or pericarditis received for individuals <18 years of age.

According to the Brighton Collaboration case definition for myocarditis and pericarditis, 1 case met Level 1; 6 cases met Level 2; 2 cases met Level 3; 38 cases met Level 4, and 2 cases met Level 5.

According to the CDC working definition (Gargano 2021), 1 case was "Confirmed"; 7 were considered "Probable"; 39 were "Unassessable" cases, and 2 were considered "Not a case".

According to the WHO causality assessment, there were 4 cases considered "Possible"; 38 cases considered "Unassessable"; 5 cases considered "Unlikely", and 2 cases were not assessed as they were not considered a case of myocarditis or pericarditis.

For the 2 cases reporting a fatal outcome, according to the WHO causality assessment, one case was considered "Possible", and the other was "Unassessable" due to lack of information.

[redacted] (WWID: [redacted]) is a regulatory authority case concerning a 77-year-old male patient, with relevant medical history of transcatheter aortic valve implantation, who experienced pyrexia, dyspnoea, chest pain, chills, and tremor on the same day after receiving a dose of elasomeran/imelasomeran. CRP was elevated and there was pericardial effusion. Patient was tolerating symptoms well to start with and was treated with anti-inflammatories at full dose and colchicine. Patient developed sudden shortness of breath, tamponade and was admitted to the hospital where a pericardial drain was inserted, but patient continued to deteriorate and died. On an unknown date patient had an electrocardiogram which showed normal sinus rhythm, echocardiogram showed good LV function. Cardiac MRI, CT pulmonary angiogram, Jugular venous pressure, CT scan, and a Transcatheter aortic valve implantation (TAVI) were done with no results reported. This case was considered a Level 2 according to the Brighton Collaboration case definition; Probable according to the CDC case definition and was considered Possible according to WHO causality assessment.

[redacted] (WWID: [redacted]) is a regulatory authority case concerning a 95-year-old female patient, with relevant medical

	history of chronic kidney disease, atrial fibrillation, angina pectoris, hypertension, left ventricular hypertrophy, and thrombosis, who experienced myocarditis. The event occurred on the same day after a booster dose of elasomeran/imelasomeran. The report mentioned the patient became unwell approximately 12 after vaccination. Her respiratory rate was high (60), with "wet" cough and low O2 Saturations (60%). Paramedics attended and suspected a heart attack, then suspect COVID, but all tests were negative. Hospitalization was refused and the patient received "end of life pathway treatment" for symptom control. She died one week after vaccination. Reported cause of death was myocarditis. It is unknown if an autopsy was performed. No further information regarding the event and cause of death have been provided. Patient's age and mentioned medical history remains as confounders for the fatal outcome. According to the WHO causality assessment this report is unassessable due to the complete lack of information. *Myocarditis and Pericarditis in Pregnancy involving Elasomeran/imelasomeran*. There was one report of pericarditis reported following exposure to elasomeran/imelasomeran during pregnancy [redacted] This regulatory report involved a 33-year-old female patient, with medical history of pre-eclampsia and current condition of factor V Leiden mutation, who 5 weeks after a dose of elasomeran/imelasomeran vaccination which was first dose of COVID-19 vaccination schedule, experienced tachycardia, dyspnea, palpitations, fatigue, and dyspnea and was diagnosed with pericarditis and pulmonary embolism. In addition, maternal exposure during pregnancy was reported in the case since the patient was vaccinated with elasomeran/imelasomeran during pregnancy of approximately 7 weeks gestation period at exposure. Last menstrual period (LMP) was 26 Jul 2022 and expected delivery date was 02 May 2023. An echocardiogram confirmed pericarditis. Cardiac troponin level was normal, and a chest x-ray did not detect any abnormality; however, the ventilation/perfusion scan reported a diagnosis of pulmonary embolism. Treatment for the event included enoxaparin and aspirin and the patient was hospitalized for 1 week. The outcome of pregnancy is pending and unknown at the time of the report. Outcome for pericarditis was resolved and for pulmonary embolism was resolving. *Company assessment*: The prolonged TTO made this report unlikely related to vaccination and the concurrent medical history of myotonic dystrophy (type 2 myotonic dystrophy) and Factor V Leiden mutation, as well as diagnosis of COVID-19 at an unknown time are important confounders in this report. There is also a report of pre-eclampsia at an unknown time and with no additional information provided. This case was considered Level 2 according to the Brighton Collaboration case definition, a probable case according to the CDC case definition, and unlikely related to vaccination according to WHO causality assessment. *Myocarditis and Pericarditis Cases Involving Elasomeran/davesomeran*. During the review period, the MAH received 26 cases (26 events) of myocarditis and pericarditis involving elasomeran/imelasomeran, all of which were considered serious cases, and 23 cases were medically confirmed. There were no cases with a fatal outcome. A total of 18 (69.2%) cases involved males and 8 cases (30.8%) involved females. The mean age of the patients was 32.8 (SD: 21.3), with a median 30.0 years (range 11.0 to

	78.0 years); 4 cases were missing age data. During this reporting period, most cases were received after an unknown dose number (12; 46.2%). Of the 14 cases with a known dose number, 9 cases (64.3%) were within 7 days of vaccination. There were 14 cases (53.8%) reporting outcome as "Recovered/ Resolved/Recovering". According to the Brighton Collaboration case definition for myocarditis and pericarditis, 1 case met Level 1; 9 cases met Level 2; 1 case met Level 3; 14 cases met Level 4, and 1 case met Level 5. According to the CDC working definition [75], 1 case was "Confirmed"; 10 cases were "Probable"; 14 cases were "Unassessable", and 1 case was considered "Not a case". According to the WHO causality assessment, there were 11 cases considered "Possible"; 12 cases considered "Unassessable"; 2 cases considered "Unlikely", and 1 case was not assessed as it was not considered a case of myocarditis or pericarditis. *Subpopulation Analyses for cases involving elasomeran/davesomeran* • **Children (2 years to 5 years):** During this reporting period, there were no cases reported in this age group. • **Children (6 years to 11 years):** During this reporting period, there was one case reported in this age group [redacted] is a report received from [redacted] involving an 11-year-old male child, who received elasomeran/davesomeran as a 3rd dose and two days later experienced chest tightness, nausea, decreased appetite, and non-radiating chest pain located in midsternal area. He was the taken to ED and his vital signs were reported to be stable without tachycardia or dyspnea. His physical examination revealed no remarkable finding and the ECG showed normal sinus rhythm. Two-dimensional echocardiography and PET scan were normal. However, lab data showed elevated hs-Troponin-I (2.55) and hs-CRP (2.2). Treatment for the events included fluid supplement and management of accompanied symptoms. The outcome of the event was recovered. • **Adolescents (12 years to 17 years):** During this reporting period, there were eight cases reported in this age group. All cases, except one that had an unknown outcome, reported a "Recovered/ Resolved/Recovering" outcome. There were no fatal reports. There were seven cases after a 3rd or a 4th dose with elasomeran/davesomeran, and 1 case with a nunknown dose number. All reports were within 8 days after vaccination. All 8 reports were considered Level 2 according to the Brighton Collaboration case definition: "Probable" according to the CDC case definition, and "Possible" according to the WHO causality assessment. See Appendix 12.17 for additional information.
Discussion	A review of the data received during the reporting period of this PBRER, showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. There were seventy-five reports of myocarditis or pericarditis following exposure to any of the bivalent vaccines (elasomeran/imelasomeran or elasomeran/davesomeran) in this

	reporting period. To date, the clinical presentation of myocarditis after any of the bivalent vaccines (elasomeran/imelasomeran or elasomeran/davesomeran) does not differ from those with elasomeran, with cases presenting as mild cases, and recovering within a short time following standard treatment and rest. Analysis of safety data housed in the MAH's GSDB, as well as review of the literature, showed that most of the individuals who experienced an event of myocarditis/ pericarditis after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran 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 [76]. Please refer to Section 8 for results from the PASS study on the evaluation of myocarditis and pericarditis. Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers cases of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for these vaccines far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Review of the data also shown no difference in the observed safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran for children (6 months to 12 years of age), the adolescent population (12 years to 17 years of age), or in those individuals receiving a 3rd dose of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran when compared to >18 years old. Reporting rates are lower for children than for adolescents and young adults. Based on the analysis of all the safety data received during the reporting period of this PBRER, Moderna Tx, Inc. considers that cases of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Periodic data analysed during the reporting period of this PBRER, supported an update of the product information, indicating that most cases recover, and that some cases required intensive care support and fatal cases have been observed. Data presented in a study conducted by Le Vu et al., and included in PBRER 4, indicated that in a period of 28 days after the second dose, there were 1.88 (95% CI: 0.956, 2.804) extra cases of myocarditis in 16- to 24-year-old males per 10,000 compared to unexposed persons. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including PASS to further characterize them. Based on the cumulative review of safety data, including literature and case reports, the SmPC and the PIL have been updated in section 4.4 Special warnings and precautions indicating that most cases recover, some required intensive case support and fatal cases have been observed. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has provided a review for myocarditis and pericarditis for the latest review period from 18 December 2022 to 17 June 2023 comprising cases and literature.

Source of information

Literature: A focused literature search has been performed. Despite that 240 papers were retrieved, the MAH did not find any new and significant information in these.

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

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

Review of the Global Safety Database

For the review period 18 December 2022 to 17 June 2023, a total of 338 cases (346 events) of myocarditis and/or pericarditis were identified

Of these, 263 cases (271 events) were following vaccination with the monovalent elasomeran vaccine, 49 cases (49 events) following the bivalent vaccine elasomeran/imelasomeran, and 26 cases (26 events) were following the bivalent elasomeran/davesomeran vaccine. All cases were considered serious, and 15 had fatal outcome.

Age and gender distribution

Age was known in 219/263 cases (83.3%) following elasomeran, the age range was 3-90 years with a median age of 40 years. For cases following elasomeran/imelasomeran, age was known in 40/49 cases (81.6%), the age range was 24-95 years and with a median age of 64.5 years. For cases following elasomeran/davesomeran, age was known in 22/26 cases (84.6%), the age range was 11-78 years and with a median age of 30 years.

In total 18 cases were in children and adolescents, of these, 9 cases following elasomeran and 9 after elasomeran/davesomeran.

For elasomeran the gender distribution was 61.6% males, 35.7% females, and 2.7% cases of unreported gender. For elasomeran/imelasomeran cases for this review period were evenly distributed between genders with 49.0% males, 49.0% females, 2.0% of unreported gender. For elasomeran/davesomeran there were 69.2% males, 30.8% females.

Dose number and time to onset

Dose number was known for 250 cases (74.0%) of all 338 cases in the reporting period; overall most cases were reported following receipt of a 2nd or 3rd dose.

Among events of known dose number, in total 88 events (25.4% of the 346 events in the period) occurred within 7 days after vaccination (these were 65 events following elasomeran, 14 following elasomeran/imelasomeran, and 9 events following elasomeran/davesomeran).

Conclusion

The MAH has provided a review for the latest period from 18 December 2022 to 17 June 2023 comprising literature and cases from the global safety database. The information retrieved in this period does not

give rise to new concern regarding the risk for myocarditis and/or pericarditis following vaccination with elasomeran-containing vaccines. This is also in light of the update of the SmPC and PIL based on information presented in the previous PSUR (please, confer the AR section 2.4. Characterisation of risks for myocarditis and pericarditis).

Comments

Comment 1: It is noted, that the MAH in the discussion has written, 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". This statement could call for attention regarding the TTO of less than 7 days: According to the cumulated numbers for the entire period since 18 December 2020, dose number is unknown for approximately the half of all events of myocarditis and/or pericarditis, which means that a TTO of 7 days or less may be imprecise as the TTO may be different in the other half of the cases. This can be exemplified by the review period 18 December 2022 to 17 June 2023 presented in this PSUR, where 88 events are known to have TTO within 7 days; if reported as percentage of all events in the review period this equals 25.4% (88/346 events), but it reported as cases by known dose number it is 35.2% (88/250). The aim of this comment is solely to kindly call for attention towards that the TTO of 7 days may be rather imprecise, and to maintain an interest in clarifying TTO in upcoming reports, and lastly to remind that the updated SmPC and PIL describes the TTO for myocarditis and pericarditis following vaccination with elasomeran as: "These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days."

Comment 2: In the first paragraph under the heading "Myocarditis and Pericarditis Cases Involving Elasomeran/davesomeran" a wrong vaccine is written (elasomeran/imelasomeran is written instead of elasomeran/davesomeran). This typo should kindly be corrected.

2.3.1.2. Important potential risks

2.3.1.2.1. Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)

Based on the final assessment report for PBRER #4 (Procedure no.: EMEA/H/C/ Periodic Safety Update Single Assessment (PSUSA)/00010897/202212, received after the DLP of this PBRER) the final recommendation regarding removal of VAED including VAERD as an Important Potential Risk from the EU RMP, was endorsed, and that "based on the cumulative evidence, this risk is refuted and no longer considered important in the context of the RMP and the PBRER. It should be removed from the PBRER list of safety concerns and an evaluation of new information on this topic in future PBRERs is not expected".

Rapporteur assessment comment:

Based on the conclusions from the previous PSUSA procedure the Important potential risk "Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)" is no longer considered important and removed from the RMP and PSUR summary of safety concerns. This is endorsed.

2.3.1.2.2. IgA Nephropathy (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the known important potential risks of IgA Nephropathy for elasomeran, elasomeran/imelasomeran, and

elasomeran/davesomeran has not identified any additional clinically relevant new safety information for this topic. The characterization of this important risk as described in PSUR Section 16.4, remains valid. IgA Nephropathy is monitored in accordance with a request from a Health Authority.

PSUR Table 16.9 IgA Nephropathy

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: PSUR Appendix 13.4 ○ Retrieved: 140 ○ New and Significant Safety Information: None (0).
Background	Following review of PBRER#4, a Health Authority requested the following information on IgAN: • *The rapporteur concludes that reporting of IgANis rare and that the evidence is currently inconclusive regarding a possible causal role of vaccination with elasomeran or bivalent. Thus, the MAH should maintain IgAN as an important potential risk in the future PBRERs. In the next PBRER, it is therefore expected that the MAH will present new information on IgA nephropathy and risk characterization in PBRER section 16.3 and 16.4, respectively.* • *The vaccine type is now specified (in the Ota paper) the MAH is requested to confirm the origin of these 3 cases ([redacted] and [redacted]) and to reclassify their causality status accordingly. This request should be addressed in the next PBRER.*
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 utilizing the WHO-UMC standard causality categories and criteria.

Results	Refer to Appendix 12.18 for information about the medical topic. During the review period, the MAH received 29 reports (36 events) that had PTs within the HLT of Glomerulonephritis and Nephrotic Syndrome. There were 25 medically confirmed reports involving elasomeran or bivalent. The 29 reports (whether or not the PT IgA Nephropathy was coded) were medically reviewed PSUR Appendix 12.18. Out of the 29 reports, there were 8 cases, all serious, that involved IgA nephropathy; there were no cases reporting a fatal outcome. Of the 8 cases, 7 involved elasomeran, and one (1) case involved elasomeran/davesomeran. Out of the 8 cases involving IgA Nephropathy, five (5) cases were new onset (de novo) IgA nephropathy, and two (2) cases were considered IgA nephropathy flares because they were reported to have exacerbation of IgA nephropathy that had been diagnosed prior to elasomeran or bivalent vaccination. One (1) case report did not provide information allowing determination of de novo vs flare. The majority of cases involved females (6 cases; 75.0%) compared to males (2 cases, 25.0 %). The mean age was 49.4 years (SD: 21.3) and median age was 38.5 years (range: 29.0 to 80.0 years). Time to onset ranged from day 0 to 248, with no common pattern observed regarding TTO. **Health Authority Requests** A Health Authority requested that the origin of three previously reported cases with unknown vaccine type be reviewed because an article reporting those cases was subsequently published that identified the vaccines involved [77]. The Moderna COVID-19 vaccine was reported for the case [redacted] PSUR Appendix 12.18). The other two cases reported in the article involved Pfizer vaccine ([redacted] and [redacted]) and are now classified as invalid in the MAH's GSDB.
Discussion	During the reporting period in the MAH's GSDB, there were 8 cases of IgA nephropathy that were identified through medical review: 7 cases involved elasomeran, no cases involved elasomeran/imelasomeran and one case involved elasomeran/davesomeran. Of the 8 cases of IgA nephropathy, five cases were de novo and two cases were flares, one case had no information on de novo vs flare. No new patterns were observed with regard to IgAN-related data for the three vaccines noted above. Renal patients are at increased risk of serious illness and death due to COVID- 19 disease; thus, vaccination is of great benefit to them. Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers cases of IgA nephropathy to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for elasomeran or bivalents far outweigh any possible vaccine-associated risks, including the risks of IgA nephropathy.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Mention of a literature article by Ma and Xu [78] was requested by a Health Authority. This article began with a summary of cases of new onset IgAN published in the medical literature before 10 Jul 2022; analyses based on these cases may be susceptible to publication bias. The authors also made general reference to the "multi-hit hypothesis of IgA nephropathy" and to the mucosal origin of hypogalactosylated IgA1 in IgA nephropathy. Also, the authors proposed three hypotheses for the possible 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 GMCSF. The authors acknowledged that they were unable to infer a causal relationship between vaccine and IgAN and that the mechanisms that they proposed for the vaccine-IgAN association are not proven. Based on the analysis of all the safety data received during the reporting period, and taking the above mentioned publication into consideration and risk characterization, the MAH considers that cases included under the medical topic of IgA Nephropathy, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern and the information provided does not support evidence of causal association between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and IgA nephropathy. The MAH will continue to monitor events for IgA Nephropathy using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

During the reporting period there were 8 cases of IgA nephropathy identified through medical review by the MAH: 7 cases involved elasomeran, no cases involved elasomeran/imelasomeran and one case involved elasomeran/davesomeran. Of the 8 cases of IgA nephropathy, five cases were de novo and two cases were flares (missing data on 1 case). According to the medical review presented in PSUR Appendix 12.18, 4 of these were assessed as WHO-UMC "Possible", while none were considered of "Probable" or "Certain" causality. The remaining 4 were considered unlikely (2) or unassessable (2).

This is endorsed. From MAH's evaluation of cases reported with the PT "IgA nephropathy" presented in PSUR appendix 12.18a, the Rapporteur did not identify new and significant safety information.

Concerning the Ma and Xu publication: See assessment comment above and in section 2.4.

Requests from previous PSUSA (no. 4) procedure

ITEM 1: IgA Nephropathy (IgAN)

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

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

MAH Response: The MAH acknowledges that it will maintain IgAN as an important potential risk in the future PSURs and that it will present new information on IgA nephropathy and risk characterisation in PSUR sections 16.3 and 16.4, respectively.

The next PSUR, with data lock point 17 June 2023, in the risk characterization (section 16.4) will include new information from the article: Ma Y, Xu G. New-onset IgA nephropathy following COVID-19

vaccination. QJM. 2023 Feb 14;116(1):26-39. doi: 10.1093/qjmed/hcac185. In addition, a summary of this article follows.

Ma and Xu searched literature published before 10 July 2022 and identified 32 articles related to COVID-19 vaccination and IgA nephropathy. These articles reported on a total of 48 patients: 31 with new onset disease and 17 with relapse. Ten patient's IgA nephropathy had onset after the first dose (time to onset median 10 days [range 1-61]; and 38 patients had onset after second dose (time to onset median 2 days [immediate-79.]) Additional clinical data from these cases were also summarized and tabulated; however, it should be noted that inferences drawn from analyses of these cases, all selected from the literature, may be susceptible to publication bias.

With reference to the "multi-hit hypothesis of IgA nephropathy and to the mucosal origin of hypogalactosylated IgA1 in IgA nephropathy", the authors proposed three hypotheses for the causation of IgA nephropathy by Covid-19 vaccination: 1) production of excess antiglycan antibodies; 2) an increase in pathogenic IgA production; and 3) cytokine storm with speculated sharp increases of inflammatory factors such as IL-6, IL-10 and GM-CSF.

The authors acknowledged multiple limitations in their report: First, 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. Second, there may be many unreported vaccine related IgAN cases, and epidemiological investigations are lacking, so they could not determine the true incidence of IgAN after vaccination. Third, the mechanisms that they proposed for the vaccine-IgAN association combine hypotheses from case reports and the literature and are not proven. Fourth, due to the small sample size, there may be errors in their statistical analyses.

Rapporteur assessment comment:

The MAH has confirmed the request to maintain IgAN as an important potential risk in the future PSURs and that it will present new information on IgA nephropathy and risk characterisation in PSUR sections 16.3 and 16.4, respectively. This is acknowledged.

Further, the MAH has commented on the Ma and Xu publication: New-onset IgA nephropathy following COVID-19 vaccination. QJM. 2023 Feb 14;116(1):26-39. This is acknowledged. Although new hypotheses on the causation of IgA nephropathy by Covid-19 vaccination are presented, the exact etiology and pathophysiology of IgA nephropathy, also in this context, remain unknown.

The PRAC Rapporteur notes that the publication by Ma and Xu also lists 15 literature case reports of IgA nephropathy following vaccination with Moderna's COVID-19 vaccine. These literature case reports have been published before 10th July 2022 (before the reporting period under review in this PSUSA) and most of these cases also appear in Eudravigilance and they should therefore already have been evaluated by the MAH. However, the PRAC Rapporteur notes that on these cases the MAH simply states: "[…] *it should be noted that inferences drawn from analyses of these cases, all selected from the literature, may be susceptible to publication bias.*" **As it is unclear whether the MAH has previously evaluated these cases or not, within this procedure the MAH is requested to clarify whether the literature case reports presented in the article by Ma and Xu have been included in previous evaluations of IgA nephropathy. If any of these cases have not previously been evaluated, the MAH should present these cases and comment on them within this procedure.**

ITEM 2: IgA Nephropathy (IgAN)

B. According to the line listing of cases in the Appendix 11.17b to the PSUR, cases number [redacted], [redacted] and [redacted] are classified as WHO-UMC Causality Conditional

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

MAH Response:

The MAH has noted the "Ota paper," in which three cases involving IgA nephropathy are reported. Case 2 in that paper involved "Moderna mRNA-1273;" in contrast, Case 1 and Case 3 involved "Pfizer BNT162b2." Case 2 in the MAH's global safety database (GSDB) is [redacted] this case has been reclassified with an updated causality assessment. Justifications are presented below and also are reported with the other cases in the appendix to PSUR #5.

[redacted]: A 22-year-old woman, with a history of tonsillitis when she was in [redacted] but had never mentioned an abnormality in her urine, received her second dose (same as the first) of mRNA-1273. She had a fever of 39 °C on the day of second vaccination and had gross hematuria 2 days later with urine occult blood 3 + , urine protein 3 + . Ten days after vaccination, the same results were observed. One month and three days after the last vaccination, urinalysis showed U-RBC 10–19/HPF and UPCR 0.04 g/gCr. Blood examination showed Cre 0.67 mg/dL, eGFR91.5 mL/min/1.73 m 2 , cystatin C 0.76 mg/L. Urinalysis showed UPCR 0.04 g/gCr, U-RBC 10–19/HPF, 24 h CCr132.0 mL/min. Six weeks after the onset of gross hematuria, renal biopsy was performed. Light microscopy (LM) revealed 54 glomeruli, with no sclerotic glomeruli. There were mild mesangial cell proliferation and mesangial matrix expansion. The adhesion of glomerular capillary to Bowman's capsule was observed in a glomerulus. There was no evidence of interstitial fibrosis or tubular atrophy.

Immunofluorescence (IF) revealed IgA and C3 mesangial deposition. In electron microscopy (EM), electron-dense deposits (EDDs) were observed in the mesangial area. The subendothelial space was slightly enlarged, and endothelial cells swelled. By the time the renal biopsy was performed, the patient's renal function had already recovered. The renal biopsy revealed IgA nephropathy with an Oxford MEST-C classification of M0S0E0T0C0, the least severe score, and no active lesions. Outpatient care without steroid therapy was decided.

Company assessment: This patient, as is common in a substantial minority of the general population, likely had deposition of IgA in the area of her glomeruli. Her fever on the day of dose 2 is consistent with reactogenicity. It is probable that inflammation from vaccination provoked a time-limited mild clinical expression of IgA nephropathy without acute kidney injury, in a previously subclinical case; this adverse event resolved without treatment. The authors apparently sought medical history and risk factors, noting only the history of tonsillitis. Based on the WHO-UMC causality assessment, this case is considered probable.

Rapporteur assessment comment:

The update on the three cases of IgAN in the "Ota paper" is acknowledged. Only 1 of these cases (MOD-2022-609565) involved elasomeran. The MAH's re-evaluation of this case results in WHO-UMC causality classification "Probable". The Rapporteur notes that the patient has an earlier medical history of tonsillitis and that according to UpToDate "patients with IgA nephropathy often present after an upper respiratory infection". The case narrative does not disclose whether the patient had a recent/ongoing upper respiratory infection or symptoms of this just prior to the presentation of the IgA nephropathy. The observed fever could be due to vaccination, as it is a known adverse reaction, but it is noted that tonsillitis is also a common cause of fever. As the patient has a medical history of tonsillitis – a risk factor for IgA nephropathy - and as it cannot be determined whether the patient had a recent upper respiratory infection, the PRAC Rapporteur evaluates the case as "possible" instead of "probable".

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 elasomeran-containing vaccines before and during pregnancy has not identified any additional clinically relevant new safety information for this topic. The characterization of these important risks as described in the approved RMP as of the DLP of this PBRER and in PSUR Section 16.4, below, remains valid.

Table 16.10 Use in pregnancy

Source of New Information	o Moderna GSDB o Literature Sources o Search Criteria Applied: PSUR Appendix 13.4 o Retrieved: 519 o New and Significant Safety Information: None (0).
Background	Use of elasomeran-containing vaccines before and during pregnancy is an area of missing information in the RMP; no CTs were conducted among pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Since elasomeran-containing vaccines 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 elasomeran-containing vaccines 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 12.19 for Methods of Evaluation
Results	Refer to PSUR Appendix 12.19 for additional information. **Overview of Pregnancy Cases Who Received Elasomeran** During the review period, the MAH received 206 pregnancy cases (802 events) with 64 serious cases (210 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. Five (5) cases reported a fatal outcome, and 69 cases were medically confirmed. A slightly lower proportion (31.1%) of cases during the review period were reported as "serious" compared to the cumulative period (35.4%). Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" in addition to known reactogenicity events and are reported as "serious" cases; See below in "Serious and Fatal Cases and Serious Pregnancy-related Events Elasomeran." Serious cases should be interpreted with caution as many do not meet the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding all events as serious in a given serious case.

	The majority (73.0%) of pregnancy-specific cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been seen in previous review periods. The most frequently reported PTs during the reporting period were reactogenicity events, consistent with the product safety profile and is similar between the reporting period and the cumulative period. During the review period, there were no pregnancy cases reporting events of myocarditis and/or pericarditis after receipt of elasomeran. *Pregnancy-specific Events – Elasomeran)* During the review period, of the 206 pregnancy cases received by the MAH, only 137 pregnancy cases reported a pregnancy-specific adverse event/outcome in individuals who received or had a medical history of maternal exposure to elasomeran. (Please note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ). These 137 cases reported 154 pregnancy-specific events with 49 serious cases (46 serious events). One case reported a fatal outcome, and 33 cases were medically confirmed. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome, "Abortion spontaneous" remains the most frequently reported adverse pregnancy event/outcome for both the reporting and cumulative periods. (Refer to Spontaneous abortions, Stillbirths, and Foetal Deaths evaluations added below). A summary table of all pregnancy outcomes, stratified by timing of exposure as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/313666/2005)" is presented in PSUR Appendix 12.19. *Serious Pregnancy-specific Events and Fatal Cases– Elasomeran* During the review period, of the 64 reported serious pregnancy cases, when restricted to pregnancy cases reporting only pregnancy-specific events, only 32 serious cases were identified as including serious pregnancy-specific events (34 events). One case reported a fatal outcome, and 15 cases were medically confirmed. Review of the serious pregnancy-specific events during this reporting period did not identify any new safety concerns. These cases reflect obstetric events observed in temporal association with elasomeran administration. Many of these cases had limited information about past medical and obstetric history, gestational age at time of vaccination, or onset of AE, diagnostics, treatment, and outcome. Where data were available, confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy [including advanced maternal a ge, concomitant medications, comorbidities (such as hypothyroidism, diabetes) and previous relevant obstetric history including fetal loss] were present. *Fatal Pregnancy Cases– Elasomeran*

	During the review period, 5 pregnancy cases were coded as fatal in individuals who received or had a medical history of maternal exposure to elasomeran. Case [redacted] concerns a neonatal death which was previously reported during the PBRER #3 review interval but had updates regarding PTs added during this reporting interval. These updates did not affect original causality assessment. Case [redacted] appears to be misclassified as a pregnancy case given the patient's age (48 years) and that there was no indication that this individual was either pregnant or lactating. The remaining 3 cases describe 2 maternal deaths ([redacted] and [redacted]) and 1 neonatal death ([redacted]). The 2 cases of maternal death are summarized below: [redacted]: This regulatory authority case concerns a 33-year-old female who about 5 months after receipt of an unspecified dose of elasomeran experienced nasal sinus cancer ("a fast-growing SNUC tumour stage 4 was detected"). A past medical history of "pregnancy (6 premature month)" was reported; outcome of the pregnancy was unknown. Patient died about 9 months after the diagnosis of cancer and the reported cause of death was listed as sinonasal undifferentiated carcinoma. It is unknown if an autopsy was performed. Causality is "Unassessable" given the limited data available regarding LMP, obstetrical history, concomitant medications, COVID-19 vaccination history, clinical course, investigations and treatment. [redacted]: This regulatory authority case was reported by another health care professional concerning a 30-year-old female with history of complete right bundle branch block, ventricular extrasystoles, and mitral valve billowing with regurgitation, who 404 days (approximately 13 months) after a dose of elasomeran, reported as third dose of her COVID-19 immunization schedule, experienced sudden death. The patient previously received two doses of Tozinameran COVID-19 vaccine. The report stated that the patient was pregnant at the time of death (gestation week was not reported). Reportedly, she was asymptomatic the morning of the event. Approximately 6 months after vaccination with elasomeran, she had a cardiological control performed with normal and stable results compared to the previous check-up (one year prior). The report revealed normal sized cardiac cavities, left ventricular ejection fraction of 61%, global longitudinal strain of -21%, normal diastology, slight billowing of the mitral valve with minimal insufficiency. The resting ECG showed a well-known block of complete right branch; the long-term ECG reported monomorphic isolated ventricular extrasystoles with a 6.1% load. The cause of death was not reported. An autopsy was performed, although the report was not provided. No further information has been disclosed. Causality is "Unlikely" given long latency (13 months) and her underlying cardiac disease provides an alternate plausible explanation to the event. The case reported as neonatal death with prenatal exposure to elasomeran is summarized below: [redacted]: This regulatory authority case reported by a consumer concerns an 18-day-old female neonate who 18 days after birth experienced brain neoplasm and congenital hydrocephalus and died 3

	days later. The cause of death was reported as neonatal respiratory failure and hydrocephaly obstructive; no autopsy was performed. It is reported that the diagnosis of brain tumour and congenital hydrocephalus was made 235 days after her mother received a third COVID- 19 vaccination with first dose of elasomeran. It is unclear if the mother received elasomeran during pregnancy given no LMP, estimated due date, or gestational age at delivery was provided. Based on the timing of vaccination, it is possible that the mother received the vaccination prior to conception if the neonate had a preterm birth. Causality is "Unassessable" given extremely limited data available to determine if elasomeran was given during pregnancy and temporal association, fetal/infant diagnostic evaluation, and treatment. No safety concerns were identified from the review of serious and fatal cases received during the reporting period for the pregnancy subpopulation. *Fetal Deaths– Elasomeran* The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth". Fetal 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 United States [79]. *Spontaneous and Missed Abortions – Elasomeran* During the review period, 10 serious pregnancy cases with a medical history of maternal exposure to elasomeran reported spontaneous abortion with 11 serious events. Of the 10 cases, 3 cases were medically confirmed, and no cases were coded as fatal. The mean age of the cases was 35.6 years (SD: 4.5) and median age of 35.5 years (range 26-41 years). Of the cases with available data on the dose number prior to the event, there were more events reported after Dose 2 (27.3%) than Dose 1 (18.2%), and Dose 3 (9.1%). This must be interpreted with caution as one does not know how many pregnant women have received one versus two versus three or more doses; and, of note, 45.5% of events are missing dose information. Although the data are limited, when TTO and dose number were known, events most frequently (50.0%) occurred 30 or more days after vaccination. The median TTO was 82.0 days (range 1-435); there was no unusual clustering by dose or TTO. *Stillbirth – Elasomeran)* Stillbirth has varying global definitions based on GA and fetal weight. For the purposes of this PBRER, and as described above, the MAH applied a definition of stillbirth as fetal death after 20 weeks gestational age [79]. Congenital anomalies, placental dysfunction associated with fetal growth restriction, and maternal medical diseases and obstetric complications (such as pre-eclampsia, chorioamnionitis, and infections such as group B Streptococcus and cytomegalovirus) are common causes of stillbirth. Advanced maternal age (over 40 years) has been associated with an increased risk of stillbirth as well. Evaluation of spontaneous reports are limited due to a la ck 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 reporting period, 4 pregnancy cases that reported stillbirth were identified through medical review of cases that were coded as "fetal death" and/or "stillbirth." These cases are summarized below: [redacted]): This spontaneous retrospective pregnancy case reported by a consumer described a female patient of an unknown age, who received an unspecified dose of elasomeran at an unknown timing and relation to pregnancy. It was reported that the outcome of the pregnancy was a stillbirth, and the cause of stillbirth was not provided. Causality is "Unassessable" given the limited data available regarding LMP, estimated due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinica l course. [redacted]: This regulatory authority case reported by another health care professional concerns a 16-year-old female who received a third dose of elasomeran at an unknown time and relation to pregnancy. It was reported that a stillbirth occurred 3 months and 14 days following vaccination. The cause of stillbirth and whether an autopsy was performed was not provided. Causality is "Unassessable" given the limited data ava ila ble regarding LMP, estimated due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinica l course. [redacted]: This regulatory authority case reported by a consumer concerns a 36-year-old female, who received an unspecified dose of elasomeran at an unknown time and relation to pregnancy. It was reported that pregnancy ended in a stillbirth at 20 weeks gestational age (seven months after vaccination). The cause of stillbirth and whether an autopsy was performed was not provided. Causality is "Unassessable" given the limited data available regarding LMP, estima ted due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinical course. [redacted]: This regulatory authority case reported by a consumer concerns a 36-year-old female, with previous vaccination history with Comirnaty (two doses), and who experienced a stillbirth at an unknown GA, 32 days after receipt of the first dose of Pfizer-BioNTech vaccine. She received a second dose of Pfizer-BioNTech vaccine 20 days after stillbirth and a first dose of elasomeran as the third dose of her COVID-19 immunization schedules, 192 days after the stillbirth. The cause of the stillbirth and whether an autopsy was performed was not provided. Causality is 'Unlikely" given that there is no temporal association with receipt of elasomeran as the stillbirth occurred prior to vaccination. Based on medical review of the "stillbirth" reported cases many reports had limited data and lacked crucial information to make a robust case and causality assessment. In addition, it is well known that, typically, up to 60% of stillbirths cannot be attributed to an identifiable fetal, placental, maternal, or obstetric etiology due to lack of sufficient information or because the cause cannot be determined at the current level of diagnostic ability [79]. It was noted that for many of the pregnancy reports coded as "prospective," there was no evidence in the report to support this classification; thus, this

	classification must be interpreted with caution as there is a high likelihood of coding errors. Overall, cases of stillbirth and spontaneous abortion received during the reporting period were similar to the cumulative period and no safety concerns were identified. A summary table of all pregnancy outcomes classified as retrospective and prospective and stratified by timing of exposure, as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/ 313666/2005)", is presented. *Congenital Anomaly– Elasomeran* During the reporting period, 15 pregnancy cases that reported a PT from the Congenital, familial and genetic disorder SOC were identified. After medical review, no reporting patterns and no safety concerns were identified. Of the 15 pregnancy cases, 5 cases occurred among foetuses and neonates from pregnancies exposed to elasomeran and 10 cases were determined to be "non-pregnancy cases" as they either represented medical history miscoded as an AE, or a pre-existing congenital anomaly detected in a non- pregnant person. All 5 pregnancy cases reported live birth at delivery. One case ([redacted] reported a fatal outcome (neonate died 3 days after birth) (See Fatal Pregnancy Cases-elasomeran section), 2 cases ([redacted] and [redacted] reported outcome as "not recovered/not resolved", and 2 cases [redacted] and [redacted]) reported outcome as "recovered/resolved. Further review of the congenital anomalies, considering the GA at vaccination and fetal development, contributed to the assessment of causality. Many cases lacked GA at the time of vaccination and thus causality was "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**: *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 (14 total events; 10 serious events) among children under 6 years of age with a medical history of maternal exposure to elasomeran during pregnancy. Two cases reported fatal outcomes and 2 cases were medically confirmed. Both fatal cases ([redacted] and [redacted]) were discussed in the Fatal Pregnancy Cases–elasomeran section above. The 4 remaining serious cases are summarized below: [redacted]: This regulatory authority case reported by a consumer concerning a [redacted]-old infant with unknown gender, who experienced talipes (clubfoot). Reportedly, the mother received elasomeran reported as third dose of her COVID-19

	immunization schedule, around the time of pregnancy conception. The foetus was diagnosed with bilateral clubfoot at 18 weeks of gestation. The outcome of the event of talipes was reported as "recovered with sequelae". Causality is "Unassessable" given the extremely limited available data regarding maternal medical, family and obstetric history, complete results of the fetal ultra sound at 18 weeks, diagnostic evaluation including genetic testing of the fetus, and clinical course. [redacted]: This regulatory authority case, reported by a consumer, concerns a full-term newborn ("0-year-old") male patient who experienced "heart disease congenital." His mother (age not provided) was vaccinated with an unspecified dose of elasomeran at approximately 3 weeks gestation (around the time of conception) and he was diagnosed with persistence of the left superior vena cava with coronary sinus dilation, accentuated trabeculature in the septum and wall of the left ventricle at an unknown time after birth at approximately 41 weeks gestation. At the time of the report, the outcome was reported as "not resolved". His mother had received two doses of Vaxzevria vaccine prior to pregnancy with no reported AEs, and last dose was eight months prior to the unspecified dose of elasomeran. Causality is "Unassessable" given the limited information regarding maternal obstetric and medical history, concomitant medications, infant diagnostic evaluation and results, as well as clinical course. [redacted]: This regulatory case reported by a physician concerns an [redacted]-old female infant with no medical history reported, who experienced "epilepsy" 314 days after maternal exposure to the third dose of elasomeran. She was exposed to the second dose of elasomeran vaccine during first trimester of pregnancy and to third dose during second trimester. The delivery occurred on an unknown date and reported as abnormal pregnancy outcome ("Term birth w Cong Anomaly"). On unknown dates, electroencephalogram, magnetic resonance imaging- head, and urine analysis with urine metabolic screening all showed normal results. Causality is "Unassessable" given the limited information regarding maternal obstetric and medical history, concomitant medications, infant diagnostic evaluation and results, as well as clinical course. [redacted]: This regulatory authority case reported by a physician concerns a [redacted]-old female neonate who experienced "cardiac aneurysm" and "atrial septal defect" following an unspecified dose of elasomeran at approximately 3 weeks gestational age. During the first trimester, the neonate was also exposed to progesterone, which was reported as a co-suspect drug. The birth was via vaginal delivery with a ventouse extraction due to a pathological continuous cardiotocography at 35+2 weeks gestational age. Delivery date was unknown, and outcome was reported as pre-term birth with congenital anomaly. Six weeks after birth, an echocardiogram showed an atrial septal aneurysm with two small ostium secundum defects (4-5 mm and 2 mm). The heart defects were still present after 1 year and 8 weeks of life. No further relevant information was disclosed. Causality is "Unassessable" given the limited information regarding obstetric

	history and diagnostic evaluation including genetic testing of the foetus. In addition, progesterone was considered a co-suspect drug. No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period. *Pregnancy Cases Among Adolescents (12-17 Years of Age – Elasomeran)* During the review period, the MAH received 2 serious medically confirmed pregnancy cases (2 serious events) among adolescents (12-17 years of age) who received elasomeran. Neither case reported a fatal outcome. These cases are summarized below: [redacted]: This regulatory authority case reported by another health care professional concerns a 16-year-old female who received a third dose of elasomeran at an unknown time and relation to pregnancy. It was reported that a stillbirth occurred 3 months and 14 days following vaccination. The cause of stillbirth and whether an autopsy was performed was not provided. Causality is "Unassessable" given the limited data available regarding LMP, estimated due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinical course. [redacted]): This is a regulatory case concerning a 17-year-old female who experienced "amniotic cavity infection" 153 days after receiving the Dose 2 of elasomeran. Causality is "Unassessable" as no additional information regarding maternal obstetric and medical history, concomitant medications, infant diagnostic evaluation and results, as well as clinical course was provided. No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period. *Pregnancy Cases Who Received Three or More Doses of Elasomeran)* During the review period, the MAH received 40 cases (104 events) with 18 serious cases (31 serious events) among individuals who received or were maternally exposed to a third or more doses of elasomeran. Two cases reported a fatal outcome, and 18 cases were medically confirmed. During the review period, after excluding PTs that do not indicate an adverse pregnancy- specific event/outcome, similar to the events reported by pregnancy cases for all doses, the majority of the most frequently reported PTs represent expected reactogenicity for elasomeran. The most frequently reported PT indicating an adverse pregnancy-specific event/outcome was "Premature baby" (3 events). The types and distribution of the most frequently reported events during this reporting period is similar to the cumulative period. The 2 fatal cases ([redacted] and [redacted]) were summarized in the *Fatal Pregnancy Cases-elasomeran* section above. Overall, based on current available information, regardless of the type of COVID-19 vaccines used for the primary series, no unusual patterns or pregnancy-specific safety concerns were identified.

Pregnancy Cases After Receiving a Booster Dose with Elasomeran/imelasomeran

During the review period, the MAH received 25 pregnancy cases (89 events) with 17 serious cases (53 serious events) among individuals who received or were maternally exposed to a booster dose of elasomeran/imelasomeran. One case reported a fatal outcome, and 3 cases were medically confirmed.

The most frequently reported clinical events/PTs represent expected reactogenicity for elasomeran. Of the 89 events reported, 29 were pregnancy-specific events. The only PT's indicating a pregnancy-specific adverse event/outcome were "Abortion spontaneous" (4 events), "Pancreas divisum" (1 event), "Poor feeding infant" (1 event), "Premature separation of placenta" (1 event), and "Stillbirth" (1 event). Events of "Spontaneous abortion," "Premature separation of placenta," and "Stillbirth," while previously reported with elasomeran exposure, mark the first reports of fetal death or stillbirth associated with elasomeran/imelasomeran exposure.

During the review period, the MAH received 1 pregnancy case [redacted] reporting events of pericarditis after receipt of elasomeran/imela someran vaccine. This was the first pregnancy case reporting events of myocarditis and/or pericarditis following a booster dose with an elasomeran bivalent vaccine. This case is further discussed in the PSUR Section 16.3.1.2.

Serious Pregnancy-specific Events and Fatal Cases– Elasomeran/Imelasomeran

During the review period, 17 serious pregnancy cases were received. Of those 17 serious cases, only 7 cases reported pregnancy-specific events. One case reported a fatal outcome, and no cases were medically confirmed. The fatal case describes events of stillbirth and is summarized in the *Fatal Pregnancy Cases-Elasomeran/Imelasomeran* section below.

Review of the serious pregnancy-specific events during this reporting period did not identify any new safety concerns. These cases reflect similar obstetric events observed in temporal association with elasomeran vaccination. Many of these cases had limited information about past medical and obstetric history, GA at time of vaccination, or onset of AE, diagnostics, treatment, and outcome.

Fatal Pregnancy Cases– Elasomeran/Imelasomeran

During the review period, the MAH received 1 case reporting a fatal outcome following maternal exposure to a booster dose of elasomeran/imelasomeran. This was the first fatal case reported following vaccination with a booster dose of an elasomeran bivalent vaccine. This case concerns a stillbirth and was described in 2 cases as a mother/neonate dyad. This case is summarized below:

[redacted]: This is a regulatory case concerning a [redacted] female, who experienced premature separation of placenta (placenta abruption) and delivery of a female infant at 28 weeks, a day after receipt of the fourth COVID-19 vaccine with elasomeran/imelasomeran. The infant died 4 days later, and the reported cause of death was "abruptio placentae." It is unknown if an autopsy was performed. Maternal obstetrical/medical history reported included history of early miscarriage and laboratory confirmed SARS-COV-2 infection at unknown date. This case is part

	of a mother/neonate dyad and linked to Case [redacted] (which was reported earlier in the review period). Causality with regard to elasomeran/imelasomeran for placenta abruption and infant death is "Unassessable" given missing information on maternal concomitant medication, social history, events that occurred around vaccination that could cause or be risk factors for abruption, maternal and infant diagnostic evaluation, treatment and clinical course. *Fetal Deaths – Elasomeran/Imelasomeran* *Spontaneous and Missed Abortions – Elasomeran/imelasomeran* During the review period, 4 serious pregnancy cases reported spontaneous abortion. None of the 4 cases were medically confirmed or coded with a maternal fatal outcome. All 4 events reportedly occurred following vaccination during the first trimester. The mean age of the cases is 34.0 years (SD: 2.9), median age 34.5 years (range: 30-37 years). Although the data are limited, when TTO was known, events most frequently (75.0%) occurred within 2 days of vaccination. The median TTO was 1.5 days (range: 1- 4). These were the first cases received by the MAH that reported events of spontaneous abortion in relationship with elasomeran/imelasomeran. *Stillbirth – Elasomeran/imelasomeran)* During the review period, the MAH received 1 case reporting stillbirth following maternal exposure to elasomeran/imelasomeran. This case ([redacted]) is described above in the *Fatal Pregnancy Cases-elasomeran/imelasomeran section.* *Congenital Anomaly– Elasomeran/Imelasomeran* During the reporting period, the MAH received 2 pregnancy cases that either reported a PT from the Congenital, familial and genetic disorder SOC or were identified after medical review, no patterns and no safety concerns were identified. Case [redacted] This is a regulatory case concerning a 43-year-old female who experienced "Pancreas divisum" 1 day after receiving a booster dose of elasomeran/imelasomeran. This case appears to be misclassified as a pregnancy case due to the woman's age (43 years) and that there was no indication in the report that she was either pregnant or lactating. [redacted]: (This case was found during medical review) This regulatory authority case reported by a consumer concerns a 1-year-old, female patient, who experienced atrioventricular block (with a ratio of 2:1 heart block), COVID-19, and fetal exposure during pregnancy. It was also reported that the infant had a mild infection which was treated at home and experienced episodic severe pain, rash, cough, congestion, fever, diarrhea, and vomiting. Temporal relation of the events to elasomeran/imelasomeran administration is unclear as vaccination date as well as the date of diagnosis of atrioventricular block were not provided. Reportedly, the infant and her mother both were exposed to the medicine in the

	third trimester (29-40 weeks). It was also reported that the mother had received Comirnaty at an unknown timing and relation to the pregnancy. Details of previous pregnancies were reported as Low PAPP-A and details of scans or investigations were reported as normal antenatal screening. It is reported that the infant "had developmental milestones". The events were reported to be "not resolved". Causality is "Unassessable" because of the limited available data regarding the date of receipt elasomeran/imelasomeran, the date of atrioventricular block, estimated due date or gestational age of delivery, obstetric history, maternal and infant medical history, diagnostic evaluation of the atrioventricular block and clinical course. Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified. **Pregnancy Cases After Receiving a Booster Dose with Elasomeran/Davesomeran** During the review period, the MAH received 14 pregnancy cases (36 events) with 1 serious case among individuals who received a booster dose of elasomeran/davesomeran. Ten (10) cases were medically confirmed. Cumulatively and during the review period, there have been no pregnancy cases reporting a fatal outcome, stillbirth, or foetus/infant with congenital anomalies following exposure to a dose of elasomeran/davesomeran. The most frequently reported events/PTs represent expected reactogenicity for elasomeran. The only pregnancy-specific PT reported has been "Maternal exposure during pregnancy." During the review period, the reported serious ca se ([redacted]) was for a previously reported case, reviewed during the PBRER#4 review period. Updates were added to the case narrative during this review period and did not affect the previous assessment of this case. Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified.
Discussion	During the reporting period, the pattern of the reports remained generally consistent when compared with the cumulative data. Review of serious pregnancy-specific events and non-pregnancy-specific events during the review period did not identify any new safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran with no other causal association to vaccination. Reported cases reflect obstetric events observed after administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of AE, diagnostics, treatment and/or outcome. Where data were available, noted confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy included advanced maternal age, concomitant medications, comorbidities (such as hypothyroidism), previous relevant obstetric history, and congenital anomalies which predated the vaccination.

	Spontaneous abortion was the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster was identified. During the review period there were 5 cases reporting stillbirth (4 cases following vaccination with elasomeran and 1 case following a booster dose of elasomeran/imelasomeran). Considering that some cases had clear alternate etiologies, there is an absence of a clear TTO cluster, and published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth after COVID vaccination. There is insufficient evidence to support a causal relationship between elasomeran-containing vaccines and stillbirth. The MAH will continue to review and evaluate cases of spontaneous abortion, fetal death and stillbirth, using routine surveillance as well as PASS. Review of the 17 cases reporting congenital anomalies (15 cases following vaccination with elasomeran and 2 cases following a booster dose of elasomeran/imelasomeran) during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with elasomeran-containing vaccines. Review of 6 serious cases received during the reporting period concerning children under 6 years of age who were exposed during gestation did not identify any unusual patterns or safety concerns. There were 2 pregnancy-related cases among adolescents received during the reporting period. Also, there continues to be a decreasing number of pregnancy-related cases following receipt of three or more doses of elasomeran (40 pregnancy cases reporting receipt of three or more doses of elasomeran). Overall, based on current available information there are no unusual patterns or pregnancy-related safety concerns identified among these subpopulations. During the reporting period, the MAH received 39 pregnancy cases reporting events after an exposure to a booster dose of elasomeran bivalent vaccines [25 cases reported an event after elasomeran/imelasomeran, and 14 cases reported an event after elasomeran/davesomeran]. Most events reflect expected reactogenicity. The most frequently reported pregnancy-specific event was "Maternal exposure during pregnancy." However, during this review period, the MAH received the first reports indicating pregnancy-specific adverse events/outcomes for elasomeran/imelasomeran. These events mark the first cases of fetal death or stillbirth and congenital anomaly associated with maternal exposure to a mother vaccinated with a booster dose of elasomeran/imelasomeran. No unusual patterns or pregnancy-specific safety concerns have been identified; MAH will continue to review cases that received the bivalent vaccines using routine surveillance. In-depth literature reviews performed have not identified any new safety concerns for the use of elasomeran during pregnancy. Thus far, published literature has not identified any evidence of an increased risk of fetal or neonatal complications related to maternal immunization with elasomeran-containing vaccines. Furthermore, published literature have reported that there is transfer of maternal antibodies, reduction in COVID-19 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. This is

	acknowledged that COVID-19 infection may be more serious and cause complications for both the mother and the fetus and published literature supports the favorable benefit/risk profile of maternal immunization with elasomeran-containing vaccines. Data continues to provide supporting evidence for the use of elasomeran-containing vaccines 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 elasomeran-containing vaccines 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern. The MAH will continue to monitor events for pregnancy using routine surveillance and ongoing post-authorization studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation remains positive

Rapporteur assessment comment:

The information provided on Use in Pregnancy is acknowledged.

No unusual patterns or pregnancy-specific safety concerns were identified during the reporting and cumulative periods, and overall, the pattern of reporting was similar in the reporting period as compared to the cumulative data.

Review of serious pregnancy-specific events and non-pregnancy-specific events during the review period did not identify any new safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran with no other causal association to vaccination. The most frequently reported events/PTs represent the expected reactogenicity for elasomeran.

<u>Elasomeran</u>

During the review period, the MAH received 206 pregnancy cases (802 events) with 64 serious cases (210 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. Five (5) cases reported a fatal outcome, and 69 cases were medically confirmed. However, in 146 of the 206 cases, pregnancy outcome was reported "Unknown" and further 18 as "Undetermined" (PSUR Appendix 12.19e). The most frequently reported pregnancy-related outcome was Spontaneous abortion (13) and Delivered (12), followed by Preterm (7), At term with Congenital Anomaly (4) and Stillbirth (3).

<u>Elasomeran/imelasomeran</u>

During the review period, the MAH received 25 pregnancy cases (89 events) with 17 serious cases (53 serious events) among individuals who received or were maternally exposed to a booster dose of elasomeran/imelasomeran. One case reported a fatal outcome, and 3 cases were medically confirmed.

Of the 89 events reported, 29 were pregnancy-specific events. The only PT's indicating a pregnancy-specific adverse event/outcome were "Abortion spontaneous" (4 events), "Pancreas divisum" (1 event), "Poor feeding infant" (1 event), "Premature separation of placenta" (1 event), and "Stillbirth" (1 event). Events of "Spontaneous abortion", "Premature separation of placenta", and "Stillbirth", while previously

reported with elasomeran exposure, mark the first reports of fetal death or stillbirth associated with elasomeran/imelasomeran exposure.

Of note, during the reporting period, the MAH received 1 pregnancy case ([redacted]) reporting events of pericarditis after receipt of elasomeran/imelasomeran vaccine. This was the first pregnancy case reporting events of myocarditis and/or pericarditis following a booster dose with an elasomeran bivalent vaccine. This case is further discussed in the PSUR Section 16.3.1.2.

Elasomeran/davesomeran

During the reporting period, the MAH received 14 pregnancy cases (36 events) with 1 serious case among individuals who received a booster dose of elasomeran/davesomeran. Ten (10) cases were medically confirmed. Of these, none were considered pregnancy-specific adverse events.

Cases with fatal outcome

During the reporting period, 5 cases of maternal death were reported in association with elasomeran exposure, and 1 case of maternal death after exposure to a booster dose of elasomeran/imelasomeran. This was the first fatal case reported following vaccination with a booster dose of an elasomeran bivalent vaccine.

Cases of spontaneous abortion, fetal death and/or stillbirth were reported for elasomeran and for elasomeran/imelasomeran.

The causality analysis of the cases with fatal outcome did not raise any new safety concerns.

Subpopulation analyses

The subgroup analyses for the reporting period included 6 serious cases received during the reporting period concerning children under 6 years of age who were exposed during gestation, 2 pregnancy-related cases among adolescents, and pregnancy cases who received three or more doses of elasomeran. No unusual patterns or pregnancy-related safety concerns identified among these subpopulations.

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 Use in Pregnancy reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern.

This is endorsed.

Studies reporting on pregnancy-related issues are ongoing. Until further notice, the MAH should continue to monitor Use in Pregnancy associated with elasomeran-containing products as Missing Information.

2.3.1.3.2. Use in Breastfeeding

Evaluation of information received during the PBRER reporting interval relating to the known important missing information risks of elasomeran-containing vaccines during breastfeeding has not identified any additional clinically relevant new safety information for this topic. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in PSUR Section 16.4, remains valid.

Table 16.11 Use in breastfeeding

Source of New Information	• Moderna GSDB • Literature Sources o Search Criteria Applied: PSUR Appendix 13.4 o Retrieved: 519 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	The topic of Breastfeeding is summarized because the use of elasomeran-containing vaccines among breastfeeding women is an area of missing information in the currently approved RMP. Real world evidence and literature demonstrate that elasomeran-containing vaccines are well tolerated by lactating women and their children, and side-effects experienced are similar to side-effects in the general population. No specific safety concerns for breastfeeding have been identified.
Methods	**Identification of Case Reports in ModernaTx, Inc. GSDB:** Lactation cases were identified as any case containing at least one lactation-specific event or PT term identified in the SMQ: "Lactation-specific topics (including neonatal exposure through breast milk)" described in the SSP 2.0. Identified lactation cases were pulled by case identification numbers to obtain all PTs reported; the PTs that are captured in the Lactation-specific topics (including neonatal exposure through breast milk) SMQ are referred to as lactation-specific events, and those that are not, are referred to as non-lactation-specific events. The MAH reviewed and performed descriptive analyzes of all events reported for the reporting period by type of vaccine (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). These analyses were also performed for lactation cases who received third or subsequent doses of elasomeran, lactation cases among 12-17 years old (adolescents) and 6-11 years old, as well as lactation cases among children younger than 6 years of age (breastfed children). For the calculation of TTO and the attribution of Dose Number to individual events an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a dose was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number. All fatal cases were medically reviewed and summarized; deaths among lactating women within 1 year of pregnancy completion is considered a pregnancy-specific death and will be discussed in Section 16.3.5.1. Deaths among lactating women occurring more than one year after pregnancy completion or breastfed infants only with a possible exposure to a ModernaTx, Inc. COVID-19 vaccine through breastmilk will be discussed here. However, the MAH receives reports in which fetal deaths among breastfeeding mothers are coded as fatal cases, originating from regulatory reports or due to coding discrepancies. Finally, serious lactation-specific cases among children younger than 6 years were medically reviewed and summarized.

Results	Refer to PSUR Appendix 12.20 for additional information. **Overview of Lactation Cases Who Received Elasomeran** During the review period, the MAH received 53 lactation cases (208 events) with 10 serious cases (33 serious events) among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran. No lactation cases reported a fatal outcome, and 21 lactation cases were medically confirmed. A higher percentage (81.1%) of the cases reported during this reporting period were non-serious compared to the prior review period (74.1%). During the reporting period, no meaningful changes have been observed in the age distribution of the cases of lactating women and their breastfeeding children and are consistent with the expected age of lactating women and their breastfeeding children. Note there are some cases that describe mastitis in non-breastfeeding individuals, particularly older women. Additionally, cases coded as males likely represent children who were exposed to breastmilk from mothers who had been vaccinated with Moderna COVID-19 vaccines or data entry and/or coding error. During the review period, the most frequently reported PTs were consistent with reactogenicity events and common breastfeeding issues such as mastitis and lactation insufficiency. When restricted to lactation-specific adverse events/outcomes, the only PTs reported in decreasing order were "Mastitis" (11 events), "Lactation insufficiency" (10 events), "Lactation disorder" (1 event), "Lactation puerperal increased" (1 event), and "Breast milk discoloration" (1 event). There has not been a significant change in the pattern of PTs reported during the reporting period when compared to cumulative data. Most of the lactation-related events were transient and occurred within 2 days of vaccination. Medical review of the HLT "Lactation Disorders" was performed and the data for the review period are similar to the previous cumulative experience; no concerning patterns or notable trends were identified. Of the 10 serious lactation cases reported during the review period, only 4 cases reported a lactation-specific adverse clinical event/outcome. Following medical review, it was determined that 2 cases ([redacted] and [redacted] describing events of mastitis were not lactation cases due to the age of the individuals (55 years and 52 years, respectively) and that there was no information indicating that either individual was breastfeeding or lactating. The remaining 2 serious cases (Case [redacted] and [redacted]) described events of mastitis and lactation insufficiency, both common challenges in breastfeeding women. **Subpopulation Analyzes** *Lactation Cases Under 6 Years of Age–Elasomeran)* During the review period, the MAH received 4 cases (15 events) with 1 serious case (7 serious events) among children under 6 years of age with exposure to breastmilk from mothers who had been vaccinated with elasomeran (referred to as lactation cases among children under 6 years of age). No cases reported a fatal outcome or were medically confirmed.

	Similar to the previous review period, the most frequently reported clinical events reported among children under the age of 6 years of age were pyrexia, diarrhea, and vomiting, which are consistent with reactogenicity events expected for elasomeran. When restricted to only lactation-specific PTs, the most frequently reported lactation-specific PT continued to be "Exposure via breast milk." During the reporting period, the mean age of lactation cases among children under 6 years was 0.4 years (SD: 0.2) and median age was 0.4 years (ra nge: 0.1 to 0.7 years). The sample size was small so there was no meaningful difference in the number of reports involving males (3; 75.0%) and females (1; 25.0%). When TTO was known, most of the lactation- related events were transient and all events occurred within two days after vaccination. During, the review period, no cases of seizure were reported. During the review period, 1 serious lactation case ([redacted]) with 7 serious events was reported in a 6-week-old male who experienced the serious (medically significant) events of flatulence, vomiting, emotional distress, diarrhea, gastroesophageal reflux disease, and abdominal discomfort after maternal exposure to breastmilk from a mother vaccinated with elasomeran. The only lactation-specific event was "Exposure via breast milk." All events resolved within 3 days. Cumulatively, all serious cases with lactation-specific events have been medically reviewed and are summarized. Many cases lack information on clinical course, outcome, pediatric medical history, or alternate etiologies/concurrent clinical events. Thus, based on the temporal relationship, causality cannot be excluded. To date, no concerning patterns or notable trends have been identified. *Lactation Cases Among Adolescents (12-17 Years of Age)* There were no lactation cases reported among adolescents during this review period. *Lactation Cases with Third or Subsequent Doses of Elasomeran* During the review period, the MAH received 5 lactation cases (20 events) with 1 serious case (1 serious event) in individuals who received or were exposed to breastmilk from mothers who had been vaccinated with a third, fourth, or fifth dose of elasomeran. No cases reported a fatal outcome or were medically confirmed. Of the 5 lactation cases reported during the review period, only 3 cases (60.0%) reported a lactation-specific event. This is a higher proportion when compared to cumulative data (25.6%); however, due to the small sample size received during the review period, these data should be interpreted with caution. Regardless of the vaccine regimen originally received, most of events reported were consistent with expected reactogenicity seen with elasomeran. No concerning patterns or notable trends were identified. **Lactation Cases After Receiving Booster Dose with Elasomeran/Imelasomeran** During the review period, the MAH received 25 lactation cases (97 events) with 16 serious cases (67 serious events) in individuals who received or were exposed to

	breastmilk from mothers who had been vaccinated with elasomeran/imelasomeran. No cases reported a fatal outcome, and 5 cases were medically confirmed. During the review period, when restricted to lactation-specific events, the only PTs reported in decreasing order were "Maternal exposure during breast feeding," "Mastitis," and "Exposure via breast milk." During the review period, the only serious case ([redacted]) received with a lactation-specific event reported the serious PT "Mastitis." However, this case appears to be misclassified as a lactation case as the narrative clearly indicates the woman was not lactating or breastfeeding. There have been no fatal lactation cases after receipt of elasomeran/imelasomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/imelasomeran. **Lactation Cases After Receiving Booster Dose with Elasomeran/Davesomeran** During the review period, the MAH received 15 lactation cases (36 events) with 1 serious case in individuals who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran/davesomeran. No cases reported a fatal outcome, and 14 cases were medically confirmed. During the review period, when restricted to lactation-specific events, the only PT reported was "Maternal exposure during breast-feeding." During the review period, the only serious case reported ([redacted]) was previously received and reviewed during the PBRER #4 review period. Updates to the narrative were made during this review period. These updates did not affect prior assessment. The only lactation-specific event reported was "Maternal exposure during breastfeeding." There have been no fatal lactation cases after receipt of elasomeran/davesomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/davesomeran.
Discussion	During the reporting period of PBRER, Moderna Tx, Inc. received 53 lactation cases, of which 4 cases were among children under 6 years of age with exposure to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran via breastmilk. There were no reported fatalities. While vaccination can induce cytokines, which can be passed via breast milk, vaccination while 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 [80] [81] [82]. There were no lactation cases reported among the 12-17 age group during this reporting period and there were 5 lactation cases reporting receipt of a third or subsequent doses, with 60.0% reporting a lactation-specific event. Among the serious lactation-specific events, there was no clustering by dose or TTO and no concerning patterns or notable trends of events reported were identified. Reported events were mild and transient. The pattern of reports remained generally

	consistent during the reporting period when compared with the cumulative data. No new safety concerns were identified. Where duration and outcome are available, many of the events occur within 2 days after vaccination, and most events were mild/moderate, transient events where information is available. Both in the GSDB and in the literature, reports of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhea , and pyrexia are consistent with the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran or what is expected in the general population [81] [83] [84]. Review of the literature to date has not identified any safety concerns related to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccination during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated 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 favorable 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 Moderna COVID-19 vaccines during lactation. The MAH is closely monitoring the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in this population through routine pharmacovigilance [85] [86] [87]. 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 elasomeran remains favorable.
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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety concern. The MAH will continue to monitor events associated with breastfeeding women who receive elasomeran-containing vaccines and their children who are exposed to these vaccines through breast milk using routine surveillance and ongoing post-authorization studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation for this subpopulation continues to remain positive.

Rapporteur assessment comment:

The MAH has presented information regarding use of elasomeran-containing vaccines in breastfeeding for the latest period 18 February 2023 through 17 June 2023. Data are achieved from the MAH's global safety database and from a new literature search.

The use of elasomeran-containing vaccines among breastfeeding women is an area of missing information. However, real world evidence and literature indicate that elasomeran-containing vaccines are well tolerated by lactating women and their children, and that side-effects seem to be similar to side-effects in the general population. No specific safety concerns for breastfeeding have been identified.

Results

Literature:

The performed literature search gave 519 manuscripts. Despite the many retrieved papers, the MAH did not identify new and significant safety information.

Lactation cases:

In the review period 18 Feb to 17 Jun 2023 there were 93 lactation cases (341 events) reported after receiving elasomeran-containing vaccines. Of these, 53 cases (208 events) were reported for elasomeran, 25 cases (97 events) for elasomeran/imelasomeran, and 15 cases (36 events) for elasomeran/davesomeran. Of the 93 lactation cases (341 events) no cases had fatal outcome.

Lactating women:

Cases reported comprised symptoms consistent to well-known side effects and breastfeeding-related symptoms as mastitis and lactation insufficiency.

Breastfed infants and children:

In the review period 4 cases (15 events) were reported for children younger than 6 years of age who were breastfed and whose mothers had received an elasomeran-containing vaccine. Symptoms in these children were consistent with well-known side effects as fever, diarrhea and vomiting.

Conclusion

In the review period 18 Feb to 17 Jun 2023 there were 93 lactation cases (341 events) reported after receiving elasomeran-containing vaccines there is no indication of a specific pattern regarding dose number or TTO among the cases, and symptoms are mainly consistent with milder side effects to vaccination and/or to lactation difficulties. The findings from the global safety database or literature review do not raise new concerns.

Lactation cases will continue to be monitored as missing information.

2.3.1.3.3. Long-term Safety

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

Table 16.12 Long-term Safety

Source of New Information	As of the DLP of this PBRER, 26 CTs were ongoing 12 of which are sponsored by ModernaTx, Inc. Cumulatively, 53,983 subjects have been are estimated to be exposed to either mRNA-1273, or its variants (mRNA 1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA 1273.617.2, mRNA-1273.529, mRNA-1273.231 a nd mRNA-1273.815), and participants exposed to mRNA- 1273 in conjunction to mRNA-1283 (including its variantsmRNA-1283.211) or mRNA- 1010 or mRNA-1345, or co-admin co-administration with mRNA-1010 or coadministration co-administration with mRNA 1345 in the mRNA clinica l development program sponsored by Moderna Tx, Inc.

Background	Per protocols, the clinical development program has a safety follow-up period of 12 months in the ongoing studies that will assess long-term safety: mRNA1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, and the completed studies mRNA-1273-P101 (DMID 20-0003), and mRNA-1273-P201. Post-a uthorization safety studies in real world that evaluate long-term safety include ongoing studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P910.
Methods	The long-term safety profile remains to be characterized through continued trial follow- up, active surveillance for safety, PASS, and routine pharmacovigilance. Study mRNA-1273-P904, an EU post-authorization safety study, aims to carry out signal detection followed, if necessary, by safety evaluation of identified possible signals of Moderna vaccines targeting SARS-CoV-2 using routinely collected health data in secondary automated electronic data sources covering all or portions of the populations in Denmark, Italy, Norway, Spain, and the UK. The study population includes all persons with a record of at least one dose of Moderna vaccines targeting SARS-CoV-2 in each database between 06 Jan 2021 and 31 Dec 2022 and members of the database source population selected for each study design, including persons providing historical rates. The final report is planned for 31 Dec 2023. Study mRNA-1273-P910 will describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV- 2 in Spain, Denmark, Norway, and the UK. The study will include two distinct designs utilizing secondary data: A case cohort will assess risk factors for development of post- vaccine myocarditis and pericarditis, a case cohort of recipients of Moderna vaccination targeting SARS-CoV-2 will be defined in each participating database. A separate cohort analysis will characterize the clinical course, outcomes, and risk factors for severe disease, a cohort of myocarditis cases (with and without prior exposure to Moderna vaccination targeting SARS-CoV-2) will be studied. Study mRNA-1273-P911 will evaluate patients with myocarditis for up to 5 years after elasomeran exposure to characterize the potential long-term outcomes of vaccine-associated myocarditis compared to myocarditis not secondary to vaccination (non-vaccine myocarditis, NVM). Vaccine exposure and case identification information will be obtained retrospectively from existing real-world data as it accrues in routine clinical practice. Study mRNA-1273-P910 will describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV- 2 in Spain, Denmark, Norway, and the UK. The study will include two distinct designs utilizing secondary data: A case cohort will assess risk factors for development of post- vaccine myocarditis and pericarditis, a casecohort of recipients of Moderna vaccination targeting SARS-CoV-2 will be defined in each participating database. A separate cohort analysis will characterize the clinical course, outcomes, and risk factors for severe disease, a cohort of myocarditis cases (with and without prior exposure to Moderna vaccination targeting SARS-CoV-2) will be studied.

	Study mRNA-1273-P911 will evaluate patients with myocarditis for up to 5 years after elasomeran exposure to characterize the potential long-term outcomes of vaccine-associated myocarditis compared to myocarditis not secondary to vaccination (non-vaccine myocarditis, NVM). Vaccine exposure and case identification information will be obtained retrospectively from existing real-world data as it accrues in routine clinical practice.
Results	The Phase 3 study mRNA-1273-P301 includes a total of 24 months follow-up; no long- term safety concerns have been identified for the two-dose mRNA-1273 100 mcg primary series on the basis of an interim analysis that includes 16,818.4 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). Participants completing CTs mRNA-1273-P101 (DMID 20-0003), mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, and mRNA-1273-P306 are followed up for a safety for 12 months. In the adolescent Phase 3 Study mRNA-1273-P203, participants from the age of 12 through 17 years had a median follow-up of 342 days after Dose 1 and 312 days after Dose 2. In the pediatric Phase 3 Study mRNA-1273-P204, participants 6 months through 11 years had a median follow-up ranging between 254 and 267 days across age groups. Post-authorization safety studies mRNA-1273-P904, mRNA-1273-P910, and mRNA- 1273-P911 are ongoing, and no findings related to long-term safety have yet been identified. As of the DLP of this PBRER, no clinically important safety concerns have been identified upon review of long-term follow-up data in CTs.
Discussion	The long-term safety profile remains to be characterized. In addition to routine pharmacovigilance activities, results from the following studies will be used to evaluate long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. <u>Ongoing Studies:</u> • Study mRNA-1273-P904 (final CSR: 31 Dec 2023) • Study mRNA-1273-P910 (final CSR: 30 Jun 2025) • Study mRNA-1273-P911 (final CSR: 31 Oct 2028) • Study mRNA-1273-P203 (final CSR: 31 Jul 2024) • Study mRNA-1273-P204 (final CSR; 31 Mar 2024) • Study mRNA-1273-P205 (final CSR: 31 Dec 2023) • Study mRNA-1273-P301 (final CSR: 31 Dec 2023) <u>Completed Studies:</u> • Study mRNA-1273-P201 (final CSR: 30 Sep 2022) • Study mRNA-1273-101/ 20-0003 (final CSR Main Study: 01 Nov 2022)

Conclusion	As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor the 2 completed studies (mRNA-1273-P201 and mRNA-1273-P101) which are being assessed to characterize long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Rapporteur assessment comment:

The MAH has provided information on 26 ongoing clinical trials which all aim to study long-term safety issues. The different studies have different protocols, but together they cover different elasomeran-containing vaccines, different patient age groups, different health outcomes.

Neither the ongoing nor the completed studies have demonstrated significant safety findings. The ongoing studies will – together with routine surveillance – be consulted to characterise the long-term safety profile.

The information provided regarding the studies including study populations, participating countries, and studied health outcome is acknowledged.

2.3.1.3.4. Use in immunocompromised subjects

Evaluation of information received during the PBRER reporting interval relating to the known important risks of elasomeran-containing vaccines in relation to immunocompromised individuals, has not identified any additional clinically relevant new safety information for this topic. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, remains valid.

Table 16.13 Use in immunocompromised subjects

Source of New Information	• Moderna GSDB • Litera ture Sources o Search Criteria Applied: PSUR Appendix 13.4 o Retrieved: 65 o New and Significant Safety Information: There was no new and significant safety information identified for the immunocompromised population.
Background	An association between immunocompromised individuals and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events associated with the administration of COVID-19 mRNA vaccines. The topic of Immunocompromised is summarized because it is an area of missing information in the currently approved RMP. No specific safety concerns for immunocompromised individuals have been identified.

Methods	For the purposes of this PBRER#5, the following operational definitions were applied in the analysis of the immunocompromised/immunosuppressed subpopulation: The "Immunocompromised Subpopulation": Specifically, cases were identified in the MAH GSDB for immunocompromised and immunosuppressed individuals using a past medical history of hematological malignant tumors SMQ, transplantation, primary/innate and acquired immunodeficiency syndromes (including Human Immunodeficiency Virus) and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs. The "General Population" (all elasomeran-containing vaccines data) in the Moderna Tx, Inc's. GSDB. This refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the Moderna Tx, 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 PSUR Appendix 12.22 for additional information. **Overview of Cases for Immunocompromised Individuals Who Received Elasomeran** During this review period, the MAH received 425 cases (1,059 events) with 123 (28.9%) serious cases (385 serious events) among immunocompromised individuals who received elasomeran. A total of 322 (75.8%) cases were medically confirmed, and 8 cases (1.9%) reported a fatal outcome. Similar to the prior reporting period, there were more cases involving females (130; 30.6%) compared to males (74; 17.4%), with 221 cases (52.0%) that did not report gender information. The median age of patients was 61.0 years (range: 19.0 – 91.0 years). Similar to the previous review period, the most frequently reported MedDRA PTs in the immunocompromised subpopulation included fatigue, pyrexia, headache, nausea, pain, and myalgia. These PTs were comparable to those reported in the general population and reflected expected reactogenicity. Events of COVID-19 infection was the most reported event during this review period (244; 23.0%). 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. This pattern was observed in reports for immunocompromised individuals for both elasomeran and elasomeran/davesomeran. Note that during the review period, 62 cases (including 35 serious and 1 fatal case) overlapped between the subpopulation of those with a medical history of autoimmune/inflammatory diseases (MedHx autoimmune or inflammatory disorders (AI)/ID) and immunocompromised/ immunosuppressed subpopulations, as many people with AI/ID are on immunosuppressive therapies. **Subpopulation 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* Evaluation of the 8 cases reporting fatal outcome showed that 2 cases were missing age and gender, 5 cases (62.5%) were elderly above 65 years, mostly males, and one case involved a 27-year-old male. All 8 cases had comorbidities including malignancies that were chronic conditions, and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Using the WHO-UMC causality assessment tool, more than half of the cases with fatal outcome (5; 62.5%) were assessed as "Unassessable" (due to insufficient information); 3 cases (37.7%) were assessed as "Unlikely" (due to long TTO outside the risk window and concurrent medical conditions that provided alternate etiologies). 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 344 cases (1,125 events) with 244 (70.9%) serious cases (829 serious events) for immunocompromised individuals who received a booster dose of elasomeran/imelasomeran. Thirty-nine (39) cases (11.3%) were medically confirmed, and 1 case (0.3%) reported a fatal outcome. A higher proportion of cases were reported for females (234; 68.0%) than males (94; 27.3%) with 16 cases (4.7%) which did not report gender information. The median age of patients was 59.0 years (range: 22.0 to 88.0 years). During the review period, the most frequently reported PTs in immunocompromised individuals who received elasomeran/imelasomeran were headache, fatigue, pyrexia, nausea, chills, myalgia, and arthralgia. These events reflect expected reactogenicity and were comparable to events reported in the general population receiving elasomeran/imelasomeran. *Fatal Reports in Immunocompromised Individuals Who Received Elasomeran/Imelasomeran:* Evaluation of the 1 case reporting a fatal outcome in a male showed that it was missing relevant information on age, clinical course of events and treatment provided. The cause of death was not reported. An autopsy was not performed. Concurrent acute myeloid leukemia provides alternate etiology. Using the WHO-UMC causality assessment tool, this ca se was assessed as unlikely (due to alternate etiology). Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received a booster dose with elasomeran/imelasomeran. **Overview of Cases for Immunocompromised Individuals Who Received Elasomeran/Davesomeran** During the review period, the MAH received 24 cases (53 events) with 6 (25.0%) serious cases (10 serious events) for immunocompromised individuals

	who received elasomeran/davesomeran. A total of 19 (79.2%) cases were medically confirmed, and no case reported a fatal outcome. Similar to the previous review period, there were no meaningful changes in the gender distribution of reports as a slightly higher proportion of cases continued to be reported in females (12; 50.0%) than males (10; 41.7%) and 2 cases (8.3%) did not report gender information. The median patient age was 67.0 years (range: 52.0 to 80.0 years). During the review period, the most frequently reported events were COVID-19 infection and issues related to product storage, expiration, or medication error. Reported "COVID-19" 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. This was observed in data for both elasomeran and elasomeran/davesomeran. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran/davesomeran. **Clinical Trial Information** Interim Clinical Study Report for mRNA-1273-P304 - OPEN-LABEL PART A (PRIMARY SERIES) and PART B (BOOSTER DOSE) - Safety Results (31 Mar 2023) Study mRNA-1273-P304 is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in solid organ transplant (SOT) recipients and healthy participants. This was a 2-part study. Part A of the study enrolled 214 SOT recipients to receive up to 3 doses of 100 µg mRNA- 1273, and 20 healthy participants to receive 2 doses of 100 µg mRNA-1273 (the healthy participant group was intended as a comparator group for SOT in the assessment of the Cell Media ted Immune responses; the vaccine-induced antibody responses in the healthy participants were also described in comparison to the SOT group). In Part A, SOT participants who were unvaccinated and those who were previously vaccinated with 2 doses of mRNA-1273 were enrolled. The primary immunogenicity objective of Part A was to evaluate serum nAb responses obtained 28 days after the second or third dose of the study vaccine. In Part B, a 100 µg booster dose (BD) was administered to participants at least 4 months from the last dose of a completed primary COVID-19 vaccination series. A 100 µg BD was selected for this study due to concern about reduced antibody responses associated with chronic immunosuppression in the SOT population and the potential immune escape associated with variants of concern. The analyses presented in the P304 interim report dated 31 Mar 2023, is based on the results from a database lock date of 22 Nov 2022. Safety follow-up after vaccination includes a median of 292.0 days (range: 37 to 406 days) from Dose 3 in SOT participants in Part A and a median of 129.0 days (range: 10 to 181 days) from BD in SOT participants in Part B. Summary of Safety Results o Reactogenicity after the 3-dose primary series and BD in immunocompromised participants was similar to that which has been reported for mRNA-1273 in immunocompetent participants. This is also

	consistent with what has been reported in other CTs and post-authorization use of mRNA-1273 in the genera l population. o Local and systemic solicited ARs were reported within 7 days after vaccination in 85% and 80% of SOT participants, respectively, after any injection. Systemic solicited ARs, chiefly fatigue, headache, and myalgia, were reported in fewer kidney transplant participants compared to liver transplant participants, particularly after Dose 1, although a trend was evident at all doses; this was attributed to heavier immunosuppressant and anti-metabolite treatment in kidney transplant participants. o Unsolicited treatment-emergent AEs (TEAEs) were reported in 42.1% of SOT participants through 28 days after vaccination after any injection and were considered related to vaccination by the Investigator in 21.5% of SOT o participants. The most commonly reported vaccine related events included fatigue (12.6%), headache and myalgia (6.1%, each), and arthralgia (5.6%), which were also frequently reported symptoms of reactogenicity. Other unsolicited TEAEs were largely due to underlying disease or intercurrent illness or injury in SOT participants. o Four cases of biopsy-proven organ rejection were reported during the study, all in SOT liver participants (one involved a kidney transplant in a prior liver transplant recipient). None of the cases were considered related to vaccination and all were due to changes in immunosuppressant medications. o Through the data cutoff date, 4 SAEs in 3 SOT participants were assessed as related to study vaccination by the Investigator. Two SAEs (worsening anemia, angina) occurred in a kidney transplant recipient on Relative Days 10 and 11 after vaccination and were considered vaccine-related by the Investigator; the Sponsor considered the events more likely attributable to underlying disease. One SAE of vomiting was reported as a solicited AR and, per protocol, considered related to vaccine, although the event was not assessed as vaccine- related by the Investigator. One SAE of autoimmune hemolytic anemia occurred 4 months after Dose 2 in a participant with a concurrent COVID-19 infection; autoimmune hemolytic anemia was considered possibly related to vaccine by the Investigator due to the temporal relationship of the decline in hematocrit after vaccination, although the Sponsor considered the event more likely due to pre-existing anemia . o One AESI of non-serious myocarditis was reported on Relative Day 1 after vaccination and was assessed as related to vaccine by the Investigator; the case was adjudicated by the cost-effectiveness acceptability curve as not meeting the CDC definition of myocarditis. One cost-effectiveness acceptability curve - adjudicated case of pericarditis occurred on Study Day 122 that was attributed to an underlying inflammatory process and was not considered vaccine related by the Investigator or Sponsor. o Two fatal events (congestive heart failure and death of unknown cause) in participants with underlying comorbidities were reported and were not considered related to vaccination.

	o Laboratory shifts did not show notable trends after vaccination with mRNA- 1273; shifts noted were attributed to underlying disease or intercurrent medica l processes. o Shifts in vital signs were explained by underlying disease or intercurrent medical processes. Elevation of systolic or diastolic blood pressure was the most common vital sign change and, in most participants, reflected underlying hypertension. o No mRNA-1273 vaccine-related safety concerns were identified during the study. Safety conclusion: The 3-dose primary series and BD of mRNA-1273 were well tolerated with an acceptable safety profile in immunocompromised post-transplant population. **Health Authority Feedback** *"Overall, the regulatory authority considered that there is sufficient evidence to concludethat thegaps in knowledgeregarding the safety of elasomeran when used in immunocompromised individuals have been adequately filled and can no longer be considered an area ofmissing information. Removal of 'use in immunocompromised subjects' from the RMP is endorsed".* *Regardless of the removal of the safety concern in the RMP, continued monitoring through routine pharmacovigilance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904 is warranted, as proposed by the MAH".* Regarding the effectiveness in immunocompromised subjects, the studies P304 and P901 are ongoing and will remain in the pharmacovigilance plan.
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 top five most frequently reported AEs in the immunocompromised population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The pattern of events observed with elasomeran/imelasomeran or elasomeran/davesomeran compared to elasomeran in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in immunocompromised 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 review period, there were no cases reported in immunocompromised children or adolescent subpopulations. 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 (1.1%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiology.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in immunocompromised individuals. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Based on the 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern. 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 use in immunocompromised individuals is that there is sufficient evidence to conclude that the gaps in knowledge regarding the safety of elasomeran when used in immunocompromised individuals have been adequately filled and can no longer be considered an area of missing information. Removal of 'use in immunocompromised subjects' from the RMP was endorsed. 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:

The MAH has presented information regarding use of elasomeran-containing vaccines in immunocompromised individuals for the latest period 18 February 2023 through 17 June 2023. Data are achieved from the MAH's global safety database and from a new literature search.

The use of elasomeran-containing vaccines in immunocompromised individuals is an area of missing information.

Methods

To define a subpopulation of immunocompromised, the MAH has searched the database for individuals with a medical history of previous hematological malignant tumors SMQ, transplantation, innate or acquired immunodeficiency syndromes (including Human Immunodeficiency Virus), and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs.

For comparison, all individuals in the database with elasomeran-containing vaccines were defined as a background population.

Results

Literature:

The performed literature search gave 65 manuscripts. Despite the many retrieved papers, the MAH did not identify any new and significant safety information in these.

In the review period 18 Feb to 17 Jun 2023 there were 793 cases (2,687 events) reported after receiving elasomeran-containing vaccines. Of these, 425 cases (1,509 events) were reported for elasomeran, 344 cases (1,125 events) for elasomeran/imelasomeran, and 24 cases (53 events) for elasomeran/davesomeran.

Of the total 793 cases (2,687 events), 373 cases (1,224 events) were serious, and 9 cases had fatal outcome. By vaccine, the numbers are 123 serious cases (385 events) for elasomeran, 244 serious cases (829 events) for elasomeran/imelasomeran, and 6 serious cases (10 events) for elasomeran/davesomeran. The distribution of fatalities by vaccine was 8 for elasomeran, 1 for elasomeran/imelasomeran, and 0 cases for elasomeran/davesomeran.

COVID-19 was the most reported event in the review period for both elasomeran and elasomeran/davesomeran. The MAH states that this may be due to an already exiting COVID-19 infection, decreased immunogenicity of vaccination, and/or the susceptibility to constantly changing variants, but there is no data to clarify this.

Overall, the most frequent adverse event reported in immunocompromised individuals were consistent with common side effects in the general population in the database and so is the safety/tolerability profile.

Conclusion

In the review period 18 Feb to 17 Jun 2023 there were 793 cases (2,687 events) reported to have occurred in immunocompromised individuals after receiving elasomeran-containing vaccines with COVID-19 being the most frequently reported event for both elasomeran and elasomeran/davesomeran.

Based on the conclusions from the previous PSUSA AR, the topic is no longer considered an area of missing information in the RMP. For the PSUR safety concern, the MAH will continue to monitor the adverse events through routine surveillance and ongoing additional pharmacovigilance activities (study P304, P903 and P904).

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

Evaluation of information received during the PBRER reporting interval relating to the known important risks of elasomeran/imelasomeran/davesomeran has not identified any additional clinically relevant new safety information in the Frail subpopulation. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in PSUR Section 16.4, below, remains valid.

Table 16.14 Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders)

Source of New Information	o Moderna GSDB
	o Literature Sources
	  o Retrieved: 169
	  o New and Significant Safety Information: There was no new and significant safety information identified.

Background	Frail patients are considered at higher risk for complications due to coronavirus disease 2019 (COVID-19) infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. Since frail subjects with unstable health conditions and co-morbidities were excluded from the registration CTs, the MAH is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Safety reports for frail subpopulation is summarized because it is an area of missing information in the currently approved RMP. 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 PSUR Appendix 12.23), which included subjects of all ages with unstable health conditions and comorbidities (including COPD, HIV, diabetes, chronic neurological disease, cardiovascular disorders).
Results	Refer to PSUR Appendix 12.23 for more information. **Overview of Frail Cases Reported for Elasomeran:** During the review period, the MAH received 1,292 cases (5962 events) reported in Frail subpopulation with 634 (49.1%) serious cases (2040 serious events), 531 cases (41.1%) were medically confirmed cases, and 42 (3.3%) cases with fatal outcome involving elasomeran. The majority of cases were reported in females (803, 62.2%) compared to males (476, 36.8%). The median patient age was 55.5 years (range: 0.0 to 98.0 years). A high proportion of reported cases in frail was among the elderly (390, 30.2%). The most frequently reported events are fatigue, headache, pyrexia, myalgia, COVID-19, dizziness, pain in extremity, vaccination site pains, chills, and arthralgia. These events were comparable to that reported in the general population and reflected expected reactogenicity. Further evaluation showed that events of COVID-19 infection (115;1.9%) were reported more frequently in the frail immunocompromised subpopulation. Please note not all frail are immunocompromised, and other comorbidities are associated with frail. This may be due to a lower immune response to vaccination and/or the susceptibility to constantly changing variants. This was observed only in individuals receiving elasomeran. Evaluation of the 42 cases (3.6%) with fatal outcomes showed that majority (29; 69.0%) were elderly above 65 years, and all 42 cases had comorbidities that were confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, most (26; 61.9%) of the cases were assessed as unlikely (due to TTO outside the risk window and concurrent medical conditions that provided alternate etiologies); 4 cases were assessed as conditional (more data needed for proper assessment), 2 cases assessed as possible (due to temporal association), and 10 cases assessed as unassessable (due to insufficient information). **Overview of Frail Cases reported for Elasomeran/Imelasomeran:**

	During the review period, the MAH received 797 cases (2,679 events) reported in Frail subpopulation, with 545 serious cases (1,967 serious events), 189 medically confirmed cases, and 21 cases with fatal outcome. involving elasomeran/imelasomeran. The majority of cases were reported in females (491 cases, 61.6%) compared to males (261 cases, 32.7%). The median patient age was 64.0 years (range: 18.0 to 98.0 years). The most frequently reported MedDRA PTs were fatigue, headache, pyrexia, dyspnea, nausea, chills, dizziness, myalgia, arthralgia, ADRs and palpitations. These events were comparable to that reported in the general population and reflected expected reactogenicity. Evaluation of the 21 cases with fatal outcomes showed that the majority (20; 90.2%) were elderly above 65 years, and all 20 cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, most (12; 57.1%) of the cases were assessed as unlikely (due to TTO outside the risk window and concurrent medical conditions that provided alternate etiologies); and 9 cases were assessed as unassessable (due to due to insufficient information). **Overview of Frail Cases Reported for Elasomeran/Davesomeran:** During the review period, the MAH received 123 cases (367 events) reported in the frail subpopulation, with 36 serious cases (56 serious events), 111 medically confirmed cases, and 7 cases with fatal outcome involving elasomeran/davesomeran. A slightly higher proportion of cases were reported in females (65; 52.8%) compared to males (52; 42.3%). The median patient age was 70.0 years (range: 2.0 to 92.0 years). The most frequently reported MedDRA PTs in frail subpopulation receiving elasomeran/davesomeran were pyrexia, pain in extremity, myalgia, fatigue, dizziness, pain, headache, chills, and insomnia. Most of these events are expected reactogenicity and consistent with reports in the general population. Evaluation of the 7 cases with fatal outcomes showed that majority (5; 71.4%) had missing age reported, and the 2 cases were elderly age >65 years. Most of the deaths were reported in males (6; 85.7%). Four cases were linked as similar. All 7 cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality a ssessment tool, all 7 cases were assessed as unassessable, due to insufficient information.

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. 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 elasomeran/imelasomeran or elasomeran/davesomeran compared to elasomeran in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals after vaccination with elasomeran. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events or safety concern. Cases with fatal outcome in the frail subpopulation in the reporting period (3.2%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiology.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in frail subpopulation. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern. 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 use in fra il subjects with unstable individuals is that "removal of the missing information 'use in frail subjects with unstable health conditions and co- morbidities' from the EURMP, is endorsed. Nevertheless, the topic shall remain in the PBRER list of safety concerns and an evaluation of new information on this topic is required with future PBRERs." The MAH will continue to monitor events for Frail using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH has presented information regarding use of elasomeran-containing vaccines in frail subjects with unstable health conditions and co-morbidities for the latest review period 18 February 2023 through 17 June 2023. Data are achieved from the MAH's global safety database and from a new literature search.

The frail individuals are considered at higher risk for complications to COVID-19 including hospitalisations and risk of death. The use of elasomeran-containing vaccines in frail individuals has been an area of missing information. No specific safety concerns have been identified.

Results

Literature:

The performed literature search achieved 169 manuscripts. Despite the many retrieved papers, the MAH did not identify new and significant safety information.

In the review period 18 Feb to 17 Jun 2023 there were 2,212 cases (9,008 events) reported after receiving elasomeran-containing vaccines. Of these, 1,292 cases (5,962 events) were reported for elasomeran, 797 cases (2,679 events) for elasomeran/imelasomeran, and 123 cases (367 events) for elasomeran/davesomeran.

Of the total 2,212 cases, 54.9% (1,215 cases) were serious, while 3.2% (70 cases) of all cases had fatal outcome.

The majority of cases were reported in females, and most patients were more than 50 years of age.

For adults as well as for children and adolescents no unusual pattern of events or safety concerns was reported. The adverse events in frail individuals are consistent with what is seen in the general population following vaccination with elasomeran-containing vaccines and to the known safety profile for both the monovalent and the bivalent vaccines.

Conclusion

In the review period 18 Feb to 17 Jun 2023 there were 2,212 cases (9,008 events) reported after receiving elasomeran-containing vaccines. As many as 54.9% were serious, while 3.2% were fatal; this should be compared to the fact that this group is considered at higher risk for complications including death in case of COVID-19.

The events in frail individuals are consistent with the known safety profile for the monovalent and the bivalent elasomeran-containing vaccines.

The topic will no longer be considered an area of missing information in the RMP; however, it will still be listed as missing information in the PSUR.

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

2.3.1.3.6. Use in subjects with autoimmune or inflammatory disorders (AI/ID)

Evaluation of information received during the present PBRER reporting interval relating to the known important risks of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran 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 these topics.

The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in PSUR Section 16.4, below, remains valid.

Table 16.15 Use in subjects with autoimmune or inflammatory disorders (AI/ID)

Source of New Information	o Moderna GSDB o Literature Sources o Search Criteria Applied: PSUR Appendix 13.4 o Retrieved: 141 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	Because there was limited data from CTs on the use of elasomeran in individuals with AI/ID, the MAH has been closely monitoring the safety profile of elasomeran in this population through routine Pharmacovigilance. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in AI/ID population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in MedHx AI/ID patients to achieve an adequate, more robust immune response to vaccinations. Furthermore, countries are recommending a BD (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in individuals with MedHx of AI/ID, especially now with the bivalent vaccines. The third dose of elasomeran recommended in individuals with known MedHx of AI/ID is 100 mcg dose, whereas the booster (either 4th dose for individuals with AI/ID, or 3rd dose for the general population) is a 50 mcg dose. Thus far, there have been nospecific safety concerns for individuals with MedHx of AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran and have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general population receiving elasomeran. 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 a Health Authority.3.1 *"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."*.
Methods	The ModernaTx, Inc GSDB was queried for valid, clinical and spontaneous reports for elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran

	in people with a medical history of autoimmune and/or inflammatory disease, received for review period (18 Dec 2022 to 17 Jun 2023). Reports from individuals with a MedHx AI/ID were identified from MAH GSDB using Immune-mediated/autoimmune disorder SMQ "Immune-mediated/autoimmune disorders SMQ" PTs identified in past medical history. Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	Refer to PSUR Appendix 12.24 for additional information. **Overview of MedHx AI/ID Cases Reported for Elasomeran** During this reporting period, 685 cases (324 serious, 259 medically confirmed, 7 fatal cases) with 3,325 events (1,146 serious) were reported in individuals with a known MedHx AI/ID after receiving elasomeran. The majority of cases 524 (76.5%) were reported in females compared to males (151 cases, 22.0%), with a small proportion of cases (10, 1.5%) having no gender reported. The mean patient age was 52.1years (SD: 15.3) and median age was 51.0 years (range: 17.0 to 95.0 years). The most frequently reported serious events during this reporting period often reflected expected reactogenicity events, such as fatigue, headache, and pain in extremity. The types and distribution of events were generally similar to cumulatively reported serious events in individuals with a known MedHx AI/ID. **Subpopulation Analysis:** *Use in Children <18 Years of Age with MedHx AI/ID - Elasomeran* During this reporting period, there was 1 non-serious case reported in 17-year-old female. *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. Refer to PSUR Appendix 12.24 for further information. **Overview of MedHx AI/ID Cases Reported for Elasomeran/Imelasomeran:** During the reporting period, 400 cases (276 serious, 54 medically confirmed, 5 fatal) with 1,289 events (952 serious) reported in individuals with a known MedHx AI/ID after receiving elasomeran/imelasomeran. The majority of cases were reported in females 297 (74.3%) compared to males 87 cases (21.8%), with small proportion of cases (16, 4.0%) having no gender reported. The mean patient age was 58.8 years (SD: 14.5) and median age was 60.0 years (range: 20.0 to 98.0 years). The most frequently reported serious events were fatigue, headache, and pyrexia, in individuals with known MedHx AI/ID who received elasomeran/imelasomeran and often represented expected reactogenicity. **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, 5 cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran/imelasomeran. Please refer to PSUR Appendix 12.24 for further information. **Overview of MedHx AI/ID Cases Reported for Elasomeran/Davesomeran:** During the reporting period, 40 cases (15 serious, 31 medically confirmed, 1 fatal) with 145 events (28 serious) reported in individuals with known MedHx of AI/ID after receiving elasomeran/davesomeran. The majority of cases were reported in females (32 cases, 80.0%) compared to males (8 cases, 20.0%). The mean patient age was 58.7 years (SD:19.2) and median age was 65.5 years (range: 8.0 to 81.0 years). During this reporting period, except for diarrhea (2, 7.1%), all other events were reporting once (3.6%) 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, 2 cases (1 serious) were reported in children <18 years of age. The serious case [redacted]- reported Kawasaki's disease in 8-year-old male patient. Please Refer to Section 15.2.4 for further assessment and details. *Fatal Cases in Individuals with MedHx AI/ID -Elasomeran/Davesomeran:* During this reporting period, 1 case with fatal outcome was reported in an individual with MedHx AI/ID who received elasomeran/davesomeran. Please refer to PSUR Appendix 12.24 for further information.
Discussion	Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers the cases of MedHx AI/ID to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran, and the benefits for elasomeran far outweigh any possible vaccine-associated risks. Relevant literature findings to support the reporting period discuss the acceptable safety and benefit/risk profile of COVID vaccination among individuals with AI/ID. No new safety concerns were identified in the literature review concerning elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. In AI/ID patients with disease flares, there is a natural waxing and waning course, and there are no reliable referenced data on the background rates of respective flares especially given the number of various AI/ID diseases and how to accurately measure a flare. The identified flare cases did not

	demonstrate a safety concern for this reporting period. There have been reports of flares after many vaccines, including various COVID vaccines. Both health care providers and patients acknowledge the potential risk of flares after any vaccination, yet flares are not specifically described in any vaccine labels. At present, the global consensus is that the benefit of vaccination outweighs the potential risks of flares but should be discussed between patient and HCP. Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. For the fatal AI/ID cases, common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, hyperlipidemia, and chronic kidney disease are similar to those reported in the general population fatal reports.
Conclusion	Evaluation of the data during this reporting period did not identify any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. 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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran did not raise any new safety concern. 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 use in subjects with autoimmune and inflammatory disorders is that *"removal of the missing information 'use in subjects with autoimmune and inflammatory disorders' from the EU RMP, is endorsed. Nevertheless, the topic shall remain in the PBRER list of safety concerns and an evaluation of new information on this topic is required with future PBRERs."* 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:

The MAH has presented information regarding use of elasomeran-containing vaccines in subjects with autoimmune or inflammatory disorders for the latest review period 18 February 2023 through 17 June 2023. Data are achieved from the MAH's global safety database and from a new literature search.

Results

Literature:

The performed literature search achieved 141 manuscripts. Despite the many retrieved papers, the MAH did not identify new and significant safety information.

In the review period 18 Feb to 17 Jun 2023 there were 1,125 cases (4,759 events) reported after receiving elasomeran-containing vaccines. Of these the 685 cases (3,325 events) were reported for elasomeran, 400 cases (1,289 events) for elasomeran/imelasomeran, and 40 cases (145 events) for elasomeran/davesomeran.

Of all reported cases for elasomeran-containing vaccines, 44.6% of cases were serious; 1.2% were fatal.

The majority of cases were reported in females. Most patients were more than 50 years of age. Only 3 cases were reported in children or adolescents.

Flare of underlying autoimmune or inflammatory disorder is discussed by the MAH, who notes that the cases identified within the reporting period do not demonstrate a safety concern.

The adverse events in individuals with AD/ID following vaccination with elasomeran-containing vaccines are consistent with the known safety profile for the vaccines.

Conclusion

In the review period 18 Feb to 17 Jun 2023 there were 1,125 cases (4,759 events) reported after receiving elasomeran-containing vaccines. As many as 44.6% were serious, while 1.2% were fatal. Most reported cases were females and most were older than 50 years.

The topic will no longer be considered an area of missing information; however, it will still be listed as a safety concern.

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

2.3.1.3.7. Interactions with other vaccines

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 Interaction with other vaccines as Missing Information from the EU RMP, was endorsed, and that "based on the cumulative evidence, the knowledge gaps regarding this area of missing information have been filled and interaction with other vaccines has not been shown to constitute an important risk. Therefore, it is no longer considered important in the context of the RMP and the PBRER. It should be removed from the PBRER list of safety concerns and an evaluation of new information on this topic in future PBRERs is not expected.".

Rapporteur assessment comment:

Interaction with other vaccines has not been shown to constitute an important risk, and according to the conclusions from the previous PSUSA AR (no 4), the topic will be removed from both the RMP and PSUR list of safety concerns.

Endorsed.

2.3.2. Safety topics under monitoring including requests from health authorities or regulatory bodies

2.3.2.1. Arrhythmias

Table 15.2 Arrhythmias

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 157 New and Significant Safety Information: None (0)
Background	The MAH received a Health Authority request to perform for PBRER#4 (DLP 17 Dec 2022) a cumulative review of all cases concerning elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran associated with arrhythmias from all sources, including any relevant articles from literature. For the current PBRER#5, a Health Authority requested that the MAH re-evaluate cumulatively the WHO-UMC classification of all serious cases of Arrhythmias, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e., Possible vs Probable and Probable vs Certain), and to discuss the result in the context of the totality of evidence on the subject.
Methods of Evaluation	The MAH queried the GSDB cumulatively as of 17 Jun 2023, for valid case reports of arrhythmia received from HCPs, HAs, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following MedDRA version 26.0 "SMQ Cardiac Arrhythmia (Narrow scope)." There is no SPEAC or Brighton Collaboration case definition available for arrhythmias, therefore the MAH has created a case definition for evaluation of the arrhythmia cases. Cardiac arrhythmia is characterized by abnormal or irregular rhythm of heartbeat which could be either too slow (<60 beats/min) or too fast (>100 beats/min) and can happen at any age [15]. Cardiac arrhythmias can be classified according to the site of origin (e.g., atria, atrioventricular junction, or ventricles) and whether the response is abnormally fast and early (tachycardia or premature beats), or abnormally slow and delayed (bradycardia

	or escape beats) [16]. Arrhythmia reports were classified into four categories as: 1. **Confirmed case**: has less than 60 beats/min (Bradycardia) or more than 100 beats per min (tachycardia) and electrocardiogram (ECG) identifying irregular heart rhythm 2. **Possible case**: Only has information on the irregular rhythm or number of beats per minute (pulse rate, heart rate) and no diagnostic confirmation (no info on ECG) 3. **Not a case**: Case has normal rhythm 4. **Unassessable**: Has no information on heart rate or pulse rate or ECG The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17]. *Methodology Implemented to Review the Post-marketing Data* The MAH performed the cumulative search as of 17 Jun 2023 in the GSDB, using the MedDRA (v 26.0) SMQ "Cardiac arrhythmias" (Narrow scope.) The search retrieved reports that were then screened for information on ECG and that were further screened for Arrhythmia related information using the following key words (*Bradycardia, Heartbeat, Irregular heartbeat, Tachycardia, irregular rhythm, ventricles, Premature beats, and Atrioventricular junction*). The reports retrieved were separated with Tachycardia confirmed reports and the rest of the serious reports with Tachycardia alone with other key terms were medically reviewed for Arrhythmia confirmed cases.

Results:

Results for Cardiac arrhythmias are summarized below. Refer to Appendix 12.7 for additional information.

Cumulatively, as of 17 Jun 2023, the MAH received 9,453 reports (10,793 events) of Cardiac arrhythmias with 6,765 seriousreports (7,282 serious events) and 261 reports with a fatal outcome. There were 4,358 medically confirmed reports (involving elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran). Most of the reports involved elasomeran: 9,240 reports (10,558 events) of Cardiac arrhythmias with 6,578 serious reports (7,083 serious events) and 254 reports with a fatal outcome. There were 4,300 medically confirmed reports. Most reports involved females (5,317 reports, 57.5%) compared to males (3,786 cases, 41.0%); 137 (1.5%) cases did not include gender information. The mean age was 53.4 years (SD: 17.2) and median age was 54.0 years (range: 0.1 to 121 years). For events (7,089 events) associated with a known dose number, 4,546 (64.1%) had an onset of < 7 days from the time of vaccination with any dose. Of note, a total of 3,469 (32.9%) events were reported with insufficient information to determine dose number.

During the review period, the MAH received 590 reports (681 events) of Cardiac arrhythmias with 503 serious reports (539 serious events), and 13 reports with a fatal outcome. There were 153 medically confirmed reports (involving elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran). Most of the reports involved elasomeran: 460 reports (534 events) of Cardiac arrhythmias with 379 serious reports (403 serious events) and 8 reports with a fatal outcome. There were 108 medically confirmed reports. Most reports involved females (261 reports, 56.7%) compared to males (191 reports, 41.5%); 8 reports did not include gender information. The mean age was 48.5 years (SD: 15.9) and median age was 48.0 years (range: 0.3 to 90.0 years). For events associated with a known dose number (231 events), 122 (52.8%) had an onset of < 7 days from the time of vaccination with any dose. Of note, a total of 303 (56.7%) events were reported with insufficient information to determine dose number.

Compared to the PBRER#4, the distribution of reports in this PBRER#5 was similar with respect to sex,

age, reporting source, region, and TTO.

As per the methodology described above, the MAH performed the review period search for 18 Dec 2022 to 17 Jun 2023 in the GSDB, using the MedDRA (v 26.0) Standard MedDRA Query (SMQ) "Cardiac arrhythmias" (Narrow scope), and retrieved 590 reports (681 events). These 590 reports were screened for information on electrocardiogram (ECG), which identified 117 reports. These 117 reports were further analysed for Arrhythmia related information with the following key words (Bradycardia, Heartbeat, Irregular heartbeat, Tachycardia, irregular rhythm, ventricles, Premature beats, and Atrioventricular junction). The analysis of the 117 cases with the key terms found 54 reports. Of these, all Tachycardia confirmed reports (37) with no other associated symptom were eliminated. Tachycardia is an increased heart rate for any reason. It can be a usual rise in heart rate caused by exercise or a stress response such as sinus tachycardia. Sinus tachycardia is considered a symptom, not a disease. Of the remaining 17 reports, 1 was non-serious and another report was a duplicate. Thus, 15 unique serious reports from this reporting period were further reviewed in detail, to identify and assess true cases of Arrhythmia. Details of these reviews are presented below in MAH re-evaluation of cumulative data.

A Health Authority requested for this PBRER that the MAH re-evaluate cumulatively the WHO-UMC classification of all serious cases of Arrhythmias, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e., Possible vs Probable and Probable vs Certain), and to discuss the result in the context of the totality of evidence on the subject. As requested, the serious cases as of PBRER#4, 134 cases, and 15 cases during the current PBRER#5 were combined and re-evaluated for the WHO-UMC causality criteria. Overall, 149 serious cases were re-evaluated for WHO causality and categorized as follows, Possible (62), Unlikely (46), Unassessable (39), and Conditional (2). There were no cases of positive rechallenge.

Cases with age < 18 years. There was 1 case in a person < 18 years of age. A consumer reported that an infant with congenital transposition of the great arteries, who was exposed to vaccine in utero by maternal vaccination, experienced supraventricular tachycardia beginning one month before death at age 3 months; cause of death was transposition of the great arteries and supraventricular tachycardia, and an autopsy was not done. WHO-UMC causality for arrhythmia unlikely due to the congenital defect.

Please refer to Appendix 12.7 for detailed MAH comment and categorization of the 149 cases.

Discussion

Cumulatively 10,793 events (9,453 reports) were reported for elasomeran (9,240 reports), elasomeran/imelasomeran (185 reports) and elasomeran/davesomeran (31 reports) (Note: there is overlap of two reports, as the following case# [redacted] was reported in Elasomeran and Elasomeran/imelasomeran; similarly another case# [redacted] was reported in Elasomeran/imelasomeran and Elasomeran/davesomeran) of which 149 serious reports were identified as Arrhythmia casesusing the methodology explained above. Of these 149 serious cases, 134 were presented during the PBRER#4 and 15 are reported during this PBRER#5. Overall re- evaluation of all 149 serious cases was performed. The WHO-UMC classification was provided for the serious 149 cases as follows: Possible (62), Unlikely (46), Unassessable (39), and Conditional (2). The clinical spectrum of events in this reporting period was similar to that reported in the previous PBRER.

No cases qualified for classification as "Probable" or "Certain," according to the WHO-UMC classification. Although some cases had a plausible temporal relationship from time of vaccine administration to development of reported cardiac arrhythmia, other data in the case reports provided reasons that weighed against both probable and certain causality by vaccine. Such countervailing data include medical history of arrhythmia; concomitant medical conditions, medications or diseases that are associated with arrhythmia; SARS-COVID-19 illness; excessive TTO of arrhythmia from vaccination; and lack of necessary medical/clinical detail. There was also a lack of clear positive rechallenge. In addition, there is

no proven pathophysiological mechanism to explain how elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran causes arrhythmia; similarly, there is no pathognomonic sign of vaccine-induced arrhythmia. Further, many of the AE reports lack information on important factors such hydration, stress/anxiety/panic, drug use, alcohol use, non-prescription cold and allergy medications, dietary supplements, SARS-COVID-19 infection, etc. Finally, the medical literature, taken together, including a small number of epidemiologic studies that have been reviewed in detail in previous submissions, does not demonstrate that arrhythmia is associated with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran.

Based on the analysis of all the safety data available as of 17 Jun 2023, the totality of the evidence does not indicate that arrhythmia is causally associated with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran. This evidence includes the post-marketing, post-approval, and post-authorization information (including literature) noted above, as well as CT data previously submitted, that do not show an association.

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 arrhythmia events and administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Arrhythmia, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety issue of concern, and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events of Arrhythmia using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Cumulatively 10,793 events (9,453 reports) of Cardiac Arrythmias were reported for elasomeran (9,240 reports), elasomeran/imelasomeran (185 reports) and elasomeran/davesomeran (31 reports)

During the review period, the MAH received 590 reports (681 events) of Cardiac arrhythmias with 503 serious reports (539 serious events), and 13 reports with a fatal outcome.

Cumulatively, no serious/fatal reports qualified for Probable or Certain causality, according to MAH's re-evaluation on this matter (see below).

The PRAC Rapporteur agrees with the MAH that the totality of evidence does not provide evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and Cardiac Arrhythmias. The MAH will continue to monitor events of Arrhythmia using routine surveillance.

Request from previous PSUSA (no 4) ITEM 6: Arrhythmias

A. The MAH is requested to re-evaluate cumulatively the WHO-UMC classification of all serious cases of Arrhythmias, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e., Possible vs Probable and Probable vs Certain), and to discuss the result in the context of the totality of evidence on the subject.

MAH Response:

The MAH has re-evaluated cumulatively the WHO-UMC classification of all serious cases of Arrhythmias reported for PBRER #4, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e., Possible vs Probable and Probable vs Certain.) The results are discussed in the context of the totality of evidence on the subject. The requested information is provided under section 15.2 Requests from Health Authorities or Regulatory bodies, Sub-section 15.2.1 of PBRER 5.

Rapporteur assessment comment:

In response to the request cited above the MAH has cumulatively identified 149 serious cases as listed in PSUR Appendix 12.7 with the requested specifications and comments. This is acknowledged and appreciated.

Using the WHO-UMC causality criteria 62 of these cases were categorized as Possible, 46 as Unlikely, 39 as Unassessable, and 2 as Conditional. There were no cases classified as with WHO-UMC Probable nor Certain causality and no cases of positive rechallenge. In cases classified as Possible, alternative reasons explaining the association included medical history of arrhythmia; concomitant medical conditions, medications or diseases that are associated with arrhythmia; SARS-COVID-19 illness; while in other cases excessive TTO of arrhythmia from vaccination and lack of necessary medical/clinical detail made association unlikely or unassessable. This is endorsed.

It is noted that standard phrases were used to describe non-eligibility for a higher classification such as "This case is classified as possible. It was not classified as probable because the information provided was too limited. Useful information that was not provided includes presence of Congenital heart diseases, including long QT syndrome; SARS-Covid-19 infection; Imbalance of electrolytes — such as potassium, sodium, calcium and magnesium; concomitant medications; use of stimulants such as cocaine or methamphetamine; personal medical history; family medical history. Thus, the criterion "Unlikely to be attributed to disease or other drugs" is not met." However, in the opinion of the PRAC Rapporteur, the WHO-UMC criterion for Probable causality "Unlikely to be attributed to disease or other drugs" may be fulfilled even if all information mentioned above may not be explicitly provided, while in the case of Certain causality, all information above should be explicitly provided. Please refer to the discussion provided in the WHO-UMC document https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf.

A review of the medical literature did not imply an association of Cardiac Arrythmias with elasomeran-containing products, and no clear mechanism for this hypothetical association has been offered.

Thus, based on the data provided, the PRAC Rapporteur concludes that the present re-evaluation of all serious cases does not support a causal association between elasomeran-containing products and Cardiac Arrythmias.

Request from previous PSUSA (no 4) ITEM 7: Arrhythmias

B. The MAH is requested to review and present all cumulative cases of arrhythmia with a positive rechallenge including an individually justified WHO-UMC causality categorisation.

MAH Response:

The MAH has searched all arrhythmia reports to identify those that note positive rechallenge and also meet the confirmed or possible arrhythmia case definition. No such cases were identified.

Rapporteur assessment comment:

Based on a request from the previous PSUSA, the MAH reported, that no cases of a positive rechallenge with elasomeran were identified among all relevant arrythmia reports.

This is endorsed, and issue is resolved.

Request from previous PSUSA (no 4) ITEM 8: Arrhythmias

C. The MAH is requested in future PSURs to specifically report on arrhythmia cases in vaccinees <18 years in the relevant subpopulation analysis.

MAH Response:

The MAH has searched all arrhythmia reports to identify those that involved vaccinees <18 years and that also meet the confirmed or possible arrhythmia case definition. One such case was identified, and its summary is as follows.

[redacted] (WWID: [redacted]): This case was reported by a consumer and concerns a [redacted]-old male patient, who was born with transposition of the great vessels. The child was born by vaginal delivery and was full term.

Reportedly, the patient's mother received the first dose of the mRNA-1273 vaccine during pregnancy and the patient was exposed to the vaccine by transplacental exposure (approximately at 2 weeks of gestational age). During pregnancy (at about 23 to 24 weeks of pregnancy), an anatomical scan of the foetus showed heart defect, and a month later a diagnosis of congenital L- transposition of the great vessels was confirmed. Just after the birth, the patient had mild tricuspid regurgitation (tricuspid valve incompetence), however, it was stated that the patient went home within 24 hours. Two months after birth, the patient had accelerated heart rate and the patient was cleared by pediatric cardiologist after two EKGs, an echocardiogram, and 48 hours on a holter monitor. However, approximately 3 months after birth, the patient was transferred to emergency room with blue penis and tachycardia (270 bpm), and he died that day. The reported causes of death were supraventricular tachycardia and transposition of the great vessels. An autopsy was not performed. The reporter informed that genetic testing showed no relationship of the baby's diagnosis to the parents, and that genetic tests and other evaluations were ongoing at the time of the follow-up report.

This infant had the congenital defect transposition of the great vessels and that was the likely cause of infant's arrhythmia. The MAH's causality assessment of arrhythmia by (maternal) vaccination was assessed as unlikely: "Disease or other drugs provide plausible explanations."

Rapporteur assessment comment:

Based on a request from previous PSUSA, the MAH reported on a single case ([redacted]) of Cardiac Arrhythmia involving a vaccinee <18 years. This case concerned a [redacted]-old male infant born with transposition of the great vessels interpreted as the likely cause of the infant's arrhythmia. This is endorsed.

The PRAC Rapporteur notes that the association of this fatal event of transposition of the great vessels with in utero exposition to elasomeran at approximately 2 weeks of gestational age has also been reported in the context of the missing information category Use in pregnancy.

No further action is needed.

2.3.2.2. Chronic urticaria

In the final assessment report for PBRER #4, the following was noted by a Health Authority:

"Chronic urticaria" – literature

The publication by Drivenes et al [18] is claimed by the MAH to be a ModernaTx, Inc CT and has not been further commented upon by the MAH. The MAH should comment upon this paper in the next PSUR, both on the content regarding elasomeran and occurrence of urticaria-related events, in particular the events concerning chronic urticaria, and to explain the stated relationship to a ModernaTx, Inc's CT.

The MAH is requested to comment upon the publication by Duperrex et al [19] in the next PSUR. If the literature review warrants further evaluation on the topic of chronic urticaria, the MAH should prepare and present an updated review on chronic urticaria, including a proposal for amendment of the Product Information if warranted."

Drivenes et al [18]
The Drivenes article featured a Letter to the Editor which presented a case series describing sixteen patients (10 female/6 male, median age of 33 years [range: 20 to 73 years]) who experienced events of delayed onset urticaria. Thirteen patients had no prior medical history of urticaria and developed inducible urticaria and/or spontaneous urticaria post-vaccination. The remaining three patients developed an exacerbation of their pre-existing urticaria with two of those three patients experiencing newly developed symptomatic dermographism. All patients developed symptoms within 1 day to 3 weeks following booster vaccination with a median time of 14 days. Most patients had severe symptoms with six requiring acute doctor visits and four patients being admitted to the emergency room. All patients were treated with high-dose antihistamines, and four patients received treatment with systemic corticosteroids. A total of five patients received further treatment with omalizumab. Events of delayed onset urticaria were more commonly observed after vaccination with a booster dose of Moderna (12; 75.0%), despite only 13.5% of Danes receiving Moderna as booster vaccines. In all cases, the onset of delayed urticaria and symptomatic dermographism was temporally associated with the administration of the vaccine.

MAH Comment: The MAH erroneously stated that the cases described in this article were from a Moderna CT and would not necessitate the creation of post market ICSRs. The MAH regrets this misstatement and has undertaken creation of ICSRs.

Duperrex et al [19]
Chronic spontaneous urticaria (CSU) is a common medical condition and has a wide range of causes. The background rates of CSU from population-based observational studies prior to the era of COVID-19 reported ranged from 80 to 150 per 100,000 population per year in Europe [20], [21], [22]. The authors did not perform a comparison between the estimated incidences of CSU after receipt of the third dose of mRNA COVID-19 vaccine and the background rates.

Using passively reported CSU cases nationwide from Swissmedic, the authors extracted 607 CSU cases reported to Swissmedic after the third Moderna dose during 21 Jan 2021 to 31 Aug 2022 and reported the incidence rate being 30.8 per 100,000 persons (95% CI=28.4, 33.4) during one and half years. Using the lower bound of background rates (80 per 100,000 person per year) as a conservative reference rate and a risk window of six weeks based on the clinical definition of CSU, the crude O/E is 2.08 (95% CI=1.92 to 2.25), implying the observed number of cases was higher than the expected signaling an excess of risk [23]. However, spontaneous reporting systems detect signals that could be due to factors other than the vaccine itself, and the signal requires further investigation and confirmation from formal

epidemiologic studies. It is unclear whether these CSU reported cases underwent a clinical review and whether there was stimulated reporting or underreporting of CSU cases to the Swissmedic system during the case accrual period. The O/E ratio was crude without adjustment for demographics and risk factors for CSU. Misclassification of the risk window could over- or under-estimate O/E ratios; analyses assuming that cases could be reported at any time after vaccination did not suggest an increased risk.

Based on a convenience sample of CSU in the canton of Vaud of Switzerland, the authors included 69 patients with CSU after the third Moderna dose and reported an incidence rate of 43.9 per 100,000 persons (95% CI=34.5-56.0) during approximately four months of follow-up. Using the lower bound of background rates (80 per 100,000 person per year) to be conservative and a risk window of six weeks based on the clinical definition of CSU, the crude O/E ratio is 15.04 (95% CI=11.70, 18.80), implying the observed number of cases were higher than the expected signaling an excess of risk. However, this estimate requires cautious interpretation. First, misclassification of the cause of CSU is possible. The case definition or eligibility of CSU that allergists used, and attributable causes of CSU were not reported. Most CSU patients had risk factors (75% taking daily antihistamine, 14% with previous urticaria, 29% had hay fever, and 11% had drug allergies) that put them at a higher risk to develop CSU for a wide range of causes. Second, as the authors acknowledged in the Discussion, "there is a selection bias for patients with CSU in relation to COVID-19 vaccines". The questionnaire and characteristics of those who did not participate are not available. Over 80% of the patients had active CSU at data collection and were more likely to report their recent COVID-19 vaccination history when it was asked. Other alternative causes for CSU may not be elucidated. Third, the case accrual period was much shorter than the national analysis, rendering approximately five expected cases and imprecise estimate of the ratio. The O/E ratio was crude without adjustment for demographics and risk factors for CSU. Misclassification of the risk window could over- or under-estimate O/E ratios.

Comparisons between vaccine brands were limited by confounding and potential selection bias for both analysis in Vaud and Switzerland nationwide. Firstly, the authors acknowledged in the Discussion, "we could not adjust IR because individual data on vaccination by brand, age, and sex were not available", yet demographics and risk factors for CSU of CSU patients secondary to Pfizer-BioNTech vs Moderna recipients may differ. A formal head-to-head comparison with proper adjustment for confounding is needed for a fair interpretation of risk differences, if any. Secondly, in the analysis in Vaud using a convenience sample, it is unclear whether the institutes where the 16 allergists had access to CSU cases had higher proportion of Moderna receipts, compared with the brand distribution of the whole Vaud area. Also, it is unclear whether factors affecting patients' participation in the questionnaire differ between two brands (80/97 participated). In the analysis in Switzerland nationwide, it is unclear whether reports following Moderna vaccination were simulated during 21 Jan 2021 to 31 Aug 2022, compared with Pfizer vaccination, which could contribute to differential reporting rates.

MAH Conclusion:

The MAH considers that the information presented in these two articles does not offer compelling evidence of any new or emerging safety concern to warrant further evaluation for the topic of chronic urticaria. The current safety information adequately reflects the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran and an amendment of the Product Information is not warranted.

Rapporteur assessment comment:

As a request from the previous PSUSA (PSUSA/00010897/202212) the MAH should comment on two

publications by Duperrex O. et al.[1] and Drivenes JL. et al.[2] regarding elasomeran-containing vaccines and chronic urticaria. The MAH should further explain the MAH stated relationship of the study by Driveness JL. et al. [2] with a ModernaTx Inc's clinical trial. Based on the review of these publications, the MAH was requested to consider if the topic of chronic urticaria needs further evaluation and if warranted, the MAH should present an updated review of chronic urticaria.

Regarding the study by Drivenes JL. et al.[2] the MAH regrets their erroneous statement claiming that the study is a Moderna clinical trial and the MAH has undertaken the creation of ICSRs of the cases presented in the article. The MAH has presented summaries of the two publications, however, the MAH did not comment as such on the publication by Drivenes JL. et al.[2] as requested.

The publication of Drivenes JL. et al.[2] presents a case series of twelve patients receiving the elasomeran-containing vaccine. One patient vaccinated had a medical history of urticaria while two patients had a history of atopic dermatitis. All patients developed delayed onset urticaria and/or dermographism 1-21 days after the third vaccination. Dermographism was diagnosed in eleven patients and delayed urticaria in seven patients. The duration of the symptoms lasted two months or more, hence defined as chronic urticaria. All patients were treated with antihistamine and four patients were further treated with omalizumab of which two patients were further treated with systemic corticosteroids. Four patients had ongoing symptoms after 6-7 months despite treatment and four patients experienced remission after 2-7 months. Three patients experienced resolution of symptoms after 2-3 months while one patient was lost to follow-up.

The publication by Duperrex O. et al.[1] aimed to assess a potential temporal association between vaccination with Covid-19 vaccines and new onset chronic spontaneous urticaria (CSU) in the canton of Vaud (n=80) and all of Switzerland (n=782). Following the third dose of elasomeran-containing vaccine, 69 patients developed CSU in the Vaud cohort with an incidence rate of 43.9 [CI: 34.5-56.0] per 100,000 while 607 patients developed CSU in the Swiss cohort with an incidence rate of 30.8 [CI: 28.4-33.4]. The results clearly indicate an overall association between third dose vaccination and the development of CSU with the elasomeran-containing vaccine.

Based on the two studies, the MAH concludes that no new or emerging safety concerns regarding chronic urticaria is provided and that further evaluation is not warranted. The PRAC Rapporteur does not agree with the MAH's conclusion and considers that a potential association between chronic urticaria and elasomeran-containing vaccine is possible and should be further elucidated.

Regulatory background

Chronic urticaria was evaluated as a signal in the 3rd elasomeran PSUSA (PSUSA/00010897/202206). At that time point, the PRAC Rapporteur concluded that there were several aspects pointing towards a possibility for a causal association between elasomeran-containing vaccine and chronic urticaria. However, it was further concluded that a causal association between elasomeran-containing vaccine and chronic urticaria could not be established based on the available data, and the PRAC decided to refute the signal.

In the previous PSUSA procedure (PSUSA/00010897/202212) the product information was updated with the adverse drug reaction mechanical urticaria in section 4.8 and 4 while urticaria and injection site urticaria were already included in section 4.8 and 4. In section 4.8 it is further described that "Urticaria has been observed with either acute onset (within a few days after vaccination) or delayed onset (up to approximately two weeks after vaccination)". As with mechanical urticaria, urticaria was also included in the product information in a separate procedure.

Chronic urticaria is defined by the presence of recurrent urticaria, angioedema, or both, for a period of more than six weeks. In contrast to urticaria with a duration of up to six weeks, chronic urticaria can be

ongoing for months or years, consequently with a significant impact on the quality of life of the affected individual. No treatment available can cure chronic urticaria, however, different therapies may control the condition and prevent sign and symptoms. Antihistamine is the first line treatment, but also glucocorticoid, immunosuppressants or anti-inflammatory drugs may be needed dependent on seriousness of the condition[3].

Evaluation of chronic urticaria by the Danish Medicines Agency's national signal detection team

In Denmark, the Danish Patient Compensation is an association independent of the Danish Medicines Agency. The Danish Patient Compensation consists of medical doctors that helps patients evaluate if they are entitled to compensation due to injuries from healthcare treatments or side effects to drugs.

In December 2022 the Danish Patient Compensation announced that they had found sufficient evidence to re-evaluate cases of chronic urticaria despite the fact that chronic urticaria was not included in the product information as a known adverse drug reaction of the elasomeran-containing vaccine. As a consequence, the Danish Medicines Agency's (DKMA) national signal detection team decided to re-evaluate the signal. A noteworthy number of cases with chronic urticaria and elasomeran-containing vaccine had been registered in Denmark at that time point. The DKMA received information from the Danish Patient Compensation regarding the Danish compensation cases and identified additional case information (compared to the spontaneous reports) relevant for strengthening the causality assessment. The collaboration was extended so that the DKMA was granted full access to material from the patient's medical records via the Danish Patient Compensation. The new case information has been/will be made available as follow-up information in Eudravigilance.

The Danish national signal detection team has performed a review of cases of elasomeran-containing vaccines and chronic urticaria from EVDAS, including the Danish cases with additional case details from the Danish Patient Compensation, which is presented below.

EVDAS cases

In a cumulative EVDAS search per 21 September 2023, 360 cases were identified with elasomeran-containing vaccines and the PTs "Urticaria chronic" and "Chronic spontaneous urticaria". However, the actual number of cases may be even higher since all relevant cases registered with urticaria may not be re-registered as chronic urticaria after the definition limit between acute and chronic urticaria of six weeks duration. The registration procedure of chronic urticaria might also vary between countries and potentially lead to underreporting.

The causality assessment of the 360 cases of chronic urticaria identified in EVDAS is based on the WHO-UMC causality scale, which identified 58 probable, 228 possible, 33 unlikely, 9 conditional and 32 unassessable cases. Characteristics of the probable and possible cases are presented in table 1. A number of the cases are literature cases and some are referred to in the assessment.

Table 1. EVDAS cases retrieved 21. Sep 2023 with elasomeran vaccine and PTs Urticaria chronic and Chronic spontaneous urticaria assessed as probable or possible

	Age (years)	Gen-der	TTO (days)	Dose 1/2/3	Serious	Medically confirmed	Positive rechal-lenge	Co-occurent mechanical urticaria
Probable N=58	15-57 18-39: n=49	F=39 M=19	1-45	3/6/46	21 (36%)	41 (71%)	10 (17%)	21 (36%)
Possible N=228	18-87 18-39: n=161	F=132 M=94	0-25	25/17/151	96 (42%)	110 (48%)	7 (3,1%)	47 (21%)

Number of cases assessed Unlikely n=33, Conditional n=9, Unassessable n=32. Total number of cases retrieved n=360. Dose 1/2/3 defines after which vaccination dose chronic urticaria was diagnosed. Dose number was unknown in 3 probable and 35 possible cases).

The cases assessed as probable are mainly reported from [redacted] (n=44), Switzerland (n=3) and Italy (n=2). The majority of cases assessed as possible are reported from [redacted] (n=92), Germany (n=28), Switzerland (n=25), Italy (n=19), France and US (n=11) and Norway and United Kingdom (n=9). Out of the 58 probable cases, 25 patients have received patient compensation for chronic urticaria of which 24 are from [redacted] and one from Austria. As mentioned above, the [redacted] Patient Compensation is an association independent of the [redacted] Medicines Agency where medical doctors have evaluated and concluded that the patients are entitled to compensation for elasomeran-containing vaccine induced chronic urticaria in the 24 [redacted] cases. Among the cases assessed as possible, 43 [redacted] patients have also received compensation.

The cases assessed as probable are characterized by patients in the age group 18-39 years (n=49, 84%) and a majority of females (n=39, 67%). Data received from the [redacted] show that there is no difference in the distribution of the number of females and males receiving the elasomeran-containing vaccine ranging from 49.0% to 50.6% females through the period 2021-2023. From the [redacted] cases assessed as probable cases (n=44), 29 cases concerned females and 15 cases concerned males, which is in accordance with existing evidence stating that chronic urticaria is more frequent in females[4].

The age group of 18-39 years old patients dominated in the probable cases by 84% which is supported by the literature stating that the group of 20-40 years old is generally more pre-disposed to develop chronic urticaria[4]. [redacted] data provided by the [redacted] showed that in 2021 and 2022, 50% and 65%, respectively, of the administered elasomeran-containing vaccine doses were also given to the 20-39 years old. As a consequence, we cannot from these data conclude on whether the 18-39 years old patients may be in higher risk of developing chronic urticaria.

In total, 117 probable and possible cases were serious, however none were fatal. One case was life-threatening, while 22 cases required hospitalization and 38 cases were disabling. In total, 112 of the probable and possible cases were reported by a physician or other healthcare professional while 150 were medically confirmed.

Time to onset and vaccine dose

The time to onset (TTO) is defined as the time from the last dose administered to urticaria is observed. TTO of chronic urticaria from the last vaccine dose was 7-13 days for the majority of probable (n=40,

68.9%) and possible (n=132, 57.9%) cases (figure 1) which demonstrates delayed onset of chronic urticaria in the majority of cases. This pattern is similar to what has been observed for mechanical urticaria induced by elasomeran-containing vaccines, which was presented in the previous PSUSA (PSUSA/00010897/202212) showing that 75.6% of all cases had a TTO of 7-13 days. Furthermore, the majority of both probable and possible cases were reported after the third dose of elasomeran-containing vaccine which is also similar to the pattern for mechanical urticaria (52.2%).

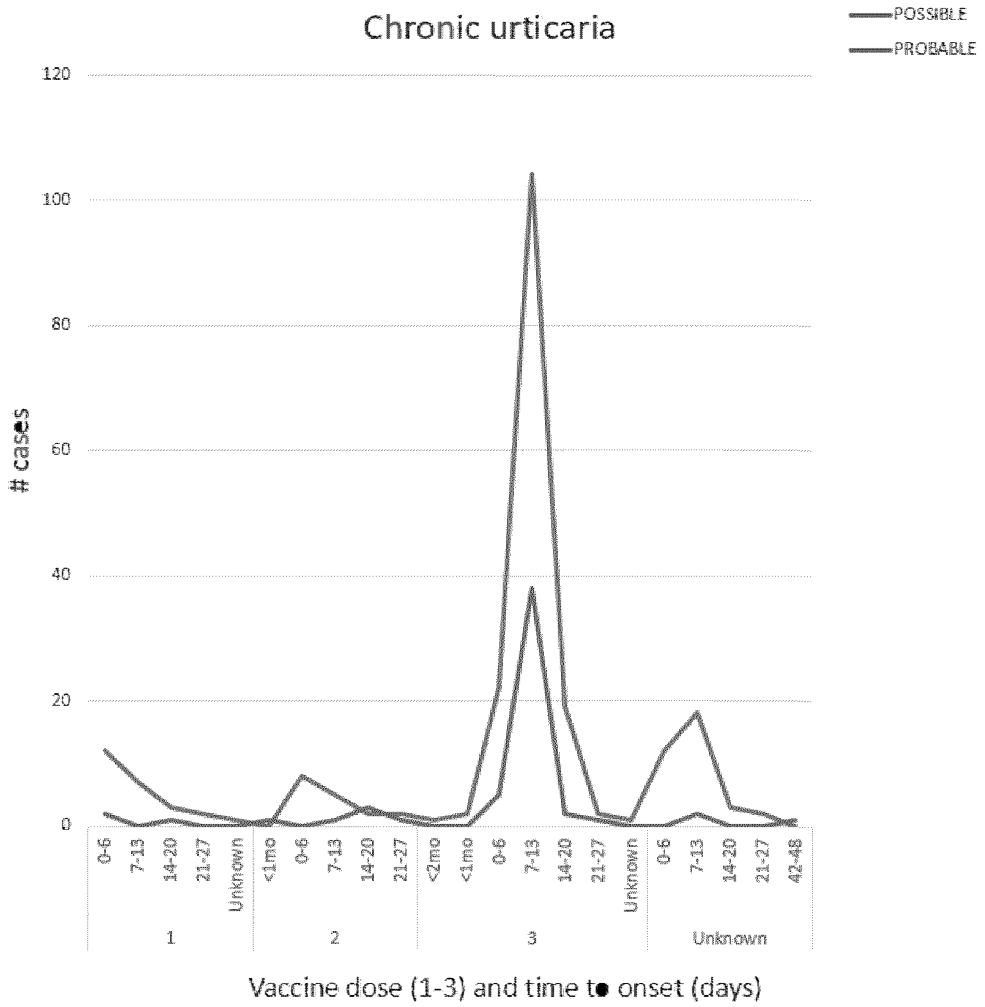

Figure 1. Time to onset (TTO) of chronic urticaria and dose number of elasomeran-containg vaccine administered in probable (n=58) and possible (n=228) cases. Dose number of the vaccine is presented as dose 1 (n=28), 2 (n=23), 3 (n=197) and unknown dose (n=38). TTO is presented in days from the last vaccine dose administered in ranges of 7 days. One probable case has TTO <1 month (0-19 days, dose 2) while two possible cases have TTO <1 month (1: less than 14 days, 1: 1-26 days, both dose 3). One possible case has TTO <2 months (5-8 weeks, dose 3). Two possible cases have unknown TTO (dose 1, 3).

It is furthermore noteworthy, that most of the patients developed chronic urticaria after the third vaccine dose with 79% of the probable cases (n=46) and 66% of the possible cases (n=151). This is a clear pattern that the booster dose is the most frequent dose reported to trigger the development of chronic

urticaria, which again reflects the pattern of mechanical urticaria with 52.2% reported with dose 3. The literature further support this[2, 5-8]. In the study by Duperrex O. et al.[1] 72 patients in the Vaud-cohort and 727 patients in the Switzerland cohorte developed chronic urticaria following the third dose of the elasomeran-containing vaccine, both numbers corresponding to 96% of the total number of new onset chronic urticaria, respectively. In this study the incidence rate of chronic urticaria following the third vaccine dose was 43.9 and 30.8 per 100,000 in the two cohorts for patients receiving elasomeran-containing vaccine.

In the current review, the duration of chronic urticaria after the first six weeks of acute urticaria was measured. In the probable cases the duration of chronic urticaria was more or less equally distributed ranging from 1,5 month to 12 months (n=45 cases), with the highest number of cases >4 to 6 months (n=13). Six cases reported duration of chronic urticaria over 1-year from which none of the patients were recovered at the reporting time. None of these six cases reported of any concomitant medicine. In all six cases the patients received treatment with two or more drugs from the list of antihistamines, fexofenadine, prednisolone, desloratadine and omalizumab.

Co-occurrence of mechanical urticaria

A potential co-occurrence of chronic urticaria and mechanical urticaria has been proposed in the previous PSUSA (PSUSA/00010897/202212). This is also demonstrated in the current review of cases, showing that mechanical and chronic urticaria co-occurred in 21 (36%) of the probable cases and in 47 (21%) of the possible cases after receiving the elasomeran-containing vaccine. This is in accordance with Dice JP. et al.[9] who has noted that inducible urticaria is present in 20-30% of adults with chronic urticaria. Different studies further present cases supporting this potential association between chronic urticaria and mechanical urticaria following administration of the elasomeran-containing vaccine [2,7,10,11]. Drivenes JL et al.[2] demonstrate this co-occurrence of mechanical and chronic urticaria in a study where 11 patients out of 12 develop dermographism and chronic urticaria 7-21 days following the booster vaccination with elasomeran-containing vaccine. A study by Strahan et al.[10] presents 2 cases of CSU following the elasomeran-containing vaccine booster. In both cases, there was no significant medical history. Urticaria and dermatographism started 11 and 12 days after the booster vaccine and continued for >6 weeks. Malcolm et al.[11] presented a case with a woman with no apparent allergic exposures who developed pruritic rash and dermatographism ten days after the elasomeran-containing vaccine booster. Symptoms continued despite medical treatment, and the patient was diagnosed later with chronic spontaneous urticaria. The evidence from cases and literature imply that the pathological mechanisms inducing mechanical urticaria and chronic urticaria, respectively, may be connected and triggered by elasomeran-containing vaccine. This support the overall evidence of acknowledging chronic urticaria as an adverse drug reaction for elasomeran-containing vaccine.

Analysis of standardised incidence ratios of chronic urticaria by Statens Serum Institut in Denmark

An un-published data analysis has been performed in Denmark by Statens Serum Institut with the aim of comparing the observed rates of chronic urticaria after elasomeran-containing vaccine and Comirnaty vaccine, respectively, with the expected rates obtained 2017-2020. The study was based on the Danish population exposed to the third vaccination dose with data retrieved on 27 February 2023. Hospital visits including a diagnosis of chronic urticaria was registered while subsequent hospital visits with diagnosis of chronic urticaria during the following 365 days were excluded from the analysis. The observed and expected rates were compared using standardized incidence ratios (SIRs) by diving the number of observed cases with the number of expected cases. Hence, in this data analysis the SIR is an estimate of the number of chronic urticaria cases registered in Denmark compared to what may be expected based

on the experience in the Danish population. The SIR for elasomeran-containing vaccine was based on 63 cases and calculated as 4.31 (95% CI, 3.31-5.51) (for comparison, the observed and expected rates for Comirnaty was less pronounced with SIR (based on 182 cases) equal to 2.21 (95% 1.83-2.46)). These unpublished data highlight an increased risk of chronic urticaria following the third dose of elasomeran-containing vaccine. These data further support the findings from the EVDAS cases and literature presented in this review, both with regard to a causal relationship between chronic urticaria and the elasomeran-containing vaccine as well as the booster dose being the primary dose triggering chronic urticaria.

Disproportionality analyses

In Vigilyze, there is a signal of disproportionate reporting (per 05 Nov 2023) for the PT 'Urticaria chronic' with 660 observed cases vs 56 expected (IC025: 3.4) and a Reporting odds ration (ROR (-)) of 15.5., and for the PT 'Chronic spontaneous urticaria' 292 cases were observed vs. 24 expected (IC025: 3.4) with a ROR(-) of 15.6.

In Eudravigilance, the ROR for the PT's 'Urticaria chronic' and 'Chronic spontaneous urticaria' rose in the first half of 2022 and the ROR(-) at present (Nov 2023) is also disproportionate at 6.18 and 4.02, respectively.

Examples of probable cases

[redacted]

A [redacted] case concerned a 26-years old female developed urticaria 10 days after the third dose of the elasomeran-containing vaccine. Urticaria presented with co-occurrence of mechanical urticaria. The patient was vaccinated on 10 December 2021 and she developed urticaria on 20 December 2021. In January 2023 the patient still suffered from urticaria with a duration of more than 12 months. The patient had no other health issues and no medication was reported. Blood test revealed no other explanations for chronic urticaria. The case was medically confirmed. The case of chronic urticaria was recognised as an adverse drug reaction associated with the elasomeran-containing vaccine for which the patient received patient compensation.

[redacted]

This is a case from [redacted] with a 25-years old female experiencing intense skin rashes and dermographism 11 days after vaccination (dose number unknown), which required therapy with antihistamines and cortisone (desloratadine, fexofenadine and betamethasone). The reaction date was 01 February 2022 and therapy continued until May. After suspension, the patient reports a worsening of the clinical picture. The duration of urticaria was more than 8 months. Blood tests and allergy tests did not report any particular allergies. The patient reported no past clinical history of allergies to drugs, foods or substances.

[redacted]

In a [redacted] case a 36-years old female developed urticaria 10 days after the third dosis of the elasomeran-containing vaccine 26 December 2021. The patient was treated with desloratаedin and cetirizin. The patient experienced local redness after the second dosis which was managed with antihistamine. The patient presented with mechanical urticaria. Blood tests were normal. In September

2022 the patient experienced episodes of urticaria every week. In March 2023 there was only episodes of urticaria every 2-3 month for which no medication was taken regularly.

[redacted]

In a [redacted] case a 34-years old female developed itching and rash 9 days after receiving the third dose of elasomeran-containing vaccine administered on 16 January 2022. The patient was treated with telfast, prednisolone, however, the urticaria continued and was especially triggered by heat demonstrating the co-occurrence of mechanical urticaria. The urticaria was controlled to some extent by antihistamine but was ongoing in March 2023 and had continued for more than 12 months. Blood tests were normal and no other comorbidities or concomitant medication were reported. The patient has received patient compensation.

Conclusion

Chronic urticaria is a condition with consequences which can vary from very light to serious with a significant effect on quality of life for the affected individual. Therefore, it is essential to evaluate carefully this safety issue.

The cumulative review of cases and literature combined with new data support a causal association of a relationship between the development of chronic urticaria and elasomeran-containing vaccine. The assessment included all 360 cases retrieved from EVDAS regarding elasomeran-containing vaccine and chronic urticaria of which 58 cases were assessed probable and 228 cases possible. However, the actual number of cases may be even higher since all relevant cases registered with urticaria may not be re-registered as chronic urticaria after the definition limit between acute and chronic urticaria of six weeks duration. The Danish study by Drivenes JL. et al.[2] describes a case series of 11 patients with chronic spontaneous urticaria and dermatographism and/or delayed urticaria following elasomeran-containing booster vaccination. This publication has probably raised awareness of the elasomeran-containing vaccine and chronic urticaria among Danish practitioners, however, it is considered unlikely that this alone could account for the large number of Danish reports. However, general awareness of chronic urticaria in Denmark could probably have had an impact on the reporting pattern.

24 of the probable and 43 of the possible cases have been thoroughly evaluated by independent medical doctors from the Danish Patient Compensation with patient compensation as an outcome. These evaluations acknowledge chronic urticaria as an adverse drug reaction of elasomeran-containing vaccines, despite not being listed in the product information, which substantiates the validity of these cases further supporting a causal association between chronic urticaria with elasomeran-containing vaccine.

The cases from the unpublished data from Denmark from Statens Serum Institut further adds evidence to a causal relationship by comparing the observed rates with expected rates of chronic urticaria following elasomeran-containing vaccine which revealed an increased risk of developing chronic urticaria by a standard incidence ratio (SIR) of 4.31 (95% CI, 3.31-5.51).

Urticaria and mechanical urticaria are known adverse drug reactions for elasomeran-containing vaccines and are characterised by delayed onset urticaria with a TTO of 7-13 days with onset primarily after the third dose. The same pattern has been demonstrated in this cumulative review on chronic urticaria showing that 69.0% of probable cases and 57.9% of the possible cases had a TTO of 7-13 days, while cases in this review assessed probable and possible have onset of chronic urticaria after the third dose in 79% and 66% of the cases, respectively. The publication by Duperrex O. et al.[1] further strongly supports that the onset of chronic urticaria most frequently occurs after the third dose of elasomeran-containing

vaccine. The proposed co-occurrence of mechanical and chronic urticaria is shown in 36% of the probable cases which is in accordance with the 20-30% as stated in the literature for chronic urticaria in general. This is further strongly supported by the characteristic pattern of delayed TTO of 7-13 days and onset after the third vaccination.

Based on this cumulative review and thorough assessment of all cases available, including several cases with patient compensation, combined with literature review the PRAC Rapporteur considers that a causal association between the development of chronic urticaria and elasomeran-containing vaccines is at least possible and therefore an update of the product information is warranted.

Based on the cumulative review presenting evidence of at least a possible causal association between chronic urticaria and elasomeran-containing vaccines, the MAH is requested within this procedure to comment on the update of the product information with chronic urticaria.

References

1. *Duperrex O et al. Incidence of Chronic Spontaneous Urticaria Following Receipt of the COVID-19 Vaccine Booster in Switzerland. JAMA Netw. Open 2023 Feb*
2. *Drivenes JL et al. Delayed onset urticaria and symptomatic dermographism following COVID-19 booster vaccination: A case series. Clin Transl Allergy 2022 Nov*
3. *Khan DA. et al. Chronic spontaneous urticaria: Treatment of refractory symptoms. UpToDate Jan 2021*
4. *Sánchez-Borges M et al. The challenges of chronic urticaria part 1: Epidemiology, immunopathogenesis, comorbidities, quality of life, and management. World Allergy Organization Journal 2021 Jun*
5. *Pescosolido E et al, Clinical and immunological data from chronic urticaria onset after mRNA SARS-CoV-2 vaccines Clin Exp Allergy 2022 Nov*
6. *Miller et al. Chronic Spontaneous Urticaria Following mRNA COVID-19 Booster Vaccination at a Military Academy, Mil Med 2023 Sep 19 (online ahead of print).*
7. *Amjad M et al, COVID-19 Vaccine Booster-Induced Dermatographism. Cureus 2022 Jul*
8. *Bianchi L, Hansel K, Biondi F, Napolitano M, Patruno C, Fabbrocini G, et al. Delayed urticaria after the third dose of mRNA COVID19 vaccine: A case series. Dermatol Ther. 2022;35(9):e15680.*
9. *Dice JP, Gonzales-Reyes E. Physical (inducible) forms of urticaria. UpToDate 2022.*
10. *Strahan A et al. Chronic spontaneous urticaria after COVID-19 primary vaccine series and boosters. JAAD Case Rep 2022 Jul*
11. *Malcolm TR, Shah YB. Woman with pruritic rash and dermatographism. J Am Coll Emerg Physicians Open. 2022;3 (2):e12709*

2.3.2.3. Heavy menstrual bleeding (Bivalent only)

Table 15.5 Heavy menstrual bleeding (Bivalent Only)

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 117 ○ New and Significant Safety Information: 1. Refer to Section 11 for additional information on this article by Uzun et al, 2023 [14].
Background	Heavy Menstrual Bleeding (HMB) following bivalent vaccination was triggered by a request received from a Health Authority on 27 Apr 2023 (see below). *"ModernaTx, Inc. is requested to submit the following:* *1. Information reviewed to date regarding HMB following Spikevax COVID-19 vaccination contained limited discussion of bivalent vaccines. In addition, long-term outcomes, reporting rates, and risk factors have not yet been characterized. Provide an updated review of Heavy Menstrual Bleeding in the next PSUR/PBRER including:* *a. Cumulative review of post-market cases, with a focus on reports following bivalent vaccination.* *An updated review of any new literature (e.g., prospective cohort studies) on the risk of HMB following monovalent and/or bivalent Spikevax COVID-19 vaccination. Any relevant feasibility assessment documents on implementing new or amending ongoing PASS that were prepared for other regulatory agencies (e.g., EMA). A discussion on the need to update the RMP to better characterize the risk of HMB following Spikevax vaccination."*
Methods of Evaluation	**Identification of Case Reports in ModernaTx, Inc. GSDB:** Search Criteria Applied: Cases of heavy menstrual bleeding associated with elasomeran/imelasomeran and elasomeran/davesomeran were retrieved from the company safety database using the following three MedDRA PTs: "Heavy menstrual bleeding," "Menometrorrhagia," and "Polymenorrhagia" with a DLP date of 17 Jun 2023 using MedDRA version 26.0.
Results	Refer to Appendix 12.12 for additional information, including summary tables of cases and events, case evaluations, and additional analyses. ***A. Cumulative review of post-market cases, with a focus on reports following bivalent vaccination.*** Cumulatively, the MAH received 86 cases (9 serious cases) with 117 events

	(8 serious) which reported symptoms of heavy menstrual bleeding in individuals who received a booster dose of elasomeran/imelasomeran or elasomeran/davesomeran. No cases reported a fatal outcome, and 5 cases were medically confirmed. The MAH received more cases with events of heavy menstrual bleeding for individuals who received elasomeran/imelasomeran than those who received elasomeran/davesomeran. For individuals who received elasomeran/imelasomeran, the MAH received 83 cases (114 events) with 8 serious cases (7 serious events). No cases reported a fatal outcome, and 4 cases were medically confirmed. For individuals who received elasomeran/davesomeran, the MAH received 3 cases (3 events) with 1 serious case (1 serious event). No cases reported a fatal outcome and 1 case was medically confirmed. Cumulatively, the majority of the reported events (77 events; 89.5%) were non-serious. The most reported PTs were heavy menstrual bleeding (85) and polymenorrhoea (17). Of the 86 case reports, none of the cases required hospitalization or blood transfusions for heavy menstrual bleeding. Treatment information was provided in 2 cases which included hormone replacement therapy and tranexamic acid. Cumulatively, 83 (96.5%) reports were from regulatory authorities and 3 (3.5%) reports were spontaneously reported to the MAH. Most of the cases were received from the EEA (71; 82.6%) and UK (11; 12.8%). As expected, most cases were reported among women of reproductive age (18 to 49 years of age). When age was reported, 38 cases (60.3%) were reported among women 25 to 49 years of age. There were no reports received in the adolescent group of 12-17 years of age. The mean age was 48.1 years, and the median age was 48.0 years (range: 29.0 to 61.0). Of the 86 cases received, 36 cases reported medical history with pre-existing conditions including COVID-19 infection (32 cases), endometriosis (1 case), polycystic ovaries (1 case), menopause (1 case), rheumatoid arthritis (1 case), epilepsy (1 case), unspecified lung disorder (1 case), and asthma (1 case). In 44 cases (51.2%), the patients had received prior COVID-19 vaccinations with Pfizer-BioNTech COVID-19 vaccine and/or Janssen COVID-19 vaccine. Cumulatively, when the dose number immediately preceding the event was known, more events were reported after Dose 4 (5 events; 83.3%) than Dose 3 (1 event; 16.7%). This data should be interpreted with caution as dose number was not reported in the majority (111 events; 94.9%) of events; and the global vaccine administration/exposure data are limited for the various doses. When time to onset and dose number was known, the average TTO was 8.2 days (SD: 9.4) with a median TTO of 5 days (range: 0 to 30 days). Cumulative data does not present clustering of cases by dose and TTO; however, it is difficult to interpret the TTO without putting it into context of the menstrual cycle including what phase of menstrual cycle vaccination occurred. Most events reported an outcome of Not recovered/ Not resolved"

	(71 events: 60.7%). The remaining events reported outcomes as "Recovered/Resolved" (21 events; 17.9%), "Recovering/Resolving" (12 events; 10.3%), "Unknown" (12 events; 10.3%), and "Recovered/Resolved with Sequelae (1 event; 0.9%). No events reported a fatal outcome. In many cases, key missing information included medical history, concomitant medications, duration of bleeding, number of pads, onset of the event, clinical course, gynaecologic examination, treatment, dechallenge/rechallenge information, and diagnostic studies. According to the WHO-UMC causality assessment, 86 cases were assessed as follows: "Unassessable" (85 cases) and "Unlikely" (1 case). *Serious Events of Heavy Menstrual Bleeding* Cumulatively, 9 serious cases (8 serious cases for elasomeran/imelasomeran and 1 serious case for elasomeran/davesomeran) were reported with events of heavy menstrual bleeding. However, only 7 cases reported the PT "Heavy menstrual bleeding" as a serious event. Two of the serious cases [redacted] and [redacted] reported the event of "post-menopausal haemorrhage" as the only serious event (both individuals were 51 years of age). The remaining 7 serious cases [redacted] and [redacted] reported the PT "Heavy menstrual bleeding" as serious. Of these 7 serious cases, no cases were fatal or medically confirmed. In cases where age was reported, all patients were female between the ages of 29 and 61 years old [median age: 45.0 years old; mean age: 45.4 years (SD: 12.4)]. In the 4 cases that reported medical history, concurrent conditions included COVID-19 infection (4 cases), menopause (1 case), asthma (1 case), and rheumatoid arthritis (1 case). The reported outcomes for these serious events were as follows: "Not Recovered/ Not resolved" (4 events; 50.0%), "Recovered/Resolved" (2 events; 25.0%), "Recovering/Resolving" (1 event; 12.5%), and outcome "Unknown" (1 event; 12.5%). According to the WHO-UMC causality assessment, all 7 serious cases reporting the specific event of heavy menstrual bleeding as serious were assessed as "Unassessable" due to insufficient information. *B. An updated review of any new literature (e.g., prospective cohort studies) on the risk of HMB following monovalent and/or bivalent Spikevax COVID-19 vaccination.* Please refer to *Source of New Information* section above. *C. Any relevant feasibility assessment documents on implementing new or amending ongoing PASS that were prepared for other regulatory agencies (e.g., EMA). A discussion on the need to update the Risk Management Plan to better characterize the risk of HMB following Spikevax vaccination.* To date, no PASS has been planned for any regulatory agencies. The MAH

	has comprehensively evaluated the topic of HMB previously using all MAH data source as well as the published literature. In the Monthly Summary Safety Report (MSSR) #8, the MAH reviewed all data sources including CT data to investigate the topic of menstrual disorders including HMB. Another comprehensive review was performed in response to the validated signal of "Heavy menstrual bleeding" (EPITT No. 19780). Having considered all the data submitted by MAH for both evaluations, PRAC concluded that the current evidence was insufficient to warrant an update to the produce information at present. Menstrual cycle disorders are challenging to study even in CTs for several reasons. The basic biology of the menstrual cycle is not so basic; it is a complex, coordinated sequence of events involving the hypothalamus, anterior pituitary, ovary, and endometrium. Variation in menstrual cycle duration, timing, and intensity is expected under normal conditions and measures of "heavy menstrual bleeding" are subjective and imply comparison to an individual's baseline. In the absence of consistent capture of data over a pre-vaccination and post-vaccination interval to form a basis for comparison, data following a vaccination event would be difficult to interpret. From a perspective of practicality, these data were not collected in existing trials. Given the serious ethical concern because of the availability of approved vaccines targeting SARS-CoV-2, the existing trials do not have a placebo arm. In setting of expected natural variation in menstruation and the high prevalence of HMB, a control arm is critical because data from an uncontrolled cohort will be difficult to interpret. Concerning the feasibility of including heavy menstrual bleeding in subsequent SARS-CoV-2 clinical studies, the aforementioned concerns remain. Although, HMB is currently captured via unsolicited reporting, sensitivity of the capture of heavy menstrual bleeding could be enhanced by soliciting this adverse event during follow-up. However, it is expected that the impact of solicited reporting might disproportionately increase this subjective measure. In the context of trials, only very large-scale studies capturing a high number of women of childbearing age at points in time that correspond to an etiologically relevant time frame influencing menstrual bleeding could be informative, however, studies of this size no longer have a placebo. Collection of additional placebo-controlled data would present a serious ethical concern given the availability of approved vaccines targeting SARS-CoV-2, and it is unclear how uncontrolled CT data could be interpreted. The MAH considers that there is no need to include HMB in the RMP for Spikevax. The MAH will continue to monitor heavy menstrual bleeding through routine surveillance as well as the ongoing prospective cohort studies that are designed to study heavy menstrual bleeding as an outcome after SARS-CoV-2 vaccination, being conducted by independent by third party investigators (e.g., NIH funded studies conducted by Boston University, Harvard Medical School, John's Hopkins University, Michigan State University, and Oregon

	Health and Science University; (https://www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation) which may yield more timely evidence.
Discussion	The clinical spectrum of events for elasomeran/imelasomeran and elasomeran/davesomeran were similar to data previously reported for elasomeran. Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported heavy menstrual bleeding, no consistent or *independent* risk factors were identified in any of the cases that could support a causal association with administration of elasomeran/imelasomeran and elasomeran/davesomeran. Evaluation of the risks of any menstrual disturbance and bleeding following SARS-CoV-2 vaccination in women who are premenopausal or postmenopausal has been discussed in the literature. A nationwide register-based cohort study in Sweden conducted by Ljung et al. concluded that "weak and inconsistent associations were observed between SARS-CoV-2 vaccination and healthcare contacts for bleeding in women who are postmenopausal, and even less evidence was recorded of an association for menstrual disturbance or bleeding in women who were premenopausal. These findings do not provide substantial support for a causal association between SARS-CoV-2 vaccination and healthcare contacts related to menstrual or bleeding disorders" [13]. Of note, Health Canada stated in the Jul2023 publication of Health Product InfoWatch (received after the DLP of this PBRER) that there were no scientific or medical evidence that vaccination with monovalent mRNA vaccines (Comirnaty [Pfizer-BioNTech COVID-19 Vaccine], Spikevax [COVID-19 Vaccine Moderna]) increased the risk of HMB [25].
Conclusion	Information presented in this report does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Published clinical literature has not provided substantial evidence for a causal association between SARS-CoV-2 vaccination in relation to menstrual or *bleeding* disorders and has not described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in regard to the topic of heavy menstrual bleeding. Based on the analysis of all the safety data received cumulatively, the MAH considers that cases included under the medical topic of heavy menstrual bleeding, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran did not raise any new safety issue of concern. The MAH will continue to monitor events for heavy menstrual bleeding using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

The MAH states that it presents the topic "heavy menstrual bleeding (bivalent only)" due to a request put forward by a Health Authority. The MAH states that it was requested to present the following:

a) Cumulative review of post-market cases, with a focus on reports following bivalent vaccination

b) An updated review of any new literature (e.g., prospective cohort studies) on the risk of heavy menstrual bleeding (HMB) following monovalent and/or bivalent Spikevax COVID-19 vaccination

c) Any relevant feasibility assessment documents on implementing new or amending ongoing PASS that were prepared for other regulatory agencies (e.g., EMA). A discussion on the need to update the RMP to better characterise the risk of HMB following Spikevax vaccination

Cumulative review of post-market cases

With regard to a), the MAH presents in total 86 cases related to heavy menstrual bleeding with elasomeran/imelasomeran and elasomeran/davesomeran exposure. Most of these are not medically confirmed and the MAH states that many cases lack key information such as medical history and concomitant medications. Using the WHO-UMC causality assessment categories, the MAH categorises 85 cases as "unassessable" and 1 as "unlikely".

Review of literature

With regard to b), the MAH identified 117 articles, and then refers to PSUR section 11 (literature) for one article with new and significant information. The MAH mentions the article by Uzun et al. However, this article investigates vaccine induced liver injury – not heavy menstrual bleeding. Furthermore, the MAH does not state why the other 116 retrieved articles did not provide new and significant information. In the literature section, the MAH presents an article (Ljung et al.) that investigated the risks of any menstrual disturbance and bleeding following SARS-CoV-2 vaccination. Please see AR section 1.3.5.

PASS and RMP

With regard to c), the MAH states that to date, no PASS has been planned for any regulatory agencies. The MAH argues that menstrual cycle disorders such as heavy menstrual bleeding are difficult to study in clinical trials due to the complex biology, lack of baseline data and the lack of a placebo group in the existing trials. Furthermore, the MAH considers that there is no need to include heavy menstrual bleeding in the RMP for Spikevax. The MAH will continue to monitor heavy menstrual bleeding through routine surveillance as well as through ongoing cohort studies conducted by independent third-party investigators. This is endorsed.

Conclusion

The Rapporteur notes that "heavy menstrual bleeding" is listed in section 4.8 of the SmPC with the frequency "not known" and a note saying: "Most cases appeared to be non-serious and temporary in nature." From the data presented, the Rapporteur has not identified significant new safety information that affects the known safety profile of elasomeran including bivalent variants. No further action is considered warranted at present.

2.3.2.4. Retinal Vein Occlusion

Table 15.6 Retinal Vein Occlusion

Source of new information	o Moderna GSDB o Literature Sources o Search Criteria Applied: PSUR Appendix 13.4 o Retrieved: 152 o New and Significant Safety Information: None (0)
Background	During the review period covered by this report, the MAH received a request from a Health Authority regarding the interim CSR for the ongoing mRNA-1273-P304 study, which is a Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls. The request from the health authority stated, *"In the next PSUR, the MAH is requested to provide a cumulative review of retinal vein occlusion, based on data from all sources including the literature."*

Methods of Evaluation	The Moderna GSDB was queried cumulative from 18 Dec 2020 to 17 Jun 2023 for cases of retinal vein occlusion after elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran using the MedDRA (v.26.0) PTs: retina l vein occlusion, retinal vascular occlusion, retinal occlusive vasculitis, central retinal vein occlusion and branch retinal vein occlusion. There is no Brighton Collaboration case definition for retina vein occlusion (RVO). Therefore, the MAH used the Guidelines for the Management of Retinal Vein Occlusion by the European Society of Retina Specialists (EURETINA) [26] to establish a case definition for RVO. Diagnosis of retinal vein occlusion is based on the retinal examination findings of the following: o Intraretinal hemorrhages o Dila ted vein o Cotton wool spots that have been described as a "blood and thunder appearance" for central retina vein occlusion (CRVO). o Macular edema may also be present. Evaluated cases reported for RVO were further gra ded as: o Level 1: Case of RVO o Level 2: Not a case of RVO o Level 3: Reported case of RVO with insufficient evidence to meet Level 1 or Level 2 of the case definition. The Company causality assessment was conducted using the WHO-UMC standardized case causality assessment.

Results:

Results of the analysis of cases reported for retinal vein occlusion are summarized below. Refer to PSUR Appendix 12.12 for additional information.

Cumulatively, the MAH retrieved a total of 146 cases (148 events) of retinal vein occlusion with 140 (95.9%) serious cases (141serious events) after vaccination with elasomeran. No case had a fatal outcome. There were 89 medically confirmed cases. (Note: A medically confirmed case is a report that is provided by a medically qualified patient, friend, relative or carer of the patient. In the same way, where one or more suspected ARs initially reported by a consumer are subsequently confirmed by a healthcare professional, the ICSR should be considered medically confirmed.) There were more cases reported in females (79, 54.1%) than males (66, 45.2%), with 1 case (0.7%) having no gender reported. Most of the patients (109; 74.6%) were older than 50 years. The median patient age was 58.0 years (range: 26.0 to 94.0 years). Three cases did not report age.

The majority of case reports were received from regulatory authorities (130, 89.0%), with most of the cases reported from France (27, 18.5%), United States (24, 16.4%), and Germany (18;12.3%).

The most frequently reported events were retinal vein occlusion (134, 90.5%), retinal vascular occlusion (12, 8.1%), and retinal occlusive vasculitis (2, 1.4%).

When dose number and TTO were reported, 82 events reported dose number, with most events occurring after Dose 2 (42, 51.2%) and Dose 3 (22, 26.8%) and most often event typically occurred within 2 weeks of vaccination. For events reported after Dose 3, there were no observed shorter TTO suggesting sensitization. Also, there were no clustering or trends observed. Of note, a total of 66 (44.6%) events were reported without dose number. The average TTO was 26.7 days (SD: 42.1 days) with a median number of days of 10.0 (range: 0 to 300 days).

Of the total 146 reported cases, 100 cases (68.5%) reported medical histories and 41 of these cases reported medical conditions that are risk factors for retinal vein occlusion, including hypertension, diabetes mellitus, oral contraception and smoking, cancer, hyperlipidemia, glaucoma, hypothyroidism, and atheroma.

Cumulatively, as at the time of report, 6 events (4.1%) had resolved, 29 events (19.6%) were resolving, and 77 events (52.0%) were not resolved. Of note, 19 events (12.8%) did not report an outcome.

Of the 146 case reports for retinal vein occlusion, 128 cases (87.7%) did not report funduscopic examination results, making a comprehensive assessment challenging. Two cases without funduscopic results had comorbidities that were confounders including Susac's syndrome (autoimmune endotheliopathy), retinal vascular occlusion, and chorioretinitis.

According to the MAH described case classification, out of the 146 case reports, there were 14 cases (9.6%), all of which provided fundoscopic results, that were classified as Level 1; 1 case (0.7%) was classified as Level 2 as this was not a case of RVO but rather a case of bilateral uveitis and panuveitis with associated occlusive vasculitis in the context of inflammatory bowel disease; and there were 131 cases (89.7%) classified as Level 3, given that there was insufficient information for meet Level 1 or Level 2.

According to the WHO causality assessment the 14 cases classified as Level 1, five cases were assessed as possible, based on temporal association with the use of the product; 5 other cases were assessed as unlikely due to long/short TTO (ranging from 41 to 187 days), pre-existing RVO, (with a long TTO of 41 days and confounded by hypertension and chorioretinopathy) and alternate etiologies that provided plausible explanation for the occurrence of the event. Three cases were assessed as conditional due to missing relevant information including medical histories and clinical course of events needed for proper causality assessment; and one case was assessed as unassessable due to insufficient information, that cannot be complemented. Reported medical conditions that were confounders/risk factors included hypertension, hyperlipidemia, diabetes mellitus, glaucoma, cancers, COVID-19 infection, smoking, hypothyroidism, and atheroma.

There were no cases of retinal vein occlusion reported for elasomeran/imelasomeran and elasomeran/davesomeran.

Discussion

Overall, majority (130; 89.0%) of case reports for RVO had insufficient information for proper assessment. Since most of the reports were by regulatory authorities, information could not be complemented or verified. The median patient age of 58 years is consistent with that reported in the general population. Over two-third of reported cases had medical conditions that are risk factors for retinal vein occlusion, including hypertension, diabetes mellitus, oral contraception and smoking, cancer, hyperlipidemia, glaucoma, hypothyroidism, and atherosclerosis.

A causal relationship could not be established between the cases reported for RVO and elasomeran, due to either insufficient relevant information for proper assessment, pre-existing RVO with a long TTO, comorbidities that were risk factors, and provided alternate etiologies.

While few cases had a temporal relationship from time of vaccine administration to development of reported retinal vein occlusion, these cases were confounded by comorbidities including atherothrombosis, myocardial infarction, atrial fibrillation, diabetes mellitus, previous smoking history and hypothyroidism, that provide plausible alternate etiologies.

Literature search results did not provide evidence of a causal association between retinal vein occlusion and elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran.

Conclusion

Cumulative evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events of retinal vein occlusion and administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran., elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received, the MAH considers that cases included under the medical topic of retinal vein occlusion reported in temporal association with the administration of elasomeran did not raise any new safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events for retinal vein occlusion using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Based on the occurrence of a single case of Retinal Vein Obstruction (RVO), the Updated Assessment Report for the Post-Authorisation Measure EMEA/H/C/005791/MEA/006.4 requested the MAH to provide a cumulative review of RVO, based on data from all sources including the literature.

The MAH found no published literature suggesting a potential link between elasomeran-containing vaccines and RVO.

Cases:

By MAH's assessment, the majority (130; 89.0%) of the total of 146 cases reporting 149 events of RVO had insufficient information for proper assessment and could not be followed up. The demographic distribution was similar to that of RVO in the general population. Over two-thirds of reported cases had medical conditions that are risk factors for retinal vein occlusion confounding the assessment.

Among the 14 diagnostically confirmed RVO cases (Level 1, fundoscopic results provided), WHO-UMC causality classification resulted in 5 cases assessed with "Possible" causality (short TTO, however, all confounded), 5 "Unlikely" (long TTO, pre-diagnosed RVO, confounding likely), 3 "Conditional" (missing information), and 1 case was assessed as "Unassessable" due to insufficient information that cannot be complemented.

All cases were reported with elasomeran. There were no cases of retinal vein occlusion reported for elasomeran/imelasomeran and elasomeran/davesomeran, probably due to the much lower exposure at this time.

At this point, data is insufficient to warrant regulatory measures regarding elasomeran and RVO.

The MAH should continue routine pharmacovigilance, maintaining a continuous effort to follow-up on Level-1 cases with missing information (including the 3 cases mentioned above), and to report on cases, including causality assessments by product (elasomeran and combinations) and including exposure related frequencies of such cases.

2.3.2.5. Haemophagocytic lymphohistiocytosis (HLH)

Table 15.7 Haemophagocytic Lymphohistiocytosis with Possible Involvement of Epstein-Barr Virus (EBV) Reactivation

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 267 ○ New and Significant Safety Information: None (0)
Background	The MAH received a request from a Health Authority to analyse the topic of HLH: "*It has come to our attention on accumulating literature articles on HLH with COVID-19 vaccines, and more particularly on a new hypothesis of a possible involvement of EBV reactivation. Some case reports describing EBV-positive HLH after COVID-19 vaccination have been recently published [27] [28] [29] [30]. We would like Moderna to discuss HLH in the next PSUR in view of the mentioned literature, but also any other literature/data available on this topic.*"
Methods of Evaluation	A focused search of published literature from PubMed was performed that identified articles including the terms HLH and EBV and any COVID-19 vaccine. In addition, the Moderna GSDB was searched cumulatively for literature reports of HLH and for adverse event reports that noted vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran and involved the MedDRA PT of Hemophagocytic lymphohistiocytosis, as well as EBV infection. This review focused on the hypothesis of a possible involvement of EBV reactivation in HLH, with attention to the HLH-2004 Diagnostic and Therapeutic Guidelines [31].

Scientific Background on HLH and EBV:

Hemophagocytic lymphohistiocytosis is a rare and potentially life-threatening disorder characterized by hyperinflammation caused by uncontrolled activation of immune cells, such as macrophages and lymphocytes [32]. Hemophagocytic lymphohistiocytosis can be triggered by various factors, including infections, genetic mutations [33], or autoimmune diseases. HLH can involve widespread inflammation and tissue damage. It can be classified into primary and secondary HLH. Primary HLH involves genetic mutations affecting the immune system; defects in transport, processing, and function of cytotoxic granules in natural killer cells and cytotoxic T lymphocytes play a role. Secondary HLH can be triggered by various factors, including infections, of which EBV (independent of vaccination) is the most common. In addition, secondary HLH is observed as a complication of malignancies, metabolic disturbances, and rheumatic diseases, such as juvenile arthritis or systemic lupus erythematosus [34]. Patients with HLH often present with persistent fever, hepatosplenomegaly (enlargement of the liver and spleen), and cytopenias (abnormal low levels of blood cells) [35]. This disease can lead to severe organ damage and multi-organ failure if left untreated. Diagnosing HLH can be challenging due to its heterogeneous presentation and rarity. The HLH-2004 Diagnostic and Therapeutic Guidelines include clinical and laboratory features that were developed to address diagnostic and other challenges [31].

Epstein-Barr virus, also known as human herpesvirus 4, is a common virus belonging to the herpesvirus family. It is one of the most prevalent viruses in humans, having infected about 95% of adults worldwide. Epstein-Barr Virus infects and replicates in B lymphocytes, which are critically important to the immune response. Most people initially infected with EBV will not experience any symptoms or have mild flu-like symptoms, including self-limited infectious mononucleosis. After initial infection, the virus can remain dormant in the body's cells for a lifetime without causing any harm. In a minority of infected persons, EBV and its reactivation may cause, or be associated with, several illnesses including certain types of

cancers and HLH. In some cases, especially in individuals with weakened immune systems, EBV infection can lead to severe complications, including death.

Role of EBV in HLH (apart from vaccination)

Epstein-Barr virus is known to play a significant role in some cases of HLH, specifically in the context of secondary or reactive HLH [35]. Epstein-Barr Virus is linked to a greater proportion of HLH cases than any other pathogen. In the case of secondary HLH associated with EBV, the virus can be involved in the triggering of a hyperimmune response. The pathophysiological mechanism of HLH is related to defective function of natural killer (NK) cells and cytotoxic T lymphocytes, resulting in uncontrolled activation of lymphocytes and macrophages that induce excessive production of cytokines, that cause the inflammatory response and characteristic inflammation seen in HLH [36] [37]. The exact mechanisms by which EBV is associated with HLH are not fully understood. The vast majority of EBV infections do not lead to HLH; however, in individuals with a predisposition or underlying immune dysfunction, such as genetic susceptibility to HLH, EBV infection can be a triggering factor for the development of HLH [32].

Results:

Results for hemophagocytic lymphohistiocytosis with possible involvement of EBV reactivation are summarized below. Refer to PSUR Appendix 12.14 for additional information, including summary tables of cases and events.

Results from Published Literature

A focused search of published literature from PubMed (see PSUR Appendix 13.4) retrieved 267 articles (including the 4 articles noted by the Health Authority). Besides those 4 articles, no new and significant safety information was noted from the search results. Below please find discussions of the four literature reports noted by the Health Authority.

- Arand et al [27]: This brief Letter to the Editor concerns a previously healthy 17-year-old male who had onset of headache, nausea and fever around 7 days after dose 2 of an mRNA vaccine (not further specified.) He tested "negative rapid EBV antibody and COVID antigen" on day 14 after dose 2 and was discharged home. By day 21 he was admitted to hospital and had developed symptoms consistent with HLH, meeting the 2004 HLH definition with fever, splenomegaly, cytopenia, positive bone marrow biopsy with prominent hemophagocytosis without evidence of malignancy, elevated ferritin and low fibrinogen. He also had new onset neck stiffness, dark urine, listlessness, tachycardia and hypotension. His EBV Immunoglobulin M (IgM) assay was highly positive at 54,000 (WNL <500) at hospital admission, indicating primary infection with EBV. Multisystem Inflammatory Syndrome in Children was considered, but there was no recent COVID exposure. Initially suspected to have cold autoimmune hemolytic anemia, he was treated with immune globulin and methylprednisolone; he then clinically stabilized on day 3 of admission. On day 10, his condition worsened with symptom recurrence, splenomegaly, bilateral pleural effusions, worsening cytopenia's, decreased fibrinogen and elevated ferritin. Laboratory testing related to HLH found elevated soluble IL-2, CXCL9, IL18 and CD163, consistent with immune dysregulation. Consequently, treatment was changed to the HLH2004 protocol: oral dexamethasone and IV etoposide. At 4 weeks of therapy EBV levels were undetectable; however, for 6 weeks there was alternation between clinical and laboratory remission and reactivation. Following 8 weeks of etoposide and 12 weeks of steroid treatment, the patient was asymptomatic and in remission.

  MAH Comment: Familial HLH was unlikely due to the whole-exome sequencing finding no causative mutations. Negative COVID-19 antigen test early in the illness and history of lack of recent COVID exposure do not fully rule out COVID-19 infection. The highly positive EBV IgM

assay indicated that this case of EBV infection was primary and not a reactivation. Primary infection with EBV, as occurred in this case, can by itself elicit HLH. The authors did not suggest that the mRNA vaccine caused the HLH in this patient but rather that the vaccine may "drive a more complex, protracted clinical course" and that further studies are needed. For this vaccination with an unspecified mRNA vaccine, WHO-UMC assessment for causality of HLH triggered by reactivation of EBV is unlikely because this case involved primary infection with EBV. Primary infection with EBV is a known cause of HLH and can be considered an alternate explanation of the disease in this case.

- Lin et al [29]: This literature case report involves a 14-year-old female with onset of fever, headache and nausea 11 days after dose 1 of BNT162b2; she was hospitalized on day 15 after vaccination. Substantial progression of disease and symptoms then occurred, meeting the 2004 HLH definition with fever, splenomegaly, cytopenia, decreased fibrinogen, elevated ferritin, and positive bone marrow biopsy demonstrating hemophagocytosis. She was initially treated with a dose of IVIG. Although the patient tested positive for EBV, the multiple different types of laboratory assays of EBV were not conclusive with regard to the timing of the infection, and the authors concluded that "Both acute and past infection would be possible according to this serological profile." The nasal swab for the SARS-CoV-2 polymerase chain reaction (PCR) was negative. On day 17 after vaccination, HLH was confirmed, and IVIG and methylprednisolone pulse therapy were given. Venoarterial extracorporeal membrane oxygenation was performed for 3 days due to hypotension, with intubation continuing 5 more days. Intracranial and subarachnoid hemorrhages were observed. The hemogram and the inflammatory biomarkers gradually returned to normal without chemotherapeutic medications. Patient was released from hospital on day 28. Steroid therapy duration was about 5 weeks. Laboratory tests to assess the possibility of familial HLH were not done due to their not being available at the authors' hospital.

  MAH Comment: With regard to treatment, it is unclear why this patient's fulminant HLH was not treated with the addition of more aggressive therapy, such as etoposide, rather than only steroids and IVIG. Also unclear is whether the patient's EBV infection was primary or reactivation; although the authors performed multiple laboratory tests for EBV, the test results did not permit them to determine this important information. The observed serological profile was consistent with either primary or reactivation of EBV. In addition, the authors stated that they could not exclude the possibility that their patient had familial HLH because they were unable to perform the necessary tests. For reasons of missing important information, WHO-UMC causality assessment is unassessable for BNT162b2 causing HLH with EBV reactivation.

- Tanaka et al [28]: This article concerns a 79-year-old male with a history of Hodgkin lymphoma (EBV RNA positive) ten years prior that was treated with chemotherapy and resulted in remission. Past history also included schistosomiasis. He was admitted to hospital about 2 weeks after dose 1 of BNT162b2, with fever since the day after vaccination. During his hospital course he met the 2004 HLH definition with fever, splenomegaly, high soluble IL2R, high ferritin and low neutrophils. "Hypoplastic marrow was observed on bone marrow examination, but there were no findings suggestive of lymphoma infiltration or leukemia, and only marginally hemophagocytosis images were observed". This bone marrow biopsy report does not strongly support the diagnosis of HLH, and the authors noted the patient's condition was similar to EBV-NK-LPD and CAEBV (EBV in CD56+ NK cells). The authors noted that identification and analysis of infected cells in peripheral blood suggested monoclonal proliferation because EBV was only present and proliferated in CD56-positive NK cells. The patient was treated with prednisolone starting day 8 of hospitalization with defervescence, but on day 20 fever recurred and high dose IVIG was added, with no improvement. On hospital day 31 the chemotherapeutic agent etoposide was added with some benefit, but neutropenia led to discontinuation of etoposide and to starting of filgrastim. After

blood cell count recovery, etoposide was restarted on day 44, but the primary disease was not controlled, and the patient died 10 days later with Acute Respiratory Distress Syndrome (ARDS).

MAH Comment: The past medical history of Hodgkin lymphoma positive for EBV RNA is a strong confounder in this case. In this regard, the authors stated "even after remission, a constant, subclinical amount of EBV-infected cells was observed." In addition, age-related immune senescence is likely to have played some role in this AE. Moreover, the authors did not rule out malignant disease in this case. WHO-UMC causality is possible for a BNT162b2 role in this case of HLH-like illness with EBV reactivation. The confounding factors noted above do not permit an assessment of probable causality.

- Tang and Hu [30]: This Letter to the Editor reported a 43-year-old female [redacted] who developed "malaise, vomiting, and persistent high fever (up to 39.7 °C) shortly after receiving the first dose of the inactivated [not mRNA] SARS-CoV-2 vaccine." Treatment with antibiotics and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) was ineffective. The patient was reported as having been healthy, with no remarkable medical history or recent medication intake. She was admitted to hospital on day 8. She met the 2004 HLH definition with cytopenia, fibrinogen, low NK cell activity, positive bone marrow biopsy showing hemophagocytosis and elevated ferritin. Laboratory testing showed EBV reactivation and elevated levels inflammatory factors hsCRP, sCD25, IL-1beta, IL-6, IL-8 and IL-10. Testing for genes related to familial HLH identified none. She was immediately treated with dexamethasone, and the signs and abnormal laboratory results resolved gradually; the patient was discharged on hospital day 17.

  MAH Comment: This case does not involve mRNA vaccination against Covid-19, but rather inactivated SARS-CoV-2 vaccine. The specific antibiotics and NSAIDS which the patient was prescribed were not reported. The medications were taken at a time when the patient may have had a viral illness or reactogenicity to the vaccine. Given this missing information concerning medication just prior to the diagnosis of HLH, the WHO-UMC causality for this inactivated SARS-Cov-2 vaccine is possible, but not probable, due to temporal association.

Considering together the articles summarized above, with regard to reactivation of EBV the two adult patients had reactivation; in contrast, one of the adolescents had primary EBV infection, and the testing of the other adolescent patient did not clearly indicate primary infection or reactivation. In addition, in the elderly patient with reactivation, the history of treated Hodgkin lymphoma that was positive for EBV RNA provides an important potential contributory factor to his reactivation of EBV. In addition, these four cases taken together do not demonstrate a clear pattern about age, gender, or reactivation of new EBV infection vs primary infection. Further, the vaccines involved were BNT162b2 (two patients), an unspecified mRNA vaccine and inactivated [not mRNA] SARS-CoV-2 vaccine; none of these literature case reports noted vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran.

Literature Reports of HLH in ModernaTx, Inc GSDB

In an additional step, the MAH searched its own GSDB for literature reports of HLH. Five literature case reports of HLH were identified in the GSDB; none of these case reports noted the presence of EBV infection.

Review of Individual Case Safety Reports from ModernaTx, Inc GSDB

Cumulatively, the MAH received reports of 36 cases (36 events) of HLH involving elasomeran (35 cases) and elasomeran/imelasomeran (1 case;) no cases involving elasomeran/davesomeran were reported. A total of 36 serious cases (36 serious events) and 4 cases with a fatal outcome were reported. There were 34 medically confirmed cases. Of these 36 reports of HLH, presence of EBV infection was noted in only 3 HLH case reports. Descriptions of these 3 cases follow.

- [redacted] (WWID# [redacted]: This case concerns a 53-year-old male with no reported past medical history or reported concomitant medications. Concurrent medical conditions were Hepatitis B core antibody positive. The day of his second vaccination (4 to 6 hours later), the patient developed fever, fatigue, cough, abdominal discomfort, and shortness of breath. Eight to 14 days later there was progression to thrombocytopenia, encephalopathy, renal failure, hypertriglyceridemia, hepatosplenomegaly, respiratory failure, and EBV-viremia. Laboratories demonstrated elevated cytokines, normal NK cells, high ferritin level and bone marrow biopsy which showed rare evidence of what looked like erythrocytes in the cytoplasm of cells (type not reported). Because of the EBV-viremia, the patient was treated with rituximab and steroids. Because of worsening condition with renal and respiratory failure, the patient was intubated and received dialysis. He was treated with Anakinra and ultimately extubated but was still on dialysis as of this report with encephalopathy of unknown origin. MRI of head was normal. The cause of HLH and other events was not reported. The patient met 2004 criteria for HLH with 5/8 met (fever, hepatosplenomegaly, high ferritin, hypertriglyceridemia, and rare hemophagocytosis "concerning for HLH.").

  MAH Comment: Interpretation of this case is hindered by the lack of information on medications, past medical history and possibility of Hep B infection. The temporal association with vaccination, but the lack of the information noted directly above, lead to WHO-UMC causality assessment: possible.

- [redacted] (WWID# [redacted]: This case concerns an 80-year-old male with a medical history that included EBV associated lymphoproliferative disorder in Aug 2014 and Angioimmunoblastic T-cell lymphoma (Stage 4B) treated and reported in complete remission in Aug 2018. At an unspecified time after an unspecified vaccine, the patient had EBV-associated lymphoproliferation after an infection. Current medical conditions only reported as GERD with no reported concomitant medications. On 21 Jan 2021 and 18 Feb 2021, the patient received the 1st and 2nd doses of elasomeran After the 1st dose there was slow deterioration of reported condition that became worse after the 2nd with hospitalization on 27 Mar 2021 (66 days post-first and 39 days post-second vaccination). The diagnosis was macrophage activation/HLH with EBV-positive proliferation. The 2004 HLH criteria [31] were met with fever, splenomegaly, cytopenia, hypertriglyceridemia, and hyperferritinemia (5/8). There was no bone marrow exam reported. The patient was treated with rituximab and high dose methylprednisolone with positive results resulting in the steroids being stopped but rituximab as maintenance therapy was continued.

  MAH Comment: The case is confounded by age (possible immune senescence), the past history of angioimmunoblastic T-cell lymphoma and past history of EBV associated lymphoproliferation. WHO Causality Assessment is possible. It is not considered probable because of these confounders.

- [redacted] (WWID# [redacted]: This case concerns a 19-year-old male with a medical history of graft rejection and kidney transplant in 02 Jul 2016 without any other information on past medical history, current medical history, past medications, or present medications. On 02 Apr 2021, he received the 1st dose of elasomeran and on 15 Apr 2021, he developed HLH and EBV reactivation and was hospitalized. There are no reports of laboratories or treatments. However, as of 10 Mar 2023, the patient had recovered from both HLH and EBV reactivation. No further information is available. There is not enough information to confirm HLH criteria, and causality cannot be determined. Assessment of this case is hindered by the lack of past medical history, especially the kidney transplant and graft rejection. Given the history of kidney transplantation and graft rejection, it is likely that at the time of vaccination the patient

was receiving immunosuppressive medications that may predispose to EBV reactivation; however, there is neither concurrent medical history nor concomitant medications reported.

MAH Comment: The critically important missing information noted directly above leads to WHO-UMC causality assessment: Unassessable.

Overall assessment of the HLH case reports from GSDB involving EBV

All three cases involved elasomeran, as is clear from the vaccination dates. All were male, and their ages varied widely: 19, 53 and 80 years. No clear pattern in TTO or dose number prior to the AE was observed. Drawing inferences from these cases is challenging due to the limited information in the reports and the small number of events. In addition, the history of angioimmunoblastic T-cell lymphoma in the 80-year-old male; and the history of graft rejection and kidney transplantation in the 19-year-old male; and the possibility of Hep B infection in the 53-year-old provide evidence of non-vaccine explanations for the patients' illnesses. These cases do not together constitute a clinical pattern supporting correlation between EBV-related HLH and elasomeran.

Discussion

The literature reports reviewed above, as well as the small number of ICSRs in the MAH's GSDB that involve HLH and EBV, do not support the hypothesis that mRNA vaccination against Covid-19 promotes HLH with reactivation of EBV. The small number of AE reports in the MAH's GSDB that note both HLH and EBV infection provide limited information and are confounded by important pre-existing medical conditions that can predispose to HLH with EBV; in addition, none of these reports involved bivalent vaccine. Moreover, there is an absence of direct evidence of a mechanism to explain the hypothetical association of vaccination against Covid-19, EBV reactivation and HLH. In any event, given the billions of doses of mRNA vaccines administered worldwide, such AEs are extremely rare occurrences.

Conclusion

Evaluation of the cumulative data does not suggest an association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran. Information presented in those reports does not change the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of HLH, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran did not raise any safety issue of concern, and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events for HLH using routine surveillance. The benefit-risk evaluation remains positive.

Rapporteur assessment comment:

Categorising HLH

Hemophagocytic lymphohistiocytosis (HLH) is a rare, hyperinflammatory and hypercytokinemic syndrome. Primary HLH (pHLH) is hereditary and mainly occurs in children, while secondary HLH (sHLH) is acquired, non-hereditary and can be seen at all ages. The sHLH can be sub-categorised as infection-related (e.g. viral, bacterial, fungal, parasitic) or non-infection-related (e.g. malignancy or autoimmune diseases); of the infection-related types, viral sHLH is the most common.

Viral sHLH can further be divided into EBV-sHLH (Epstein Barr Virus-related secondary HLH) and non-

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

Reactivated latent viruses

More viruses are known to cause latent infections after clearance of the acute infection, among these are viruses from the *Herpesviridae family* such as Epstein–Barr virus (EBV), herpes simplex virus 1 and 2 (HSV 1, HSV 2), varicella zoster virus (VZV), human cytomegalovirus (CMV), human herpesvirus 6 and 7 (HHV6, HHV7) *(Traylen CM et al. Virus reactivation: a panoramic view in human infections. Future Virol. 2011 Apr;6(4):451-463)*. The majority of individuals have been infected with several of these viruses, and the viral latency persists throughout life, but reactivation is associated with different pathologies. E.g. VZV can reactivate from latency and cause shingles, HSV-1 and 2 can reactivate with skin or mucosa lesions; more severely HSV reactivation can lead to infection of the central nervous system, and EBV reactivation is linked to malignancy including Hodgkin's lymphoma and post-transplant lymphoproliferative disease (PTLD). As EBV-sHLH following vaccination is considered a concern, other pathologies due to virus reactivation (EBV and non-EBV) could also be considered a concern based on the principle of parallelism.

Reactivated latent viruses and sHLH

Several of the viruses that can cause latent infection and be reactivated are also known to be of relevance for virus-triggered sHLH *(Imashuku S, Morimoto A, Ishii E. Virus-triggered secondary hemophagocytic lymphohistiocytosis. Acta Paediatr. 2021 Oct;110(10):2729-2736).* It could therefore be considered whether only EBV-sHLH should be of interest or also non-EBV sHLH.

SARS-CoV-2 and sHLH

The uncontrolled cytokine storm seen in HLH has also been described in patients with severe COVID-19 *(Fadlallah MM et al. Hemophagocytic Syndrome and COVID-19: A Comprehensive Review. Cureus. 2023 Mar 14;15(3):e36140)*. An early step in the pathogenesis of the COVID-19 cytokine storm is the binding of virus to ACE2 receptors prior to virus entering the host cell where the ssRNA of the virus is recognised by the innate immune system. This could call for attention regarding whether a similar pathogenesis could be seen following vaccination with (mRNA) vaccines against COVID-19, and in such case whether it should raise concern about whether sHLH can be triggered solely by (mRNA) vaccines against COVID-19.

The literature presented by the MAH

The MAH has performed a literature search and retrieved 267 articles, and found the same four papers as previously highlighted in a health authority request relevant for presentation. Based on the review presented by the MAH, these papers are of diverse topics and are not sufficient to support that sHLH related to EBV reactivation following vaccination is a concern: Only one (Lin et al) is compatible with EBV reactivation-related HLH following vaccination with mRNA vaccine, although the case is unclear in distinguishing between pHLH and sHLH. Another one (Tang and Hu) is a case which is also compatible with EBV reactivation-related HLH and seen following 1st vaccine dose, but is related to an inactivated SARS-CoV-2 vaccine. One (Arand et al) was about a case of HLH related to a primary EBV-infection, and therefore outside the focus of sHLH related to EBV reactivation. And one (Tanaka et al) was a patient with a history of EBV-related Hodgkin's lymphoma and findings compatible to chronic active EBV, therefore also with weighty confounders.

27. Arand A, Overholt K, Jacob SA, Belsky JA. Epstein–Barr Virus-Positive Hemophagocytic Lymphohistiocytosis Following COVID-19 Vaccination in a Pediatric Patient. Pediatric Blood & Cancer 2023;70(5):e30189.

28. Tanaka A, Kawaguchi T, Imadome KI, Hara S. [Epstein-Barr virus-associated lymphoproliferative disorders after BNT162b2 mRNA COVID-19 vaccination]. Rinsho Ketsueki 2023;64(4):277-82.

29. Lin T-Y, Yeh Y-H, Chen L-W, Cheng C-N, Chang C, Roan J-N, et al. Hemophagocytic Lymphohistiocytosis Following BNT162b2 mRNA COVID-19 Vaccination. Vaccines 2022;10(4):573.

30. Tang LV, Hu Y. Hemophagocytic lymphohistiocytosis after COVID-19 vaccination. J Hematol Oncol 2021;14(1):87.

Results from the Global Safety Database

Searching the MAH's GSDB showed cumulatively 36 cases of HLH, but only in three was EBV infection described. The low number of cases comprising EBV does not strongly support EBV-related sHLH. However, the much larger number of reported cases with HLH could call for attention for considering whether the focus of EBV-related sHLH is too limited and whether the topic should be extended to comprising sHLH more widely to see, whether there are indications of sHLH related to reactivation of latent viruses including but not limited to EBV.

Conclusion

Neither the selected literature presentation nor the data from the global safety database gives rise to concern for EBV-sHLH. However, based on principle of parallelism in etiology, the topic could be extended to comprise virus reactivation-related sHLH (EBV-related, non-EBV-related). Furthermore, after DLP of the present PSUR, a paper including a case report and a literature review has been published (Premec H, Živko M, Mijić M, Jelić-Puškarić B, Lalovac M, Filipec Kanižaj T, Sobočan N. Acute Liver Failure Caused by Secondary Hemophagocytic Lymphohistiocytosis After COVID-19 Vaccination - Case Report and Literature Review. Int Med Case Rep J. 2023 Aug 7;16:449-455. doi: 10.2147/IMCRJ.S417347. PMID: 37577009; PMCID: PMC10416787.). **The MAH is requested to comment on this paper in the next PSUR and comply with appropriate measures based on the cumulative information including mechanism of actions concerning sHLH and elasomeran containing vaccines.**

2.3.2.6. Postural orthostatic tachycardia syndrome (POTS)

PSUR Table 15.8 Postural orthostatic tachycardia syndrome

Source of New Information	○ Moderna GSDB ○ Evaluation of cases of POTS is presented in this PBRER, cumulative as of 17 Jun 2023, given that the observed number of cases was higher than the expected number of cases. In the observed to expected analyses, the lower bound of 95% confidence interval of rate ratio was > 1 for the 40-49 years and the 50-64 years subgroups. ○ Literature Sources ○ Search Criteria Applied: PSUR Appendix 13.4 ○ Retrieved: 96 articles ○ New and Significant Safety Information: None (0)

Background	Postural orthostatic tachycardia syndrome is a chronic and often disabling disorder characterized by orthostatic intolerance with excessive heart rate increase without hypotension during upright posture. Patients often experience a constellation of other typica l symptoms including fatigue, exercise intolerance and gastrointestinal distress. A typica l patient with POTS is a fema le of child-bea ring age, who often first displays symptoms in adolescence. The onset of POTS may be precipitated by immunological stressors such as a viral infection. A variety of pathophysiologies are involved in the abnormal postural tachycardia response; however, the pathophysiology of the syndrome is incompletely understood and undoubtedly multifaceted [38]. The prevalence of POTS is based largely on clinical experience, ranging from 0.2% and 1% of the US population, which would suggest approximately 1–3 million affected persons [39] [40] [41]. Most patients present with POTS between the ages of 12 to 50 years old and more than 75% are female (F:M ratio > 4:1). POTS is also common in patients with chronic fatigue syndrome [41]. The cause of this condition remains unclear. Although there is a consensus clinical definition for POTS, misdiagnosis is common. The syndrome is heterogeneous in the sense that the spectrum of clinical features varies among patients, multiple etiologies may produce similar clinical phenotype and there is overlap with other clinically defined syndromes. The clinical evaluation of patients with suspected POTS is not standardized, nor are treatment approaches. There is a la ck of familia rity with POTS in the medical community, and the epidemiology of the disorder and natural history are not known [42]. According to Sheldon et al., POTS is a clinical syndrome usually characterized by (1) frequent symptoms that occur with standing, such as light-headedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue; (2) an increase in heart rate of ≥30 beats per minute (bpm) when moving from a recumbent to a standing position (or ≥40 bpm in individuals 12 to 19 years of age); and (3) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure). The symptoms associated with POTS are those that occur with standing, such as light-hea dedness and palpitations; not associated with particular postures, such as bloating, nausea, dia rrhea , and abdominal pain; and systemic, such as fatigue, sleep disturbance, and migraine headaches. The standing (or orthostatic) heart rate of individuals with POTS is often ≥120 bpm and undergoes greater increases in the morning than in the evening. The increases in orthostatic heart rate gradually decrease with age and not abruptly at age 20. Many patients with POTS faint occasionally, although presyncope is much more common. It is important to note that the diagnoses of POTS and vasovagal syncope are not mutually exclusive. In addition, POTS has been found to overlap with or occur in certain conditions such as migra ine, hypermobile Ehlers-Da nlos syndrome (hEDS), mast cell activation syndrome (MCAS) or chronic fatigue syndrome (CFS), inappropriate tachycardia syndrome and some other forms of orthostatic intolerance such as neurocardiogenic syncope [43]. Amyloidosis, Sjogren's syndrome, multiple sclerosis, mast cell activation disorders and hypermobility syndrome (Ehlers-Danlos syndrome type III) are other diseases a ssociated with or thought to cause POTS. This subset of POTS patients commonly reports episodes of flushing, urticaria, dyspnea, headache, excessive diuresis, and gastrointestinal symptoms such as dia rrhea , nausea, and vomiting, which may be accompanied by elevated urine methylhistamine or 11-ß-Prostaglandin F2 excretion or elevation of other mast cell mediators [44]. Some researchers have suggested that there is a neuropathic basis underlying at least half of patients

	with POTS and found that about 1:7 of patients studied had ganglionic acetylcholine receptor antibodies suggesting an autoimmune etiology for this proportion of patients with POTS. Several mechanisms have been described in patients with POTS, including autonomic denervation, hypovolemia, hyperadrenergic stimulation, deconditioning, and hypervigilance, which is a careful and at times unusual focus on bodily sensations. These mechanisms often appear to co-exist in patients with POTS. The onset of POTS may be precipitated by a typical immunological stressor such as viral syndrome (often upper respiratory or gastrointestinal and for example, with EBV), physical trauma (such as concussion), menarche, pregnancy, or surgery and autoimmunity as with paraneoplastic conditions in small cell lung and pancreatic cancers as well as with autoimmune autonomic neuropathy. An antecedent history of suspected viral infection is reported in 20–50% of patients [45]. The presentation seems to have two patterns – acute onset after one of the above triggers or with slowly progressive symptoms over a longer period of time [46]. Significant symptomatic recovery has been reported by a subset of patients, but a majority report chronic symptoms with recurrent exacerbations. POTS is now known as one of many possible features of post-acute COVID-19 syndromes that can develop after SARS-CoV-2 infection. While the acute impacts of COVID-19 were the initial focus of concern, it is becoming clear that in the wake of COVID-19, many patients are developing chronic symptoms that have been called Long- COVID. Some of the symptoms and signs include those of POTS [47]. Commonly described symptoms of Long-COVID include some combination of breathlessness, palpitation, chest discomfort, fatigue, pain, cognitive impairment ("brain fog"), sleep disturbance, orthostatic intolerance, peripheral neuropathy symptoms (pins and needles, and numbness), abdominal discomfort, nausea, dia rrhea , joint and muscle pains, symptoms of anxiety or depression, skin rashes, sore throat, headache, earache and tinnitus. These symptoms, when combined with excessive orthostatic tachycardia, can lead to a diagnosis of POTS post-COVID-19 [47]. The United Kingdom National Institute for Health and Care Excellence (NICE) has defined various symptomatic phases of COVID-19 [48]. These include: o "Acute COVID-19" which includes signs and symptoms up to 4 weeks following onset of illness o "Ongoing symptomatic COVID-19" for signs and symptoms of COVID-19 from 4 to 12 weeks after the onset of illness o "Post-COVID-19 syndrome" for signs and symptoms that develop during or after an infection consistent with COVID-19, continue for > 12 weeks and are not explained by an alternative diagnosis o "Long-COVID" that includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Given that SARS-CoV-2 infection can trigger POTS and other cardiovascular dysautonomia's, it has been hypothesized that COVID-19 infection might be a potent immune trigger that evokes an autoimmune response in susceptible individuals [49]. The post-COVID-19 cardiovascular autonomic dysfunction can affect global circulatory control, producing not only a POTS-like pattern but also tachycardia at rest, blood pressure instability with both hypotension and hypertension, and local circulatory disorders such as migraine, coronary microvascular dysfunction, or Raynaud-like symptoms. Microvascular dysfunction with inadequate regional microvascular and macrovascular

	responses, such as vasospasm and circulatory mismatch between local oxygen demands and supply, and venous retention leading to pooling and reduced venous return after standing, might explain the plethora of symptoms that are frequently observed in POTS. There are sparse reports suggesting that microvascular dysfunction is an important mechanism of post-COVID-19 complications. All these dysautonomic phenotypes might coexist, and, more importantly, they preferentially affect young and middle-aged women, possibly suggesting a genetic predisposition and/or a mechanistic role for sex hormones. Of note, POTS is extremely rare among either prepubertal girls or postmenopausal women. There have been reports of POTS in the medical literature, from Japan, Korea, and the US, about newonset POTS in previously healthy people who had recently received a messenger RNA (mRNA) COVID-19 vaccine. A large cohort study [50] identified a possible association between COVID-19 vaccination and POTS as well as a much stronger link between SARS-CoV-2 infection and POTS. Kwan AC et al. used a retrospective cohort of patients who received at least one dose of COVID-19 vaccine in the Cedars-Sinai Health System in US from 2020 to 2022, to compare odds of POTS diagnosis identified by International Classification of Diseases (ICD) codes in the outpatient encounters within 90 days post the first dose of COVID-19 vaccine with odds of POTS 90 days pre-vaccination in a sequence symmetry analysis (SSA). Similar analyses were conducted for myocarditis, common primary care (CPC) diagnoses, and post Dose 2 in the vaccinated cohort and another retrospective cohort of patients with SARS-CoV-2 infection. The authors found the post-Dose 1 odds of new POTS-associated diagnoses (1.33, 95% confidence interval=1.25–1.41) was slightly higher than for CPC diagnoses (odds=1.21, 95%CI=1.18–1.23) in the vaccinated cohort, and post-infection odds of new POTS-associated diagnoses (1.52, 95%CI=1.33–1.72) was slightly higher than that for CPC diagnoses (odds = 1.40, 95%CI=1.31–1.50) in the infected cohort. Although this single medical center study identified a slightly elevated risk of receiving a POTS diagnosis after COVID-19 vaccination, the interpretation of the results requires caution given the following limitations, and additional studies are required to verify the association as the authors recommended. First, the primary analysis was restricted to vaccinated persons and consequently may have had bias away from the null because people who experienced POTS may have delayed or may not have received a COVID-19 vaccine, violating a key assumption of the SSA analytic methodology (i.e., the event of interest [POTS] does not alter the probability of subsequent exposure [vaccination]). No distribution of POTS diagnoses pre- and post-vaccination is presented to evaluate. Healthy vaccinee effect, however, was reflected by the also elected OR for CPC diagnoses. The authors attempted to address this bias by reporting the crude ratio of ORs between POTS diagnosis and CPC diagnosis (1.10, 95%CI 1.03–1.17). However, such estimate was likely confounded, and the significance was likely driven by the large sample size. Second, the authors acknowledged that "the lack of a standard single ICD code for capturing a formal diagnosis of POTS can lead to overlap with other medical conditions and variation in the application of available ICD codes". Moreover, POTS diagnoses were not fully adjudicated and are subject to outcome misclassification, as the author mentioned "a significant degree of non-POTS diagnoses were captured within our ICD codes". The degree of misclassification pre- and post-vaccination may not necessarily be non-differential because diagnostic vigilance of POTS may be intensified after vaccination, biasing the association away from the null;

	moreover, symptoms associated with common vaccine reactogenicity such asfever and fatigue might lead to patient complaints that overlap some POTS criteria. Furthermore, it was unclear how "new diagnosis" of POTS was identified and whether patients with a previous code related to POTS were included in the analysis and whether the distribution differed in the pre- and post-vaccination events, biasing the association in either direction depending on the distribution of prevalent events. Third, the OR estimates and ratios of ORs were crude without adjustment for confounding. The confounding distribution, such as risk factors for POTS, may be different in events that occurred pre and post vaccination. Fourth, diagnosis of POTS, as noted above, requires a three-month duration of symptoms; however, the authors did not confirm this important temporal aspect, relying instead on ICD codes that are not specific for POTS and may only represent acute diagnoses. In summary, POTS is a chronic multi-system disorder involving the autonomic nervous system that is cha racterized by an exaggerated sinus tachycardia, and symptoms upon standing. POTS primarily affects females starting around puberty and through their child-bea ring age and is associated with significant functional disability, such as decreased ability to participate in education, limited ability to work and generate an income, and decreased quality of life. The pathophysiology is incompletely understood, which is likely responsible for limited data on effective treatments. Postural tachycardia syndrome ca ses a ssocia ted with COVID-19 infection have been reported, as well as cases occurring after COVID-19 vaccination.
Methods of evaluation	The Moderna GSDB was queried cumulative to 17 Jun 2023 for valid case reports received from HCPs, HAs, consumers, and literature worldwide, for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, using the MedDRA PT of "Postural orthostatic tachycardia syndrome". Identified cases were evaluated according to the latest case definition presented by Vernino et al., [38] as part of the National Institute of Health Expert Consensus meeting of 2019, based on the different previous definitions by major international neurologic, autonomic, cardiac and pediatric societies [51], [52], [41] as requiring: **Confirmed:** • A sustained HR increment of not less than 30 beats/minute within 10 min of standing or head-up tilt. For individuals who are 12 to 19 years old, the required HR increment is at least 40 beats/minute; **and** • An absence of orthostatic hypotension (i.e., no sustained systolic blood pressure drop of 20 mmHg or more); **and** • Frequent symptoms of orthostatic intolerance during standing, with rapid improvement upon return to a supine position. Symptoms may include light-hea dedness, palpitations, tremulousness, generalized weakness, blurred vision, and fatigue; **and** • Duration of symptoms for at least 3 months; **and** • Absence of other conditions explaining sinus tachycardia such as anorexia nervosa, primary anxiety disorders, hyperventilation, anemia, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, use of cardioactive drugs (e.g., sympathomimetics, anticholinergics) or severe deconditioning caused by prolonged bed rest.

	Unassessable: A reported event of POTS with insufficient evidence to meet the case definition. **Not a Case**: Alternative diagnosis for the described events. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

Results:

Refer to PSUR Appendix 12.15 for additional information, including summary tables of cases and events, case evaluations, and additional analyses.

Cumulatively, through 17 Jun 2023, a total of 157 cases (159 events), 105 serious cases (81 serious events) with the reported term of POTS have been received for all the elasomeran vaccines, including the two bivalents. A total of 96 cases were medically confirmed, and no case report noted a fatal outcome. The majority of cases involved females (121 cases, 77.1%) than males (34 cases, 21.7%); 2 cases (1.3%) did not include gender information. Of these, 151 cases were reported for elasomeran (mean age: 38.5 years old [SD 12.8]; median age: 36 years old [16 to 82 years old]) and 3 cases each for elasomeran/imelasomeran (mean age 27 years [SD 0]; median age 27 years old) and elasomeran/davesomeran (mean age: 44.5 years old [SD 29]; median age: 44.5 years old [24 to 65 years old]). Of note, a total of 85 events (53.5%) events were reported with insufficient information to determinedose number. Most of the events (67; 42.9%) were reported within 7 days after vaccination regardless of dose number.

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

Out of the 157 cases reported cumulatively as of 17 Jun 2023:

- For Elasomeran (151 cases):
    - There were 12 cases that were considered new onset cases (including one case for possible new onset) based on the information provided. Out of those, there were 5 reports considered possibly related to the vaccine due to temporal association, as well as the absence of other conditions that may explain the symptoms presented by the patients; however, some important information was missing including full clinical course and information on any confirmatory testing that may have been conducted. There were 4 reports considered unlikely, two based on a TTO of hours after the 1st dose of elasomeran (TTO too short), as well as concurrent medical history of Long- COVID in two of the reports. There were 3 cases that were unassessable based on the lack of important information regarding medical history, final test results, etc.
    - There were 17 cases that were considered as possible flares of POTS given their previous medical history of POTS. Out of those, 1 case was considered possibly related to vaccination, given the recurrence of symptoms the same day after receiving a 3rd dose with elasomeran. In this report, most of the POTS symptoms experienced by the patient can also be confounded by expected reactogenicity events like nausea, pyrexia, dizziness, etc. There were 11 reports that were considered unlikely related to the vaccine given a recent history of COVID-19 infection, ongoing Long-COVID, other autoimmune conditions, including CFS, Ehlers-Danlos syndrome, among others; a short TTO (same

day after vaccination) and concurrent amphetamine use and polypharmacy. There were 3 reports that were unassessable due to missing important information needed to perform causality assessment. The causality in 2 other reports was not applicable as these were not representative of true POTS cases based on the available details (one case described symptoms likely of anaphylaxis and the other for vaccine reactogenicity).

  - There were 13 reports that were not considered new onset cases based on the description of the symptoms, but previous medical history of POTS was missing. Out of those, 3 were considered unlikely related to the vaccine due to concurrent medical history that provided a more plausible explanation for the occurrence of the reported events, including COVID-19 infection, Ehlers-Danlos syndrome; one case was diagnosed as an atypical case of GBS. In 5 reports, causality was unassessable due to important missing information. The causality in 5 other reports was not applicable as these were not true POTS cases.

  - In a further 23 reports, the causality was assessed as unlikely related to the vaccine as alternative etiologies were suspected that provide a more plausible explanation of the reported events (post/Long-COVID setting, concurrent EBV, RSV other acute viral infections, co-morbidities some having known association with POTS, migraine, celiac disease, mast cell activation syndrome, concomitant use of lurasidone [orthostatic hypotension, tachycardia, syncope, dizziness are listed events; Latuda (lurasidone) SmPC], polypharmacy), etc. Few of these cases involved a time to drug intake which makes the causal relationship improbable (short TTO, same day of vaccination or delayed latency (5 months or more)) or involved a misdiagnosis.

  - There were another 85 cases that were unassessable based on the lack of information including medical history, clinical course of the condition, any testing (laboratory or diagnostic) conducted, and in some instances dose number and TTO, important to establish causal association with the vaccine.

  - The causality in 1 another case was not applicable as this was not a true POTS case (hyperthyroidism in a patient with recent chemotherapy).

- For elasomeran/imelasomeran (3 cases)

  - There were 3 reports, and all were considered unassessable as a case according to the case definition as well as causality assessment. One report described a possible flare-up of pre-existing POTS, however, the latency information is unknown. Important information was missing for all the case reports.

- For elasomeran/davesomeran (3 cases)

  - There have been 3 reports, which were all considered unassessable as a case according to the case definition as well as causality assessment. Important information was missing for these case reports.

There have been no new significant safety findings related to POTS from the ongoing clinical development program for elasomeran, elasomeran /imelasomeran and elasomeran/davesomeran.

Discussion

Evaluation of cases of reported POTS is presented, cumulative as of 17 Jun 2023, given that the observed number of cases were higher than the expected number of cases. In the observed to expected analyses, the lower bound of the 95% CI of the rate ratio was > 1 for the 40-49 years and the 50-64 years subgroups. Cumulatively, there were 157 cases reports for individuals that had been vaccinated with one

or more doses of elasomeran (151 cases; 96%), velasomeran/imelasomeran (3 cases; 2%) and elasomeran/davesomeran (3 cases; 2%).

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

A large number of POTS-related events identified in the GSDB included some of these conditions as part of their concurrent medical history, including EBV, RSV infections, hypermobile Ehlers-Danlos syndrome, CFS, mast cell activation syndrome, as well as recent history of COVID-19 infection as well as diagnosis of Long-COVID.

Based on the total number of doses administered estimated (as of 17 Jun 2023), the reporting rates for cases reported as POTS in the GSDB per million doses administered of elasomeran is 0.2 cases; for elasomeran/imelasomeran is 0.04 cases and elasomeran/davesomeran is 0.02 cases. There have been no reports with a fatal outcome.

Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported POTS event, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

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

Rapporteur assessment comment:

In this PSUR, the MAH has reviewed the item POTS prompted by the observation that the number of cases was higher than the expected number of cases for the 40-49 years and the 50-64 years subgroups in the O/E analysis (PSUR section 15.3.1)

It is recognized, that symptoms of POTS are associated with "long COVID" syndromes, suggesting that SARS-CoV-2 infection can trigger POTS. A large cohort study (Kwan et al, 2022) identified a possible association between (any) COVID-19 vaccination (31% Moderna (mRNA-1273)) and POTS (35% of cases Moderna vaccinated) as well as a link between SARS-CoV-2 infection and POTS. Overall, the post-vaccination odds of new POTS-associated diagnoses (n = 4,526, odds = 1.33 (1.25–1.41), P < 0.001), and the post-infection odds of new POTS-associated diagnoses (n = 1,004, odds = 1.52 (1.33–1.72), P < 0.001) had overlapping confidence intervals. As discussed by the MAH, several study limitations apply. This study was already assessed in the previous PSUR#4, the PRAC Rapporteur comment concluding that "this study points to the importance of further research and routine pharmacovigilance on POTS, while not questioning the importance of COVID-19 vaccination in general nor with elasomeran specifically."

A cumulative case evaluation as of 17 June 2023 found 157 cases of POTS. Among 151 cases with elasomeran, only 6 cases (5 new onset and 1 flare) were – based on temporal association – considered WHO-UMC possibly related to vaccination. Among the remaining 145 cases most were considered Unassessable, followed by Unlikely, and Not-true cases. No cases were considered Certain or Probable.

The PRAC Rapporteur has reviewed the 6 cases considered of Possible causality by the MAH (PSUR appendix 12.15):

[redacted]:44F, D2, TTO 5d, Serious. Missing key information. "Possible" causality confirmed.

[redacted]:36F, D2, TTO 28d (OBS symptoms initiated "within a few weeks"). Non-serious. Causality update by the rapporteur: Unlikely to be attributed to disease or other drugs: WHO-UMC causality "Probable".

[redacted]: 35M, D3, TTO 0d, Serious. Previous POTS and other vaccine confounding. "Possible" causality confirmed.

[redacted]: 40M, Non-serious, D1, TTO 7d, gradually resolved within 5 mo. Literature case, No mHx reported. The rapporteur has requested the author to provide supplementary information on the medical history. Final evaluation pending. Literature ref.: Park J, Kim S, Lee J, An JY. A case of transient POTS following COVID-19 vaccine. Acta Neurol Belg. 2022;122 (4):1081-3

[redacted]: 37F, Non-serious, D1, TTO 7d, resolving at 1 week. Literature case report. For mRNA-1273 (Spikevax), the author "considered POTS 1 week after receiving the first dose of Moderna vaccine.) to be related." and "It was concluded that the classification was consistent, and it seemed likely that the vaccine caused the event." Literature ref.: Eldokla AM, Numan MT. Postural orthostatic tachycardia syndrome after mRNA COVID-19 vaccine. Clin Auton Res. 2022;32:307-11

The MAH argued that "Important information is missing in this literature report, including detail information on the use of vortioxetine by the patient, as well as duration of the symptoms by the patient. For a diagnosis of POTS, the case definition includes having symptoms for more than 3 months and in this report such information was not provided. Additionally, her antidepressant medication is labelled for all the symptoms the patient manifested; Testing for SARS-CoV-2 information was not provided, and given that this is the first dose of a COVID-19 vaccine, this information is vital for an appropriate causality assessment evaluation." The MAH's assessment of "Possible" causality is endorsed.

[redacted]: 54F, Non-serious, D1, TTO: few days. The authors reported to their knowledge this was the first case worldwide reporting severe Postural tachycardia syndrome (POTS) most likely triggered by COVID-19 vaccination with mRNA1273 (Moderna) since no other causes could be detected. The event occurred a few days after first dose of mRNA-1273. As reported, multiple analyses were conducted with no abnormalities (beside already known celiac disease) and other potential causes of patient condition have been ruled out. Literature ref.: Reiner MF, Schmidt D, Saguner AM. Severe postural tachycardia syndrome (POTS) in a patient after COVID-19 vaccination with mRNA-1273 (Moderna). Swiss Med Wkly.

2022;152(Suppl.260):27S *to be substituted with* Eur Heart J Case Rep . 2023 Aug 19;7(8):ytad390. doi: 10.1093/ehjcr/ytad390. eCollection 2023 Aug.

The MAH stated (at the end of the narrative, PSUR Appendix 12.15b) that "The company causality for the event is assessed as related". However, the WHO-UMC causality category was considered "Possible" as opposed to "Probable". This is not in line with the authors conclusion that "The temporal association of POTS with COVID-19 vaccination in a previously healthy patient and the lack of evidence of an alternative underlying aetiology suggests COVID-19 vaccination is the potential cause of POTS in this patient." Consequently, as POTS is found unlikely to be attributed to previous medical history or other drugs, the PRAC Rapporteur evaluates the case as WHO-UMC causality "Probable".

Further 6 cases vaccinated with either elasomeran/imelasomeran (3 cases) or elasomeran/davesomeran (3 cases) were all considered Unassessable.

There have been no new significant safety findings related to POTS from the ongoing clinical development program for elasomeran, elasomeran /imelasomeran and elasomeran/davesomeran. No new clinical studies on vaccination associated POTS were presented.

The current evidence associating elasomeran with POTS is considered insufficient at this time. However, case reports – including 2 cases considered WHO-UMC causality class "Probable" (see above) - indicate that such association may be valid, but further evidence is considered needed.

It is noted, that two papers concerning POTS have been published after DLP of the present PSUR. The MAH is requested to comment on these two papers in the next PSUR and comply with appropriate measures based on the cumulative information concerning POTS and elasomeran containing vaccines. The papers are as follows:

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

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

2.3.2.7. Subpopulation analysis: children

Request ITEM 11: The MAH reported on a 17-year-old serious case with febrile convulsion ([redacted]) in the presentation of the youngest babies/children (6 months to 5 years of age), which is inconsistent. Furthermore, this case is not included in the annex 11.26a and annex 11.26b (Use in Children (< 18 Years of Old): Serious Cases During the Reporting Period-Case Evaluations and Case Narratives (All) (elasomeran)). The MAH is requested to clarify this discrepancy within the next PSUR.

MAH Response:

[redacted] was evaluated in PBRER #3 (18 Dec 2022 to 18 Jun 2022). The case was received on 14JUNE2022 just before the datalock point of PBRER #3 and was booked into the GSDB on 21JUNE2022

just after the datalock point of PBRER #3 and during the reporting period of PBRER #4 (19 Jun 2022 to 17 Dec 2022) which led to the case being inadvertently presented in PBRER #4. Furthermore, the patient's age was misstated as a 17-year-old female when in fact the patient was a 17-month-old female. The MAH regrets the consequent confusion.

Rapporteur assessment comment:
Clarification accepted, issue resolved.

Request ITEM 12: The following three serious cases of elasomeran/davesomeran ([redacted]) are not found in the appendix 11.26 (Use in children (<18 Years of Old): Serious cases during the reporting period). The MAH is requested to clarify this discrepancy within the next PSUR.

MAH Response:

Appendix 11.26 included only the serious cases for the original elasomeran formulation and should have included the serious cases for the bivalent elasomeran/davesomeran formulation which were inadvertently omitted. The MAH presents these cases below for completeness.

[redacted] (WW Identifier [redacted]: This regulatory authority case concerns a 17-year-old female patient with no reported medical history who experienced chest pain (reported as medically significant) one day after administration of dose 4 of mRNA-1273.222 bivalent vaccine. There was no dyspnea, no palpitation, no fever, or cough. No abnormality was found on electrocardiogram and blood work. There is no indication that the patient was admitted to the hospital.

MAH Comment: Based on the temporal association, this likely represents reactogenicity.

[redacted] (WW Identifier [redacted]: concerns a 14-year-old male with no medical history reported, who experienced serious pyrexia and chest pain 1 day after mRNA-1273.222 vaccination as Dose 4. One day after vaccination, the patient reportedly was admitted for complaints of chest pain, chest distress, suspected cardiogenic chest pain with pain index of 8 points. Troponin value was slightly elevated on the first day and back to normal values afterward. CPK was elevated at 195 IU/L with other labs unremarkable. An EKG was performed and reported as abnormal but actual results were not provided. After one day patient was transferred to another hospital and discharged within 3 days with chest pain reported as resolved.

MAH Comment: According to the Brighton Collaboration case definition this case is considered Level 2. According to the CDC case definition this case is considered probable, and according to the WHO causality assessment this case is considered possible. The report is lacking important information including medical history, concomitant medications, actual ECG results.

[redacted] (WW Identifier: [redacted]: concerns a 13-year-old male with no medical history reported, who experienced chest pain, dizziness and pyrexia one day after mRNA-1273.222 vaccination as Dose 3. Laboratory results provided showed normal Troponin and negative D-dimer, but elevated CRP with other lab results unremarkable. EKG was reported as normal. Patient had high blood pressure and elevated heart rate and was subsequently discharged.

MAH Comment: According to the Brighton Collaboration case definition this case is considered Level 5 – Not a case of myocarditis. According to the CDC case definition this case is considered "Not a case" and therefore, WHO causality assessment was not performed. Events reported by the patient more likely represent reactogenicity.

Rapporteur assessment comment:

Subpopulation analysis: Children

Three cases of children with chest symptoms following administration of elasomeran/davesomeran were not previously reported since former reports have only presented cases of myocarditis/pericarditis following elasomeran. All three cases occurred in adolescents aged 13 – 17 years. All three experienced chest symptoms the day after the vaccination. Dose numbers were 3rd (for one) and 4th (for two). Only one case narrative comprises sufficient information to be categorised as myocarditis. One case does not meet the criteria for myocarditis but based on provided information pericarditis can neither be confirmed nor excluded. The third case only reports chest pain, which is an unspecific symptom.

The information provided from the three cases is in accordance with the known safety/risk profile for elasomeran and does not raise new concerns.

Issue is resolved.

Request ITEM 13: In the guidance of assessment and understanding of data the MAH is requested to specify within the next PSUR the MAH's definition of a noteworthy report, which has been used by the MAH as an argument to present cases.

MAH Response:

The MAH acknowledges the lack of precision in the characterization of reports as noteworthy when presenting cases. The MAH will present individual pediatric cases in a manner that communicates their safety relevance, e.g. containing new and significant safety information.

Rapporteur assessment comment:

Clarification accepted, issue resolved.

2.3.2.8. Requests from previous PSUSA (no 4) (not addressed elsewhere)

Request ITEM 3: Multisystem inflammatory syndrome (MIS-C/MIS-A)

A. In the current PSUR (#4) the MAH states, that "Cumulatively, through 17 Dec 2022, a total of 166 cases (167 events) with MIS-related terms have been reported, with 159 serious cases (95.8%) and 143 cases medically confirmed. There were 7 cases (4.2%) with fatal outcomes." However, in the previous PSUR (#3) it was stated that "Cumulatively, through 18 June 2022, a total of 401 cases (426 events) with MIS-related terms have been reported, with 354 cases medically confirmed. There were 139 cases (32.6%) with fatal outcomes. The MAH is requested with the next PSUR to explain the numerical incompatibility of the two statements.

MAH Response: The MAH would like to clarify the discrepancy in the number of MIS-related cases between PBRER #3 and PBRER #4. For the information provided in PBRER #3, the MAH used a search strategy that was requested by the PRAC when the MAH was providing Summary Safety Reports to the agency. This search strategy included the following PTs: Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, and Systemic inflammatory response syndrome, Multiple organ dysfunction syndrome, Toxic shock syndrome, Distributive shock, Hypotensive crisis, Vaccine associated enhanced disease, Vaccine associated enhanced respiratory disease, Haemophagocytic lymphohistiocytosis, Macrophage activation, Macrophages increased, Septic shock, and Autoinflammatory disease.

For PBRER #4 the MAH returned to the classical search strategy recommended by the Brighton Collaboration group, which included the following PTs: Multisystem inflammatory syndrome in children,

Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults [mentioned twice], Multisystem inflammatory syndrome in children [mentioned twice], Cytokine storm, Cytokine release syndrome, Kawasaki's disease, and Systemic inflammatory response syndrome.

This change in the search strategy, in which less PTs were included, justify the numerical differences between PBRER #3 and PBRER #4.

Rapporteur assessment comment:

The MAH has explained that the search strategy for MIS-related cases in PBRER/PSUR#4, as recommended by the Brighton Collaboration group, included the PTs Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, and Systemic inflammatory response syndrome, while the PTs used for PBRER/PSUR#3 MIS search strategy, as requested by the PRAC, included also the PTs Multiple organ dysfunction syndrome, Toxic shock syndrome, Distributive shock, Hypotensive crisis, Vaccine associated enhanced disease, Vaccine associated enhanced respiratory disease, Haemophagocytic lymphohistiocytosis, Macrophage activation, Macrophages increased, Septic shock, and Autoinflammatory disease, explaining the numerical differences between PBRER #3 and PBRER #4.

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

Request ITEM 4: Multisystem inflammatory syndrome (MIS-C/MIS-A)

> B. The MAH is requested with the next PSUR to clarify how the case listing criteria differ between Appendix 11.15g: MIS During the Reporting Period BC Criteria Case Evaluations (All) (Booster) (elasomeran), and Appendix 11.15c: MIS During the Reporting Period - Case evaluations (All) (Booster) (elasomeran). Appendix 11.15g includes 3 cases, while appendix 11.15c lists 2 cases.

MAH Response: The MAH acknowledge the confusion with the appendices for MIS titles.

- Appendix 11.15c includes only cases reported after booster administration during the reporting period (there were 2 cases during the reporting period)
- Appendix 11.15g includes the evaluation of all elasomeran cases that fulfilled the BC Level 1-3.

Appendix 11.15c title should have been "MIS Cases during the reporting period -case evaluations (booster)"; and 11.15g appendix title should have been "MIS Cases During the reporting period- BC (Level 1-3) case evaluations."

Rapporteur assessment comment:

Clarification accepted, issue resolved.

The PRAC Rapporteur trusts that the MAH will do an extra effort to ensure correct headings of all tables in

future PSURs, as this kind of confusion may lead to incorrect assessments and is significantly time consuming for everyone involved.

Request ITEM 5: Multisystem inflammatory syndrome (MIS-C/MIS-A)

C. In the section Subpopulation Analysis of children < 18 years, a MIS-C suspected case is referenced by the MAH ([redacted] (WW Identifier [redacted]
However, this case is not included in the MAH's MIS data. The MAH is requested in the next PSUR to clarify why this case is not included in the MIS data, and the MAH is also requested to provide a detailed assessment of this case within the current procedure, and collect additional data if sufficient information is lacking.

MAH Response: The MAH would like to clarify that it was an oversight not to link the information provided in the Children section to the information provided in the MIS evaluation.

Information on the requested case was already provided to the PRAC during the PBRER #4 procedure. No additional information is currently available.

Rapporteur assessment comment:

Clarification accepted, issue resolved.

Request ITEM 10: Single organ cutaneous vasculitis (SOCV)

Cases of SOCV in patients after Bivalent booster dose of Moderna vaccine targeting SARSCoV2 was reported in association with elasomeran/imelasomeran (n=2), but not in recipients of elasomeran/davesomeran (n=0). The information provided on the 2 cases did not allow for causality evaluation at this time. The MAH is requested to make an extra effort to gather further information concerning these two SOCV cases exposed to a Bivalent booster dose of Moderna vaccine targeting SARS-CoV2 and present status and updated information in the next PSUR.

MAH Response: The cases of elasomeran/imelasomeran, [redacted] and [redacted] were received via health authorities. The MAH searched the Regulatory Authority database, and no new updated information was available for these cases as of the DLP of this PBRER#5.

Rapporteur assessment comment:

Clarification accepted, issue resolved.

Request ITEM 14: Thrombosis with thrombocytopenia syndrome (TTS)

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

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

MAH Response: The MAH would like to clarify that it was indeed a typographical error and apologizes for it. The MAH does review and proof-read before submitting the reports.

Rapporteur assessment comment:

Clarification accepted, issue resolved.

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.

However, in the previous PSUSA procedure and in relation to the important potential risk IgA Nephropathy (only included in PSUR Summary of safety concerns), the MAH was requested to include the publication by Ma and Xu in the risk characterisation presented in this PSUR. However, it appears that the MAH has only discussed the article in PSUR section 16.3 and not in PSUR section 16.4. The Rapporteur deems that this article adds value to the risk characterisation as it presents proposed mechanisms of action by which COVID-19 vaccination might induce IgA nephropathy. Therefore, the Rapporteur reiterates its request. **The MAH is requested to include the following publication in the risk characterisation of IgA nephropathy in section 16.4 of the next PSUR with special focus on the proposed mechanisms of action:**

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

As noted by the MAH, evaluation of information received during the PSUR reporting interval relating to the known important potential risk of IgA nephropathy for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran has not identified any additional clinically relevant new safety information for this topic.

It is noted that in response to the requested re-evaluation of previously assessed cases, one case with IgAN in relation to elasomeran was considered of "probable" causality by the MAH and of "possible" causality by the Rapporteur.

Cumulatively, this case is, according to the PRAC Rapporteur's manual review of the PSUR no. 4 Appendix 11.17b, (at least) the 6th case of IgAN associated with elasomeran assessed by the MAH with "Probable" causality, thus reinforcing the importance of continuing surveillance of this issue as previously agreed.

Concerning the important identified risks myocarditis and pericarditis the following is noted:

Both myocarditis and pericarditis have been seen following vaccination with elasomeran-containing vaccines used for COVID-19 immunisation. Although the aetiology is not fully understood, a main hypothesis is that the Spike protein or Spike-S1 protein - which are antigens produced after vaccination with the mRNA-vaccine against COVID-19 - are involved in myocarditis as well as in pericarditis when these occur as adverse events to the vaccine.

For both myocarditis and pericarditis, these are reported as very rare cases of adverse events following vaccination with elasomeran-containing vaccines, primarily within 14 days following vaccination, mostly but not only in younger men, and mostly but not only after the 2nd dose, some cases have required intensive care, and fatal cases have been observed. SmPC and PIL have been properly updated according to this. The MAH will continue to monitor reported adverse events of myocarditis and/or pericarditis by routine and enhanced surveillance activities.

3. Benefit evaluation

Elasomeran is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults (18 years and above), adolescents (12-17 years of age), and children (6 months of age and older) in the EU at the time of DLP of this PSUR. In addition, two bivalent vaccines, elasomeran/imelasomeran, and elasomeran/davesomeran, are approved.

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

Elasomeran is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in adults (18 years and above), adolescents (12-17 years of age), and children (6 months of age and older) in the EU at the time of DLP of this PSUR. In addition, two bivalent vaccines, elasomeran/imelasomeran, and elasomeran/davesomeran, are approved.

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

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

During the reporting interval, new information concerning chronic urticaria was identified that warrants an amendmend of the PI for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

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

5. Rapporteur Request for supplementary information

5.1. Request no 1: IgA Nephropathy

The Rapporteur notes that the publication by Ma and Xu lists 15 literature case reports of IgA nephropathy following vaccination with Moderna's COVID-19 vaccine. These literature case reports have been published before 10th July 2022 (before the reporting period under review in this PSUSA) and most of these cases also appear in Eudravigilance and they should therefore already have been evaluated by the MAH. However, the Rapporteur notes that on these cases the MAH simply states: "[…] *it should be noted that inferences drawn from analyses of these cases, all selected from the literature, may be susceptible to publication bias.*" **As it is unclear whether the MAH has previously evaluated these cases or not, within this procedure the MAH is requested to clarify whether the literature case reports presented in the article by Ma and Xu have been included in previous evaluations of IgA nephropathy. If any of these cases have not previously been evaluated, the MAH should present these cases and comment on them within this procedure.**

5.2. Request no 2: Chronic urticaria

The signal chronic urticaria was evaluated as a signal in the PSUR #3, however the signal was rejected. Based on new information on chronic urticaria the Rapporteur has raised the signal in the current PSUSA procedure and provided a cumulative review on chronic urticaria and elasomeran-containing vaccines. **Based on the cumulative review presenting evidence of at least a possible causal association between chronic urticaria and elasomeran-containing vaccines, the MAH is requested within this procedure to comment on the update of the product information with chronic urticaria in section 4.8 and PL section 4.**

6. MAH responses to Request for supplementary information

6.1. MAH's response to request no 1: IgA Nephropathy

Request: The Rapporteur notes that the publication by Ma and Xu lists 15 literature case reports of IgA nephropathy following vaccination with Moderna's COVID-19 vaccine. These literature case reports have been published before 10th July 2022 (before the reporting period under review in this PSUSA) and most of these cases also appear in Eudravigilance and they should therefore already have been evaluated by the MAH. However, the Rapporteur notes that on these cases the MAH simply states: "[…] *it should be noted that inferences drawn from analyses of these cases, all selected from the literature, may be susceptible to publication bias.*" **As it is unclear whether the MAH has previously evaluated these cases or not, within this procedure the MAH is requested to clarify whether the literature case reports presented in the article by Ma and Xu have been included in previous evaluations of IgA nephropathy. If any of these cases have not previously been evaluated, the MAH should present these cases and comment on them within this procedure.**

MAH response:

The MAH would like to confirm that of the 15 literature case reports presented in the Ma and Xu article highlighted by PRAC, 13 have been included in previous evaluations of IgAN and are listed below, with first author name following Moderna case ID and WWID number:

[redacted] (WWID# [redacted]) Klomjit
[redacted] (WWID# [redacted]) Klomjit
[redacted] (WWID# [redacted]) Anderegg
[redacted] (WWID# [redacted]) Abramson
[redacted] (WWID# [redacted]) Park
[redacted] (WWID# [redacted]) Lim
[redacted] (WWID# [redacted]) Kudose
[redacted] (WWID# [redacted]) Kudose
[redacted] (WWID# [redacted]) Srinivasan
[redacted] (WWID# [redacted]) Negrea
[redacted] (WWID# [redacted]) Valenzuela
[redacted] (WWID# [redacted]) Watanabe
[redacted] (WWID# [redacted]) Klomjit

Two cases (see below) have not been included in previous evaluation of IgAN, due to the coding (MedDRA terms) used for these two reports. The [redacted] case was coded as acute kidney injury (not in HLT

Glomerulonephritis and Nephrotic Syndrome). The [redacted] case was coded as hematuria (also not in HLT GN and NS).

[redacted] (WWID# [redacted] MOD- [redacted]) [redacted]

This brief 2021 Letter-to-the-Editor publication reported a 38-year-old woman diagnosed with IgAN in 2019. She had gross hematuria at presentation and was initially treated for six months with cyclophosphamide and prednisone, then renin-angiotensinaldosterone system inhibition. She had persistent microscopic hematuria, and proteinuria of 0.43 g/d in 2020. The patient developed reactogenicity symptoms within several hours of the second dose; however, two patients' reactogenicity symptoms were combined in the report, so that this patient's specific symptoms are not known. Within about a day after the reactogenicity symptoms, the patient noticed gross hematuria that resolved after 3 days; her proteinuria three weeks after the second dose was 0.40 g/d, lower than the prior year.

MAH Assessment. There is a temporal association between the flare of IgAN and vaccination in this case. Possible triggers to the flare, such as SARS-Covid-19 infection, other infections or other exposures were not mentioned or ruled out. In addition, this patient's treatment had been reduced from cyclophosphamide and prednisone to reninangiotensin-aldosterone system inhibition, and that "step-down" in treatment intensity may have played some role in this flare, although the relationship between timing of treatment changed and vaccination is unclear. Moreover, treatment with cyclophosphamide is not typical for IgAN and may indicate somewhat refractory disease. Given these factors, WHO Causality assessment is possible.

[redacted] (WWID# [redacted]) [redacted]

This brief Letter-to-the-Editor publication reported a 25-year-old female who had been diagnosed with IgAN two years prior to vaccination. She had serum creatinine of 0.7mg /dL and urine protein creatinine ratio (UPCR) 1410 mg/g prior to vaccination. Patient was reported as having normal and stable kidney function and sub-nephrotic proteinuria without hematuria. Symptom onset was reported as one day after dose two of Spikevax, including gross hematuria, mild acute kidney injury (sCr 1.07 mg/dL) and worsening of proteinuria (UPCR of 4760 mg/g). In three weeks, sCr and UPCR returned to baseline.

MAH Assessment. There is a temporal association between the flare of IgAN and vaccination in this case. Possible triggers to the flare, such as SARS-Covid-19 infection, other infections or other exposures were not mentioned or ruled out. The patient's renal function was reported as normal prior to vaccination; however, the sub-nephrotic proteinuria is not normal and indicates active renal pathology prior to vaccination. The natural history of IgAN includes relapse and remissions, as was observed in this case with the return of sCr and UPCR to baseline. Given these considerations and the limited details, WHO Causality Assessment for this case report is possible.

Based on the analysis of all safety data available, the MAH considers that these two additional reports do not change the benefit risk for Spikevax-containing vaccines, and this information does not substantiate evidence of causality between exposure to Spikevax vaccines and IgAN. The MAH will continue to monitor events of IgAN using routine surveillance.

Rapporteur assessment comment:

The MAH confirms that 13 out of 15 cases included in the literature reference have previously been included in the MAH's evaluation of IgA nephropathy. This is acknowledged.

The MAH presented information on the 2 cases not previously evaluated ([redacted] and [redacted]). Both cases concern IgAN flare up in association with Spikevax vaccination. The MAH

states that the two cases were not included in previous evaluations of IgAN, as the cases were coded as haematuria and acute kidney injury, respectively. The Rapporteur notes that the cases do not report whether the suspected IgA flare ups have been confirmed with renal biopsy. However, the observed gross haematuria in both cases and increased proteinuria in one case could suggest an IgA nephropathy flare up. Both cases lacked information on other possible triggers to the flare, however, TTOs were several hours/within one day of the second dose of vaccine. Regarding the case by Srinivasan et al., the MAH notes that the patient had proteinuria prior to vaccination. The Rapporteur agrees that the patient's urine protein creatinine ratio is significantly elevated prior to vaccination which could suggest some degree of disease activity before vaccination. The causality assessments were by the MAH considered possible for both cases. However, the Rapporteur evaluates both cases as unassessable due to lack of information.

The information presented from the two cases does not change the current understanding of the PSUR important potential risk of IgAN. Routine surveillance should continue.

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

6.2. MAH's response to request no 2: Chronic urticaria

Request:

The signal chronic urticaria was evaluated as a signal in the PSUR #3, however the signal was rejected. Based on new information on chronic urticaria the Rapporteur has raised the signal in the current PSUSA procedure and provided a cumulative review on chronic urticaria and elasomeran-containing vaccines. **Based on the cumulative review presenting evidence of at least a possible causal association between chronic urticaria and elasomeran-containing vaccines, the MAH is requested within this procedure to comment on the update of the product information with chronic urticaria in section 4.8 and PL section 4.**

MAH response:

The ADR term "chronic urticaria" has been added to all 4 products for Spikevax in section 4.8 of the SmPC and section 4 of the PIL as per request from the PRAC.

Rapporteur assessment comment:

The MAH agrees to include the ADR "Chronic urticaria" in the SmPC section 4.8 and PIL section 4 with the frequency "not known" as proposed by the PRAC Rapporteur. Please see section 3 Recommendations for further details.

Endorsed.

7. Comments from Member States

7.1. Member state (MS) (MS1, MS2, MS3, MS4, MS5, MS6)

We fully endorse the PRAC Rapp assessment report and conclusions for the PSUR of Spikevax/ We fully endorse the PRAC Rapporteur's assessment, and have no further comments

MS5 comment: We agree with the Rapp´s proposal to include chronic urticaria to the product information as a new ADR with frequency not known. The consistency of data from the spontaneous cases and from the literature supported with disproportionality in the databases and the Danish analysis is supportive to establish a causal relationship between chronic urticaria and Spikevax.

Rapporteur assessment comment:

The full endorsements are appreciated and acknowledged.

One MS specifically agrees with the PRAC Rapporter's proposal to include chronic urticaria to the product information as a new adverse drug reaction with the frequency "not known".

FIFTH PERIODIC SAFETY UPDATE REPORT

For

ACTIVE SUBSTANCEs: Elasomeran (SPIKEVAX [COVID-19 Vaccine, mRNA-1273]), Elasomeran/imelasomeran (SPIKEVAX Bivalent.214 Original/BA.1, mRNA-1273.214) and Elasomeran/davesomeran (SPIKEVAX Bivalent.222 Original/BA.4/5, mRNA-1273.222)

ATC CODE: J07BN01 (previously J07BX03)

MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Products	Dates of Authorization	Marketing Authorization Holder
Spikevax (elasomeran and COVID-19 mRNA Vaccine [nucleoside-modified])	06 Jan 2021	Moderna Biotech Spain S.L.
Spikevax bivalent Original/Omicron BA.1 (elasomeran/imelasomeran)	12 Aug 2022	
Spikevax bivalent Original/Omicron BA.4-5 (elasomeran/davesomeran)	31 Aug 2022	

AUTHORIZATION PROCEDURE in the EU: Centralized

INTERNATIONAL BIRTH DATE (IBD): 18 Dec 2020

EUROPEAN UNION REFERENCE DATE (EURD): 18 Dec 2020

INTERVAL COVERED BY THIS REPORT:
from 18 Dec 2022 to 17 Jun 2023
DATE OF THIS REPORT:
18 Aug 2023

OTHER INFORMATION:
Elasomeran (Previously COVID-19 Vaccine Moderna), Bivalents (elasomeran/imelasomeran and elasomeran/davesomeran).

MARKETING AUTHORIZATION HOLDER'S NAME AND ADDRESS:

ModernaTx, Inc.
200 Technology Square
Cambridge, MA 02139, USA

Moderna Biotech Spain SL
Del Principe De Vergara 132 Plt 12
28002 Madrid-Spain

NAME AND CONTACT DETAILS OF THE QPPV (or designated person):

Dr. Marie-Pierre Caby-Tosi
Executive Director, EEA/UK QPPV
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75007 Paris, France
[redacted]

SIGNATURE (QPPV or designated person):

DATE:

DISTRIBUTION LIST

Competent Authority	Number of copies
European Medicines Agency (EMA)	1
US Food Drug Administration (FDA	1
Medicines and Healthcare products Regulatory Agency (MHRA)	1
Health Canada	1

EXECUTIVE SUMMARY

This Fifth Periodic Safety Update Report (PSUR) (referred to as Periodic Benefit-Risk Evaluation Report [PBRER] throughout the report) on SPIKEVAX® (elasomeran or mRNA-1273, formerly known as Moderna's COVID-19 mRNA Vaccine), SPIKEVAX Bivalent.214 Original/BA.1 (elasomeran/imelasomeran; mRNA-1273.214) booster, and SPIKEVAX Bivalent 222 Original/BA.4/5 (elasomeran/davesomeran; mRNA-1273.222) booster was compiled for regulatory authorities in the PBRER format detailed in the European Medicines Agency (EMA) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2C guidelines (Good Pharmacovigilance Practice guideline Module VII PSURs, 2012 and ICH E2C[R2]). This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran based on review of cumulative safety information with a focus on new safety information from available worldwide data sources received during the reporting period. The reporting period for this PBRER#5 is from 18 Dec 2022 to 17 Jun 2023. Currently, the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates (EURD) and to stay aligned with the EURD, one additional 6-monthly PBRER (data lock point [DLP] 17 Dec 2023) will be submitted, then the first yearly PBRER (DLP 17 Dec 2024), to be followed by further yearly PBRERs. The first three PBRERs (PBRER#1, PBRER#2, and PBRER#3) submitted included the single International Nonproprietary Name elasomeran, however, beginning with the PBRER#4, bivalent vaccines; elasomeran/imelasomeran, and elasomeran/davesomeran were also included.

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" with the Anatomical Therapeutic Chemical (ATC) code: J07BN01 (previously J07BX03).

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid based- vaccine against the 2019 novel coronavirus (CoV) (CoV; severe acute respiratory syndrome [SARS-CoV-2]). Elasomeran/imelasomeran active substance is mRNA encoding the prefusion stabilized spike glycoprotein of original SARS-CoV-2 embedded in LNPs (elasomeran) and mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 Omicron variant (B.1.1.529) embedded in LNPs (imelasomeran). Elasomeran/davesomeran active substance is mRNA encoding the prefusion stabilized spike glycoprotein of original SARS-CoV-2 embedded in LNPs (elasomeran) and mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 Omicron lineages BA.4 and BA.5 (Omicron variants B.1.1.529.4 and B.1.1.529.5)

embedded in LNPs (davesomeran). As per Company Core Data Sheet (CCDS) (v16.0, dated 03 Jan 2023), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. Elasomeran/imelasomeran and elasomeran/davesomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

During this reporting period, ModernaTx, Inc. was in pharmacovigilance agreement with co-sponsors: GlaxoSmithKline plc (GSK), Sanofi S.A., the Division of Microbiology and Infectious Diseases (DMID)/National Institute of Allergy and Infectious Diseases (NIAID), National Cancer Institute (NCI), University of California, Los Angeles (UCLA), South Africa Medical Research Council (SAMRC), Merck, Sharp and Dohme (MSD), and University of Southampton. The agreements began on 16 Dec 2021 (GSK), 21 Feb 2020 (Sanofi and DMID/NIAID), May 2020 (NCI), 15 Mar 2022 (UCLA), 14 Apr 2022 (SAMRC), 02 Dec 2021 (MSD), and 08 Feb 2022 (University of Southampton). The entities agreed to share all the relevant safety data from trials 20-0003, 21-0002, 210012, 22-0004 (DMID/NIAID sponsored), 217670ZOSTER091 (GSK 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, is formulated as a dispersion for injection to be supplied in multidose vial and dispersion for injection in pre-filled syringe and is administered intramuscularly (IM). Elasomeran/imelasomeran is formulated as a dispersion for injection to be supplied in single dose vial, multidose vial and single use pre-filled syringe. Elasomeran/davesomeran is formulated as a dispersion for injection to be supplied in multidose vial.

- Elasomeran 0.20 mg/mL dispersion for injection

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

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

Elasomeran is supplied as a multidose vial that contains five doses of 0.5 mL each or a maximum of ten doses of 0.25 mL each. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs). One dose (0.25 mL) contains 25 µg of elasomeran, a

COVID-19 mRNA Vaccine (embedded in LNPs). It has also been supplied as single use pre-filled syringe that contains one dose of 0.5 ml. One dose (0.5 mL) contains 50 µg of elasomeran, a COVID-19 mRNA Vaccine (embedded in LNPs).

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

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

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

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

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

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

Posology for primary series, a third dose in severely immunocompromised and booster doses for elasomeran-containing vaccines is provided in Table 1.1 below.

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

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

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

Strength	Vaccination Type	Age and Dose	Recommendations
		Children 6 months through 5 years of age Elasomeran is administered as a course of one (one) dose of 0.25 mL, containing 25 µg mRNA	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran, 0.5 mL, containing 50 µg mRNA	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series
Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 6 years through 11 years of age* Dose is administered as one dose of 0.25 mL containing 12.5 ug of elasomeran and 12.5 ug of imelasomeran.	There should be an interval of at least 3 months between administration of elasomeran/imelasomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/imelasomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.
		Individuals 12 years of age and older Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of imelasomeran	

Strength	Vaccination Type	Age and Dose	Recommendations
Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 12 years of age and older* Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of davesomeran	There should be an interval of at least 3 months between administration of elasomeran/davesomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/davesomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

*For primary series for individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.
†For the third dose in severely immunocompromised patients 12 years of age and older, the 0.2 mg/mL strength vial should be used.
‡ For details on the primary vaccination course for ages 12 and above, the 0.2 mg/mL strength vial should be used.

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

During the reporting period, no ModernaTx, Inc. sponsored clinical trials (CTs) were completed and there were a total of 12 ModernaTx, Inc. sponsored CTs ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P305, mRNA-1283-P101, mRNA-1283-P201, mRNA-1273-P206, mRNA-1273-P306, mRNA-1283-P301, and mRNA-CRID-001).

Cumulatively, 53,983 subjects are estimated to be exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA-1273.617.2, mRNA-1273.529, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administration with mRNA-1010 or co-administration with mRNA-1345 in the mRNA clinical development program sponsored by ModernaTx, Inc. The total count of 53,983 represents unique subjects (Subjects enrolled in both trials P301 and P201 (Part C)/P205 or in both P204 and P306 and are only counted once in total).

During the reporting period, 5,207 subjects were estimated to be exposed to either mRNA-1273, or its variants (mRNA-1273.214, mRNA-1273.222, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 in conjunction mRNA-1345 or co-administration with mRNA-1345 in the mRNA clinical development program sponsored by ModernaTx, Inc.

Till DLP, 16,507 subjects were exposed to mRNA-1273 in CTs sponsored by licensing partners. Out of 16,507 subjects, 1,280 subjects were exposed to mRNA-1273 in CTs sponsored by DMID, 1,534 subjects from a CT sponsored by GSK, 17 subjects from a CT sponsored by NCI, 19 subjects from a CT sponsored by UCLA, 12,340 subjects from a CT sponsored by SAMRC, 1,012 subjects from CTs sponsored by MSD, and 305 subjects from a CT sponsored by University of Southampton. Cumulatively, 3,290 subjects were enrolled in investigator-initiated trials.

The International Birth date of elasomeran is 18 Dec 2020. The product is currently authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelasomeran was granted by the Medicines and Healthcare products Regulatory Agency for use in the United Kingdom (UK) on 12 Aug 2022. Elasomeran/davesomeran was granted Emergency Use Authorization (EUA) status by the Food and Drug administration on 31 Aug 2022.

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

Cumulatively, at the end of the reporting period, 17 Jun 2023, a total of 1,664,690,323 doses of elasomeran (original and bivalents including elasomeran/imelasomeran and elasomeran/davesomeran) were delivered to 91 countries and an estimated total of 978,005,565 doses of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran had been administered. Out of 1,664,690,323 doses, 1,318,183,956 were elasomeran doses that had been distributed to 91 countries and an estimated total of 774,433,074 doses had been administered cumulatively. A total of 128,997,293 booster doses of elasomeran/imelasomeran had been distributed to 42 countries and an estimated total of 70,948,511 doses had been administered. A total of 217,509,074 booster doses of elasomeran/davesomeran had been distributed to 41 countries and an estimated total of 119,629,991 doses had been administered.

In this reporting period, between 18 Dec 2022 to 17 Jun 2023, a total of 110,940,854 doses of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran) had been distributed and an estimated total of 65,177,752 doses had been administered. Out of 110,940,854 doses, 2,594,240 were elasomeran doses which were distributed and estimate of 1,524,116 elasomeran doses were administered.

The cumulative evidence on the safety and efficacy for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran fully supports the indication as described in the Reference Safety Information (RSI), authorized as a suspension for injection for active immunizations to prevent COVID-19 caused by SARS-CoV-2 in individuals six months of age and older. Clinical trial data and the results of the post-authorization non-interventional studies conducted to date support the positive safety and efficacy profile of mRNA-1273.

During the reporting period, the following safety-related action was taken by ModernaTx, Inc:

A Spikevax Risk management plan version 7.0 was submitted during the reporting period along with PBRER#4 within procedure European Medicine Evaluation Agency (EMEA)/H/C/Periodic Safety Update Single Assessment (PSUSA)/00010897/202212 to propose removal of the following safety concerns:

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

The RSI for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in effect at the end of the reporting period (DLP 17 Jun 2023) and used for this report is the CCDS v16.0 (dated 03 Jan 2023). During this reporting period, the RSI (CCDS) was updated from v15.0 (dated 15 Nov 2022) to v16.0 (dated 03 Jan 2023) and safety-related changes included addition of elasomeran/davesomeran adverse drug reaction details in Section 4.8 and addition of elasomeran/imelasomeran D91 persistence data and elasomeran/davesomeran clinical data.

During the reporting period of this PBRER, four (4) signals; Amenorrhea (re-evaluation), Pemphigus and pemphigoid, Diarrhea (re-evaluation) and Idiopathic inflammatory myopathy/Myositis were closed as refuted by the marketing Authorization Holder (MAH). In addition, two (2) signals, IgA nephropathy flare-up and Sensorineural hearing loss were ongoing at the DLP of the reporting period.

The important identified and potential risks as per Risk Management Plan version 6.3 dated 15 Dec 2022 are:

Important identified risks:

- Myocarditis
- Pericarditis

Important potential risk:

- VAED including vaccine-associated enhanced respiratory disease (VAERD).

Examination of the data contained within this report supports the conclusion that the overall benefit-risk balance for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran continues to be positive and remains unchanged.

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Acronym	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI/ID	Autoimmune and Inflammatory Disorder
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
BD	Booster Dose
BI-RADS	Breast Imaging-Reporting and Data System
BNP	Brain Natriuretic Peptides
bpm	Beats Per Minute
CAD	Coronary Artery disease
CCDS	Company Core Data Sheet
CD	Case Definition
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukaemia
CLS	Capillary Leak Syndrome
cMRI	Cardiac Magnetic Resonance Imaging
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CoV	Coronavirus
COVE	Corona Virus Efficacy
COVID-19	Coronavirus Disease-19
CRAO	Central Retinal Artery Occlusion
CRP	C-Reactive Protein
CRVO	Central Retinal Vein Occlusion

Acronym	Definition
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
CT	Clinical Trial
CU	Chronic Urticaria
CVST	Central Venous Sinus Thrombosis
DART	Developmental and Reproductive Toxicity
DLP	Data Lock Point
DM	Diabetes Mellitus
DMID	Division of Microbiology and Infectious Diseases
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
EBV	Epstein-Barr Virus
ECDC	European Center for Disease Prevention and Control
ECG	Electrocardiogram
ED	Emergency Department
EEA	European Economic Area
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMEA	European Medicine Evaluation Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
ERR	Event Rate Ratio
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EUA	Emergency Use Authorization
EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
EVDAS	EudraVigilance Data Analysis System
FDA	Food and Drug Administration
FVFP	First Visit First Patient
GA	Gestational Age
GBS	Guillain-Barré Syndrome

Acronym	Definition
GHS	Gutenberg Health Study
GISAID	Global Initiative on Sharing Avian Influenza Data
GMC	Geometric Mean Concentration
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GSDB	Global Safety Database
GSK	Glaxo SmithKline
HA	Health Authority
HCP	Healthcare Care Professional
HHV	Human Herpesvirus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLH	Hemophagocytic Lymphohistiocytosis
HLT	High Level Term
HMB	Heavy Menstrual Bleeding
HNL	Histiocytic Necrotizing Lymphadenitis
IBD	International Birth Date
ICD	International Classification of Diseases
ICH	International Council on Harmonization
ICMR	Indian Council of Medical Research
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
ID	Inflammatory disease
IIM	Idiopathic Inflammatory Myopathies
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular

Acronym	Definition
INN	International Nonproprietary Name
IQR	Interquartile Range
IR	Incidence Rate
IRR	Incidence Rate Ratio
IST	Internal Safety Team
IVIg	Intravenous Immunoglobulin
LGE	Late Gadolinium Enhancement
LLOQ	Lower Limit of Quantification
LNP	Lipid Nanoparticle
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MHRA	Medicines and Healthcare products Regulatory Agency
MedHX	Medical History
MI	Myocardial infarction
MIS-C	Multisystem Inflammatory Syndrome in Children
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MSD	Merck, Sharp and Dohme
MSSR	Monthly Safety Summary Report
NAM	National Academy of Medicine
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NICU	Neonatal Intensive Care Unit
NIS	Non-Interventional Study
NK	Natural Killer
NOC	Notice of Compliance

Acronym	Definition
NOS	Not Otherwise Specified
NSAID	Nonsteroidal Anti-inflammatory Drug
O/E	Observed Expected
OR	Odds Ratio
PAN	Polyarteritis Nodosa
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase Chain Reaction
PD1	Programmed Cell Death 1
PDL1	Programmed Cell Death Ligand 1
PDV	Program Data Vector
PF	Pemphigus Foliaceus
PIL	Patient Information Leaflet
PMDA	Pharmaceutical and Medical Devices Agency
PMS	Post-Marketing Surveillance
POTS	Postural orthostatic tachycardia syndrome
PRAC	Pharmacovigilance Risk Assessment Committee
PSSF	Product Signaling Strategy Form
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
PT	Preferred Term
PTS	Post-Thrombotic Syndrome
PV	Pemphigus Vulgaris
PVA	Pharmacovigilance Agreement
QR	Quick Response
RAs	Regulatory Authorities
RLU	Relative Luminescence Units
RMP	Risk Management Plan
RNA	Ribonucleic Acid
ROR	Rate of Return

Acronym	Definition
RR	Risk Ratio
RSI	Reference Safety Information
RSV	Respiratory Syncytial Virus
RTQ	Response to Query
rVE	Relative Vaccine Effectiveness
SAE	Serious Adverse Event
SAMRC	South Africa Medical Research Council
SARS	Severe Acute Respiratory Syndrome
SARs-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SCRI	Self-controlled risk interval
SD	Standard Deviation
SIR	Standardized Incidence Ratio
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardizes MedDRA Query
SNHL	Sensorineural Hearing Loss
SOC	System Organ Class
SOCV	Single Organ Cutaneous Vasculitis
SOT	Solid Organ Transplant
SRMT	Safety and Risk Management Team
SRR	Sero Response Rate
SSNHL	Sudden Sensorineural Hearing Loss
TCR	T-cell receptor
TEAE	Treatment-Emergent Adverse Event
TGA	Therapeutic Goods Administration
TTO	Time to Onset
UCLA	University of California, Los Angeles
ULOQ	Upper Limit of Quantification
UMC	Uppsala Monitoring Center

Acronym	Definition
UK	United Kingdom
US/USA	United States/United States of America
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VILI	Vaccine Induced Liver Injury
VITT	Vaccine-induced immune thrombotic thrombocytopenia
VOC	Variants of Concern
VOI	Variant of Interest
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
WAO	World Allergy Organization
WHO	World Health Organization
WHO-UMC	World Health Organization-Uppsala Monitoring Center

1. INTRODUCTION

This Fifth Periodic Safety Update Report (PSUR) (referred to Periodic Benefit-Risk Evaluation Report [PBRER] throughout the report) on SPIKEVAX® (elasomeran or mRNA-1273, formerly known as Moderna's COVID-19 mRNA Vaccine), SPIKEVAX Bivalent.214 Original/BA.1 (elasomeran/imelasomeran; mRNA-1273.214) booster, and SPIKEVAX Bivalent.222 Original/BA.4/5 (elasomeran/davesomeran; mRNA-1273.222) booster was compiled for regulatory authorities in the PBRER format detailed in the European Medicines Agency (EMA) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E2C guidelines (Good Pharmacovigilance Practice guideline Module VII PSURs, 2012 and ICH-E2C[R2]). This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran based on review of cumulative safety information with a focus on new safety information from available worldwide data sources received during the reporting period. The reporting period for this PBRER#5 is from 18 Dec 2022 to 17 Jun 2023. Currently, the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran PBRER is on a 6-monthly submission schedule based on the European Union (EU) reference dates (EURD) and to stay aligned with the EURD, one additional 6-monthly PBRER (data lock point [DLP] 17 Dec 2023) will be submitted, then the first yearly PBRER (DLP 17 Dec 2024), to be followed by further yearly PBRERs. The first three PBRERs (PBRER#1, PBRER#2 and PBRER#3) submitted included the single International Nonproprietary Name elasomeran, however, beginning with the PBRER#4, bivalent vaccines; elasomeran/imelasomeran, and elasomeran/davesomeran were also included.

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

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran belong to the pharmacotherapeutic group "Vaccines, COVID-19 Vaccines" and has Anatomical Therapeutic Chemical (ATC) code: J07BN01 (previously J07BX03).

Elasomeran is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; SARS-CoV-2). As per Company Core Data Sheet

(CCDS) (v16.0, dated 03 Jan 2023), elasomeran is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals six months of age and older. Elasomeran/imelasomeran and elasomeran/davesomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19.

Elasomeran is Single-stranded, 5'-capped messenger Ribonucleic acid (RNA) (mRNA) produced using a cell-free in vitro transcription from the corresponding Deoxyribonucleic acid templates, encoding the full-length Spike protein of SARSCoV2, modified to introduce two proline residues to stabilize the S-protein into a prefusion conformation (S-2P). Elasomeran consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: 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, codonoptimized prefusion stabilized conformation variant (K983P and V984P) of the SARSCoV-2 spike (S) glycoprotein (Omicron variant, B.1.1.529). Davesomeran is a single-stranded, 5'capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding Deoxyribonucleic acid templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). The Sproteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.

For the ongoing clinical trial, mRNA-1273-P205, a new study arm J was introduced which included two new variants i.e., mRNA-1273.815 andmRNA-1273.231. These 2 new variants were only used for study mRNA-1273-P205. mRNA-1273.815 contains CX-038839, the monovalent mRNA that encodes for the S-2P of the SARS-CoV-2 Omicron subvariants XBB.1.5/XBB.1.9.1. mRNA-1273.231 contains CX-034476, the mRNA that encodes for the S-2P of the SARS-CoV-2 B.1.1.529 Omicron subvariants BA.4/BA.5, and CX-038839, the mRNA that encodes for the S-2P of the SARS-CoV-2 subvariants XBB.1.5/XBB.1.9.1. The formulatedmRNA in mRNA-1273.231 are mixed in a 1:1 ratio. Both mRNA-1273.815 and mRNA-1273.231 consist of mRNA formulated in a mixture of four lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG. mRNA-1273.231 and mRNA-1273.815 injections will be provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.1 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 2.1 mM acetate at pH 7.5. mRNA-1273.815 and mRNA-1273.231 will be administered at a 50 µg dose level. Doses will be administered by Intramuscular (IM) injection according to the procedures

specified in the mRNA-1273-P205 Pharmacy Manual. Preferably, the vaccine should be administered into the nondominant arm.

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

- Elasomeran 0.20 mg/mL dispersion for injection

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

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

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

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

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

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

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

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

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

Posology for primary series, a third dose in severely immunocompromised and booster doses for elasomeran-containing vaccines is provided in below Table 1.1.

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

Strength	Vaccination Type	Age and Dose	Recommendations
Elasomeran 0.20 mg/mL concentration	*Primary series*	*Individuals 12 years of age and older* Elasomeran is administered as a course of 2 (two) 100 µg doses (0.5 mL each).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 through 11 years of age Elasomeran is administered as a course of 2 (two) 50 µg doses (0.25 mL each, containing 50 µg mRNA, which is half of the primary dose for individuals 12 years and older).	
	Third dose in severely immunocompromised	*Individuals 12 years of age and older* Elasomeran is administered as course of one dose of 0.5 mL, containing 100 µg mRNA.	A third dose may be given at least 28 days after the second dose.
		Children 6 through 11 years of age Elasomeran is administered as a course of one dose of 0.25 mL, containing 50 µg mRNA.	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran 0.25 mL, containing 50 µg mRNA.	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or a adenoviral vector vaccine at least 3 months after

Strength	Vaccination Type	Age and Dose	Recommendations
			completion of the primary series.
Elasomeran 0.10 mg/mL concentration and 50 µg dispersion for injection in pre-filled syringe	*Primary series*[*]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of 2 (two) 50 µg doses (0.5 mL each, containing 50 µg mRNA).	It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age Elasomeran is administered as a course of 2 (two) 25 µg doses (0.25 mL each, containing 25 µg mRNA each, which is half of the primary dose for children 6 years through 11 years of age).	
	Third dose in severely immunocompromised[†]	*Children 6 years through 11 years of age* Elasomeran is administered as a course of one dose of 0.5 mL, containing 50 µg mRNA.	A third dose may be given at least 28 days after the second dose.
		Children 6 months through 5 years of age Elasomeran is administered as a course of one (one) dose of 0.25 mL, containing 25 µg mRNA.	
	Booster dose	*Individuals 12 years of age and older* A booster dose of elasomeran, 0.5 mL, containing 50 µg mRNA.	Moderna COVID-19 Vaccine may be used to boost individuals 12 years of age and older who have received a primary series with Moderna COVID-19 Vaccine, or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
Elasomeran/imelasomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*[‡]	*Individuals 6 years through 11 years of age* Dose is administered as one dose of 0.25 mL containing 12.5 ug of elasomeran and 12.5 ug of imelasomeran.	There should be an interval of at least 3 months between administration of elasomeran/imelasomeran and the last prior dose of a COVID-19 vaccine.

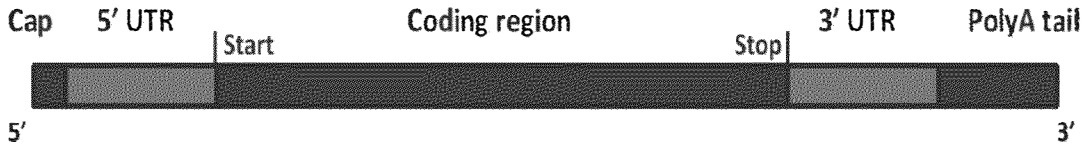
Strength	Vaccination Type	Age and Dose	Recommendations
		Individuals 12 years of age and older Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of imelasomeran.	Elasomeran/imelasomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.
Elasomeran/davesomeran (50 µg/50 µg)/mL dispersion for injection	*Booster dose*‡	*Individuals 12 years of age and older* Dose is administered as a course of one dose of 0.5 mL, containing 25 µg of elasomeran and 25 µg of davesomeran.	There should be an interval of at least 3 months between administration of elasomeran/davesomeran and the last prior dose of a COVID-19 vaccine. Elasomeran/davesomeran is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

*For primary series for individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.
†For the third dose in severely immunocompromised patients 12 years of age and older, the 0.2 mg/mL strength vial should be used.
‡ For details on the primary vaccination course for ages 12 and above, the 0.2 mg/mL strength vial should be used.

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

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

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



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

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

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

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

Table 1.2 Variants and WHO labels for mRNA-1273

Suffix	Variants
mRNA-1273.351	Beta
mRNA-1273.617.2	Delta
mRNA-1273.211	Bivalent: 1:1 ratio of prototype and beta (.351)
mRNA-1273.213	Bivalent: 1:1 ratio of beta (.351) and delta (.617)
mRNA-1273.214	Bivalent: 1:1 ratio of prototype and omicron BA.1 (.529)

Suffix	Variants
mRNA-1273.222	Bivalent: 2 mRNAs: CS-023314 and CX-034476
mRNA-1273.529	Omicron BA.1
mRNA-1273.815	B.1.351 lineage S variant
nRNA-1273.231	1.5 sub lineage of SARS-CoV-2

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

The expressed Spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

Further details on mechanism of action, indications, pharmaceutical forms, and instructions for use are presented in the CCDS for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran (current v16 dated 03 Jan 2023) in Appendix 1.

2. WORLDWIDE MARKETING APPROVAL STATUS

The IBD of elasomeran is 18 Dec 2020. The product is currently authorized in 49 unique countries, regions, and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2. First marketing approval for elasomeran/imelasomeran was granted by the MHRA for use in the UK on 12 Aug 2022. Elasomeran/davesomeran was granted EUA status by Food and Drug administration on 31 Aug 2022.

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

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

Table 2.1 Worldwide Marketing Authorizations

List of Authorizations	Link to Table
Use in adults aged 18 years and older (primary series)	Table 20.1

List of Authorizations	Link to Table
Use in adolescents aged 12 to < 18 years (primary series),	Table 20.2
Use in for ages 6 to <12-year-old pediatrics indication (primary series)	Table 20.3
Use in 6 months to < 6-year-old indication (pediatrics)	Table 20.4
Use as a booster indication in adults (50 ug)	Table 20.5
Use as a booster indication in adolescents (50 ug)	Table 20.6
Third dose in immunocompromised patients	Table 20.7
Elasomeran/imelasomeran booster indication for adults aged 18 years and older	Table 20.8
Elasomeran/imelasomeran booster indication for adolescents aged 12 to <18 years	Table 20.9
Elasomeran/imelasomeran booster indication for the 6 years to <12-year-old (pediatrics)	Table 20.10
Elasomeran/davesomeran booster indication for adults aged 18 years and older	Table 20.11
Elasomeran/davesomeran booster indication for use in adolescents aged 12 to <18 years of age	Table 20.12
Elasomeran/davesomeran booster indication for the 6 years to <12-year-old (pediatrics)	Table 20.13
Elasomeran/davesomeran booster indication for the 6 months to <6-year-old	Table 20.14
Elasomeran/davesomeran Booster Adults 18+	Table 20.15
Elasomeran/davesomeran Booster Adults 18+ Booster 12 to <18-Years of Age (Adolescents)	Table 20.16
Elasomeran/davesomeran Booster 6 to < 12-Year-Old Indication (Pediatrics)	Table 20.17
Elasomeran/davesomeran Booster Indication 6 months to < 6-Year-Old	Table 20.18

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

During the reporting period, the following safety-related action was taken by ModernaTx, Inc:

A Spikevax Risk Management Plan (RMP) version 7.0 was submitted during the reporting period along with PBRER#4 within procedure European Medicine Evaluation Agency (EMEA)/H/C/Periodic Safety Update Single Assessment (PSUSA)/00010897/202212 to propose removal of the following safety concerns:

- Important potential risk: Vaccine-associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD).
- Missing information: Use in immunocompromised subjects, Interaction with other vaccines, Use in frail subjects with unstable health conditions and co-morbidities (e.g.

chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) and Use in subjects with autoimmune or inflammatory disorders.

The evaluation of the PBRER#4 was still ongoing at the end of the reporting period.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The Reference Safety Information (RSI) for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in effect at the end of the reporting period (DLP 17 Jun 2023) and used for this report is the CCDS v16.0 (dated 03 Jan 2023). This CCDS was used to assess listedness of adverse reactions (ARs), risks in risk sections, and to support benefit-risk evaluation in this report. The RSI contains a complete review of the safety profile for the product. This document is provided in Appendix 1.

During this reporting period, the RSI (CCDS) was updated from v15.0 (dated 15 Nov 2022) to v16.0 (dated 03 Jan 2023). The safety-related changes are summarized below in Table 4.1.

Table 4.1 CCDS safety-related changes during the reporting period

Version	Date	Summary of changes
16.0	03 Jan 2023	**Section 4.8,** Addition of elasomeran/davesomeran Adverse drug reaction details. **Section 5.1,** Addition of elasomeran/imelasomeran D91 persistence data and elasomeran/davesomeran clinical data

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 53,983 subjects are estimated to be have been exposed to either mRNA-1273, or its variants (mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA-1273.617.2, mRNA-1273.529, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administration with mRNA-1010 or co-administration with mRNA-1345 in the mRNA clinical development program sponsored by ModernaTx, Inc. The total count of 53,983 represents unique subjects (Subjects enrolled in both trials P301 and P201 (Part C)/P205 or in both P204 and P306 and are only counted once in total).

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials (CTs) and the enrolment/randomization schemes for ongoing and blinded trials is

provided in Table 5.1. Further details on cumulative subject exposure categorized by age, gender, racial group and ethnicity are provided in Table 5.2, Table 5.3, Table 5.4 and Table 5.5, respectively.

Table 5.1 Estimated Cumulative Subject Exposure from Clinical Trials

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P201	Placebo	42[a]
mRNA-1273-P201	mRNA-1273	558[a]
mRNA-1273-P201	mRNA-1273 Booster	344
mRNA-1273-P201	mRNA-1273.351 Booster	40
mRNA-1273-P201	mRNA-1273/mRNA-1273.351 Booster	20
mRNA-1273-P203	Placebo	1,144[a]
mRNA-1273-P203	mRNA-1273 100 ug	2,582[a]
mRNA-1273-P203	mRNA-1273 50 ug	52[a]
mRNA-1273-P203	mRNA-1273.222 50 ug	388[a]
mRNA-1273-P203	EUA+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	2,767
mRNA-1273-P204	mRNA-1273.214 25 ug Booster	209
mRNA-1273-P204	mRNA-1273.214 50 ug Booster	6
mRNA-1273-P205	mRNA-1273 Booster	681[a]
mRNA-1273-P205	mRNA-1273.211 Booster	759[a]
mRNA-1273-P205	mRNA-1273.211 Booster+mRNA-1273.214 Booster	135[a]
mRNA-1273-P205	mRNA-1273.213 Booster	951[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1273-P205	mRNA-1273.214 Booster	437[a]
mRNA-1273-P205	mRNA-1273.222 Booster	424[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.231 Booster	45[a]
mRNA-1273-P205	mRNA-1273.222 Booster+mRNA-1273.815 Booster	42[a]
mRNA-1273-P205	mRNA-1273.529 Booster	508[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	1,167[a]
mRNA-1273-P205	mRNA-1273.815 Booster	8[a]
mRNA-1273-P205	mRNA-1273.231 Booster	6[a]
mRNA-1273-P206	mRNA-1273.214	54[a]
mRNA-1273-P301	Placebo	2,513[a]
mRNA-1273-P301	mRNA-1273	27,833[a]
mRNA-1273-P301	mRNA-1273 Booster	19,609
mRNA-1273-P304	mRNA-1273	81[a]
mRNA-1273-P304	EUA+mRNA-1273	71[a]
mRNA-1273-P304	EUA+mRNA-1273 Booster	82[a]
mRNA-1273-P304	Primary series+mRNA-1273 Booster	87
mRNA-1273-P305	Overall (mRNA-1273, mRNA-1273.214, or mRNA-1273.529 booster)	3,548[a]
mRNA-1273-P306	mRNA-1273.214	391[a]
mRNA-1273-P306	mRNA-1273.214 Booster	539[a]
mRNA-1283-P101	Placebo+mRNA-1283+mRNA-1273	5[a]
mRNA-1283-P101	mRNA-1273	22[a]
mRNA-1283-P201	mRNA-1273 Booster	57[a]

Study ID	Vaccine Type	Total Subjects Exposure by Study and Product
mRNA-1283-P301	mRNA-1273.222	3,886[a,b]
mRNA-CRID-001	mRNA-1273	60[a]
mRNA-1073-P101	mRNA-1010+mRNA-1273 co-administration	101[a]
mRNA-1073-P101	mRNA-1273+Placebo	49[a]
mRNA-1083-P101	mRNA-1273.222	102[a,b]
mRNA-1230-P101	mRNA-1273.214	44[a,b]
mRNA-1345-P302	Overall (mRNA-1273.214 alone or co-administration with mRNA-1345)	1,690[a]

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

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

Age Range	mRNA-1273									mRNA-1283			mRNA-CRID	mRNA-1073	mRNA-1083	mRNA-1230	mRNA-1345	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	P301[c]	001	P101	P101[c]	P101[c]	P302	
<2 years	0	0	2,828	0	54	0	0	0	244	0	0	0	0	0	0	0	0	**3,001[b]**
2 to <6 years	0	0	4,244	0	0	0	0	0	686	0	0	0	0	0	0	0	0	**4,458[b]**
6 to <12 years	0	0	4,843	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**4,843**
12 to <16 years	0	3,251	0	0	0	0	0	0	0	0	0	98	0	0	0	0	0	**3,349**
16 to <18 years	0	1,070	0	0	0	0	0	1	0	0	0	56	0	0	0	0	0	**1,127**
18 to <65 years	508	0	0	3,871	0	22,826	184	2,349	0	27	51	5,200	56	127	622	291	1,070	**34,182[b]**
65 to <75 years	128	0	0	1,034	0	6,121	43	1,118	0	0	5	1,735	4	22	504	95	498	**10,478[b]**
75 to <85 years	21	0	0	236	0	1,309	7	75	0	0	1	485	0	1	92	6	115	**2,167[b]**
>=85 years	3	0	0	22	0	90	0	5	0	0	0	51	0	0	0	0	7	**163[b]**
Missing	0	0	0	0	0	0	0	0	0	0	0	146	0	0	0	0	0	**146**

Age Range	mRNA-1273									mRNA-1283			mRNA-CRID	mRNA-1073	mRNA-1083	mRNA-1230	mRNA-1345	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	P301[c]	001	P101	P101[c]	P101[c]	P302	
Total	660	4,321	11,915	5,163	54	30,346	234	3,548	930	27	57	7,771	60	150	1,218	392	1,690	63,914[b] [d]

[a]=Data from ongoing and completed trials till 17 Jun 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.
c=Study is currently blinded. This is the overall count including Placebo/comparators or other investigational products.
d=The total 63,914 includes subjects from three blinded studies which could not be further estimated based on age, gender, ethnic origin or racial group, thus does not match with estimates of 53,983.

Table 5.3 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Sex[a]

Sex	mRNA-1273									mRNA-1283			mRNA-CRID	mRNA-1073	mRNA-1083	mRNA-1230	mRNA-1345	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	P301[c]	001	P101	P101[c]	P101[c]	P302	
Male	238	2,221	6,050	2,407	27	15,974	124	1,757	478	18	25	3,301	22	56	552	165	760	**31,860[b]**
Female	422	2,100	5,865	2,756	27	14,372	110	1,791	452	9	32	4,324	38	94	666	227	930	**31,908[b]**
Missing	0	0	0	0	0	0	0	0	0	0	0	146	0	0	0	0	0	**146**
Total	**660**	**4,321**	**11,915**	**5,163**	**54**	**30,346**	**234**	**3,548**	**930**	**27**	**57**	**7,771**	**60**	**150**	**1,218**	**392**	**1,690**	**63,914[bd]**

[a] =Data from ongoing trials and completed trials till 17 Jun 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.
[c]=Study is currently blinded. This is the overall count including Placebo/comparators or other investigational products.
[d]=The total 63,914 includes subjects from three blinded studies which could not be further estimated based on age, gender, ethnic origin or racial group, thus does not match with estimates of 53,983.

Table 5.4 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Racial Group[a]

Race	mRNA-1273									mRNA-1283			mRNA-CRID	mRNA-1073	mRNA-1083	mRNA-1230	mRNA-1345	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	P301[c]	001	P101	P101[c]	P101[c]	P302	
White	627	3,308	8,713	4,369	37	24,034	160	3,348	661	19	47	6,026	51	122	950	329	1,300	**50,237[b]**
Black or African American	16	292	760	391	14	3,096	39	12	150	1	6	1,094	7	19	210	50	337	**6,168 [b]**
Asian	8	228	843	208	1	1,395	13	92	32	1	3	268	2	5	34	7	14	**2,954[b]**
American Indian or Alaska Native	4	21	43	22	0	234	2	0	5	0	0	35	0	1	4	1	12	**364[b]**
Native Hawaiian or Other Pacific Islander	1	3	13	9	0	68	0	0	2	0	0	13	0	0	3	1	4	**108[b]**
Multiple	2	180	1236	75	2	638	3	56	73	1	1	99	0	2	6	0	4	**2,259[b]**
Other	2	259	207	59	0	593	9	17	2	0	0	39	0	0	8	2	4	**1,147[b]**
Not Reported	0	22	76	21	0	171	6	20	4	5	0	45	0	0	2	2	15	**369[b]**
Unknown	0	8	24	9	0	117	2	3	1	0	0	6	0	1	1	0	0	**162[b]**
Missing	0	0	0	0	0	0	0	1	0	0	0	146	0	0	0	0	0	**146**
Total	**660**	**4,321**	**11,915**	**5,163**	**54**	**30,346**	**234**	**3,548**	**930**	**27**	**57**	**7,771**	**60**	**150**	**1,218**	**392**	**1,690**	**63,914[b] [d]**

[a]=Data from ongoing and completed trials till 17 Jun 2023.

[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.
[c]= Study is currently blinded. This is the overall count including Placebo/comparators or other investigational products.
[d]=The total 63,914 includes subjects from three blinded studies which could not be further estimated based on age, gender, ethnic origin or racial group, thus does not match with estimates of 53,983.

Table 5.5 Cumulative Subject Exposure to Investigational Drug from Ongoing and Completed Clinical Trials by Ethnicity[a]

Ethnicity	mRNA-1273									mRNA-1283			mRNA-CRID	mRNA-1073	mRNA-1083	mRNA-1230	mRNA-1345	Total
	P201	P203	P204	P205	P206	P301	P304	P305	P306	P101	P201	P301[c]	001	P101	P101[c]	P101[c]	P302	
Hispanic or Latino	49	850	1,888	669	13	6,229	22	0	120	9	11	1,207	15	17	130	39	651	**11,265[b]**
Not Hispanic or Latino	610	3,435	9,918	4,459	41	23,839	210	0	806	17	45	6,319	45	127	1,077	347	1,028	**48,382[b]**
Not Reported	1	32	81	30	0	188	2	0	2	1	1	81	0	4	7	6	11	**425[b]**
Unknown	0	4	28	5	0	90	0	0	2	0	0	18	0	2	4	0	0	**148[b]**
Missing	0	0	0	0	0	0	0	3,548	0	0	0	146	0	0	0	0	0	**3,694**
Total	**660**	**4,321**	**11,915**	**5,163**	**54**	**30,346**	**234**	**3,548**	**930**	**27**	**57**	**7,771**	**60**	**150**	**1,218**	**392**	**1,690**	**63,914[bd]**

[a]=Data from ongoing and completed trials till 17 Jun 2023.
[b]=The patient enrolled in both P301 and P201(part C)/P205, or in both P204 and P306 is only counted once in total number.
[c]=Study is currently blinded. This is the overall count including Placebo/comparators or other investigational products.
[d]=The total 63,914 includes subjects from three blinded studies which could not be further estimated based on age, gender, ethnic origin or racial group, thus does not match with estimates of 53,983.

5.2. Cumulative and Interval Exposure from Marketing Experience

Cumulatively, at the end of the reporting period, a total of 1,664,690,323 doses of elasomeran (original and bivalents including elasomeran/imelasomeran and elasomeran/davesomeran) had been distributed to 91 countries (a proportion of doses distributed have been subsequently donated via either bilateral agreements or collaborative efforts such as COVAX). North America, Europe, and Asia accounted for approximately 91% of elasomeran (original and bivalents including elasomeran/imelasomeran and elasomeran/davesomeran) doses distributed (Table 5.6). Cumulatively, 217,505,466 (13.1%) doses had been distributed in lower- and middle-income countries.

In this reporting period, between 18 Dec 2022 to 17 Jun 2023, a total of 110,940,854 doses of elasomeran (original and bivalents including elasomeran/imelasomeran and elasomeran/davesomeran) had been distributed and an estimated total of 65,177,752 doses had been administered. North America, Europe, and Latin America accounted for approximately 88% of elasomeran doses distributed (Table 5.6). During this reporting period, 9,016,390 (8%) elasomeran doses had been distributed in lower- and middle-income countries.

A total of 1,318,183,956 elasomeran doses had been distributed to 91 countries and estimated total of 774,433,074 doses had been administered cumulatively. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed. In the reporting period, a total of 2,594,240 elasomeran doses were distributed and estimated 1,524,116 elasomeran doses were administered.

A total of 128,997,293 booster doses of elasomeran/imelasomeran had been distributed to 42 countries and an estimated total of 70,948,511 doses had been administered. Latin America, North America, and Asia accounted for approximately 95% of doses distributed and approximately 89% of doses administered (Table 5.8). A total of 217,509,074 booster doses of elasomeran/davesomeran had been distributed to 41 countries and an estimated total of 119,629,991 doses had been administered. The United States, Canada, Europe, and Asia accounted for >95% of all doses distributed and administered (Table 5.9).

Table 5.6 Total doses distributed and administered for elasomeran and elasomeran/imelasomeran and elasomeran/davesomeran

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	**1,664,690,323**	**100.0**	**978,005,565**	**100.0**	**110,940,854**	**100.0**	**65,177,752**	**100.0**
North America	**633,723,694**	**38.1**	**348,548,032**	**36.0**	**1,935,954**	**1.7**	**1,064,775**	**1.6**
US	573,221,554	34.4	315,271,855	32.6	1,433,804	1.3	788,592	1.2
All Europe	**490,094,123**	**29.4**	**269,551,768**	**27.4**	**39,301,350**	**35.4**	**21,615,743**	**33.2**
European Economic Area	419,450,593	25.2	230,697,826	23.4	33,001,750	29.7	18,150,962	27.8
Asia	**383,818,236**	**23.1**	**211,100,030**	**21.4**	**57,766,520**	**52.1**	**31,771,586**	**48.7**
Latin America	**70,470,000**	**4.2**	**38,758,500**	**3.9**	**8,984,750**	**8.1**	**4,941,612**	**7.6**
Africa	**32,469,280**	**2.0**	**17,858,104**	**1.8**	**7,680**	**0.0**	**4,224**	**0.0**
Oceania	**27,731,200**	**1.7**	**15,252,160**	**1.5**	**1,554,600**	**1.4**	**855,030**	**1.3**
Middle East	**26,383,790**	**1.6**	**14,511,085**	**1.5**	**1,390,000**	**1.3**	**764,500**	**1.2**
International donations	**-**	**-**	**62,425,887**	**6.4**	**-**	**-**	**4,160,282**	**6.4**

Table 5.7 Doses distributed and administered for elasomeran

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	**1,318,183,956**	**100.0**	**774,433,074**	**100.0**	**2,594,240**	**100.0**	**1,524,116**	**100.0**
North America	**553,855,010**	**42.0**	**304,620,256**	**39.3**	**503,800**	**19.4**	**277,090**	**18.2**
US	505,353,070	38.3	277,944,189	35.9	3,000	0.1	1,650	0.1
All Europe	**341,040,600**	**25.9**	**187,572,330**	**24.2**	**115,200**	**4.4**	**63,360**	**4.2**
European Economic Area	301,453,700	22.9	165,799,535	21.4	115,200	4.4	63,360	4.2
Asia	**282,393,826**	**21.4**	**155,316,604**	**20.1**	**265,260**	**10.2**	**145,893**	**9.6**
Latin	**62,187,600**	**4.7**	**34,203,180**	**4.4**	**1,702,300**	**65.6**	**936,265**	**61.4**

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
America								
Africa	**32,369,680**	**2.5**	**17,803,324**	**2.3**	**7,680**	**0.3**	**4,224**	**0.3**
Oceania	**23,676,600**	**1.8**	**13,022,130**	**1.7**	**0**	**0.0**	**0**	**0.0**
Middle East	**22,660,640**	**1.7**	**12,463,352**	**1.6**	**0**	**0.0**	**0**	**0.0**
International donations	**-**	**-**	**49,431,898**	**6.4**	**-**	**-**	**97,284**	**6.4**

Table 5.8 Doses distributed and administered for elasomeran/imelasomeran

Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	**128,997,293**	**100.0**	**70,948,511**	**100.0**	**1,583,320**	**100.0**	**870,826**	**100.0**
North America	**10,521,450**	**8.2**	**5,786,798**	**8.2**	**0**	**0.0**	**0**	**0.0**
US*	21,600	0.0	11,880	0.0	0	0.0	0	0.0
All Europe	**83,496,993**	**64.7**	**45,923,346**	**64.7**	**871,520**	**55.0**	**479,336**	**55.0**
European Economic Area	58,739,963	45.5	32,306,980	45.5	871,520	55.0	479,336	55.0
Asia	**29,554,550**	**22.9**	**16,255,003**	**22.9**	**220,200**	**13.9**	**121,110**	**13.9**
Latin America	**1,100,150**	**0.9**	**605,083**	**0.9**	**100,200**	**6.3**	**55,110**	**6.3**
Africa	**99,600**	**0.1**	**54,780**	**0.1**	**0**	**0.0**	**0**	**0.0**
Oceania	**2,891,400**	**2.2**	**1,590,270**	**2.2**	**391,400**	**24.7**	**215,270**	**24.7**
Middle East	**1,333,150**	**1.0**	**733,233**	**1.0**	**0**	**0.0**	**0**	**0.0**

*The 21,600 doses of elasomeran/imelasomeran distributed by ModernaTx to the US were ultimately provided to UNICEF after the initial delivery.

North America: Canada and US

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

Asia: Bangladesh, Bhutan, Cambodia, 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

Table 5.9 Doses distributed and administered for elasomeran/davesomeran

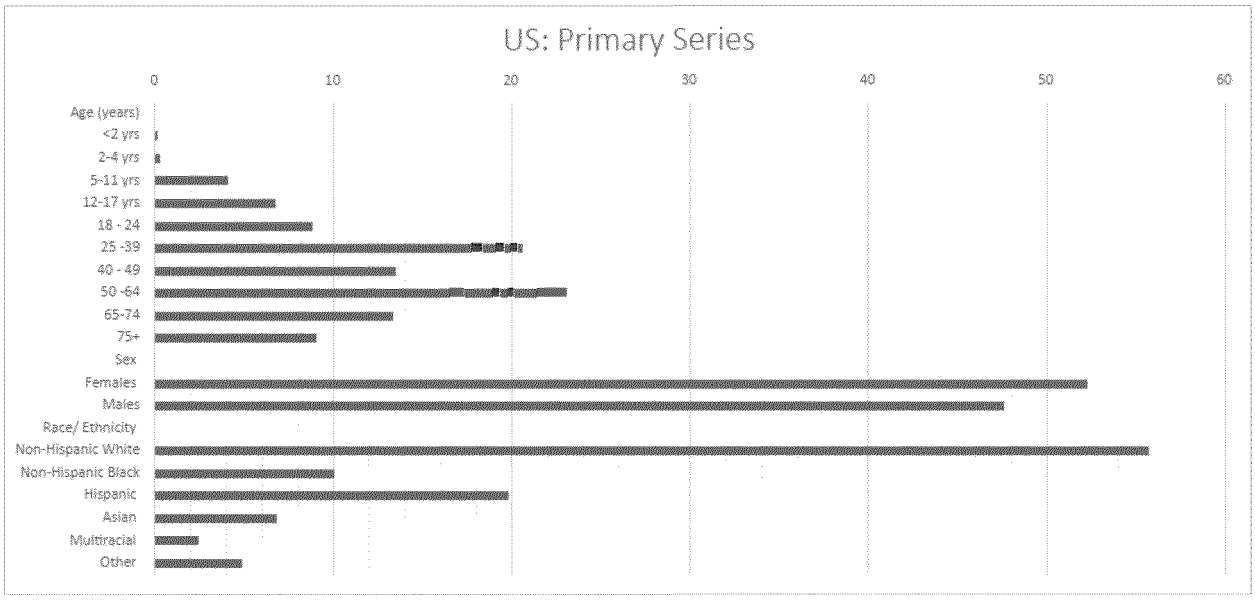
Region	Cumulative				Interval			
	Distributed	%	Administered	%	Distributed	%	Administered	%
Total	**217,509,074**	**100.0**	**119,629,991**	**100.0**	**106,763,294**	**100.0**	**58,719,812**	**100.0**
North America	**69,347,234**	**31.9**	**38,140,979**	**31.9**	**1,432,154**	**1.3**	**787,685**	**1.3**
US	67,846,884	31.2	37,315,786	31.2	1,430,804	1.3	786,942	1.3
All Europe	**65,556,530**	**30.1**	**36,056,092**	**30.1**	**38,314,630**	**35.9**	**21,073,047**	**35.9**
European Economic Area	59,256,930	27.2	32,591,312	27.2	32,015,030	30.0	17,608,267	30.0
Asia	**71,869,860**	**33.0**	**39,528,423**	**33.0**	**57,281,060**	**53.7**	**31,504,583**	**53.7**
Latin America	**7,182,250**	**3.3**	**3,950,238**	**3.3**	**7,182,250**	**6.7**	**3,950,238**	**6.7**
Africa	**0**	**.**	**0**	**.**	**0**	**0.0**	**0**	**0.0**
Oceania	**1,163,200**	**0.5**	**639,760**	**0.5**	**1,163,200**	**1.1**	**639,760**	**1.1**
Middle East	**2,390,000**	**1.1**	**1,314,500**	**1.1**	**1,390,000**	**1.3**	**764,500**	**1.3**

North America: Canada and US
Europe: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Ukraine, Switzerland, United Kingdom
Asia: Bangladesh, Bhutan, Cambodia, Indonesia, Japan, Kyrgyzstan, Nepal, Pakistan, Philippines, Singapore, Taiwan, Tajikistan, Thailand, Turkmenistan, Uzbekistan, Vietnam, South Korea
Middle East: Israel, Kuwait, Qatar, Saudi Arabia, United Arab Emirates, Palestine
Latin America: Argentina, Bolivia, Chile, Colombia, Dominica, Grenada, Haiti, Mexico, Paraguay, Peru, St. Lucia, St. Vincent, and the Grenadines
Oceania: Australia, Fiji, Vanuatu
Africa: Angola, Benin, Botswana, Brunei Darussalam, Burkina Faso, Central African Republic, Democratic Republic of Congo, Egypt, Guinea, Kenya, Nigeria, Rwanda, Sao Tome and Principe, Tanzania, Tunisia, Uganda, Zambia.

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

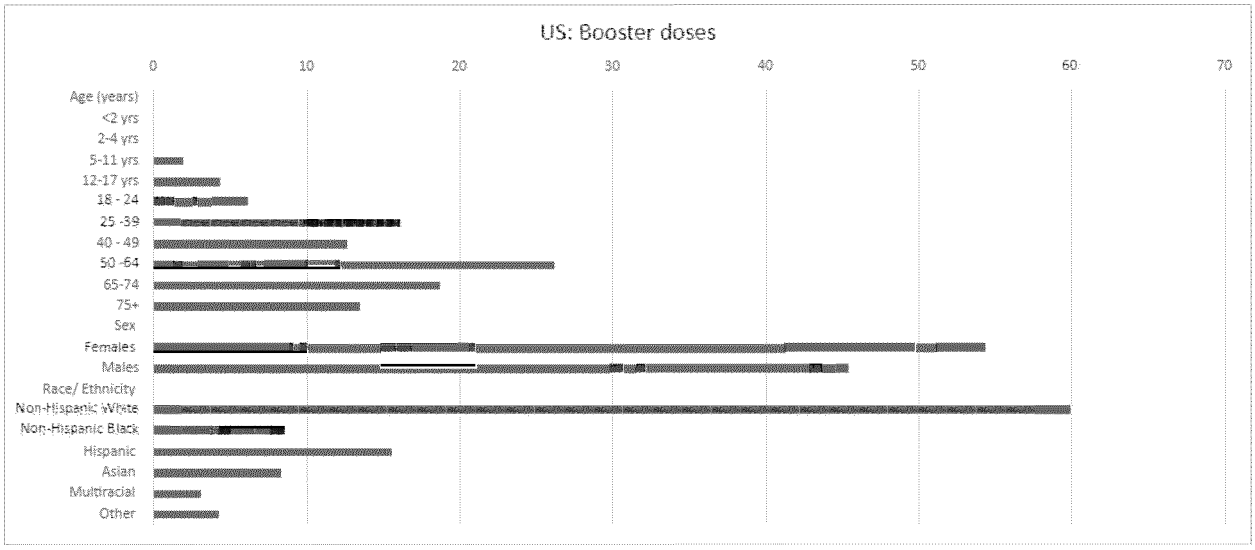
Demographic characteristics of US recipients of all COVID-19 vaccine products for primary series are shown in Figure 5-1, data for booster doses are shown in Figure 5-2 and data for elasomeran/imelasomeran and elasomeran/davesomeran are shown in Figure 5-3. Because product specific demographic data (age,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

Figure 5-1 Characteristics of US Recipients of All COVID-19 Vaccine Products for Primary Series by Age, Sex, and Race/Ethnicity



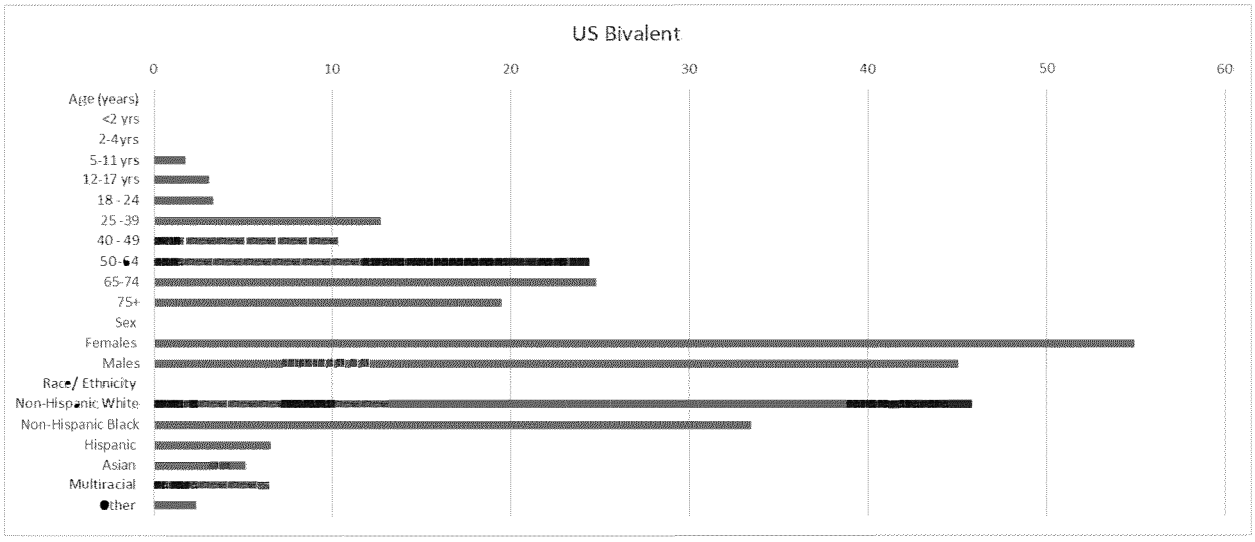
Data as of 10 May 2023 from CDC COVID-19 Data tracker [6].

Figure 5-2 Characteristics of US Recipients of All COVID-19 Vaccine Products, Booster Doses, by Age, Sex, and Race/Ethnicity



Data as of 10 May 2023 from CDC COVID-19 Data tracker [6].

Figure 5-3 Characteristics of US Recipients of All COVID-19 Vaccine Products, elasomeran/davesomeran, by Age, Sex, and Race/Ethnicity

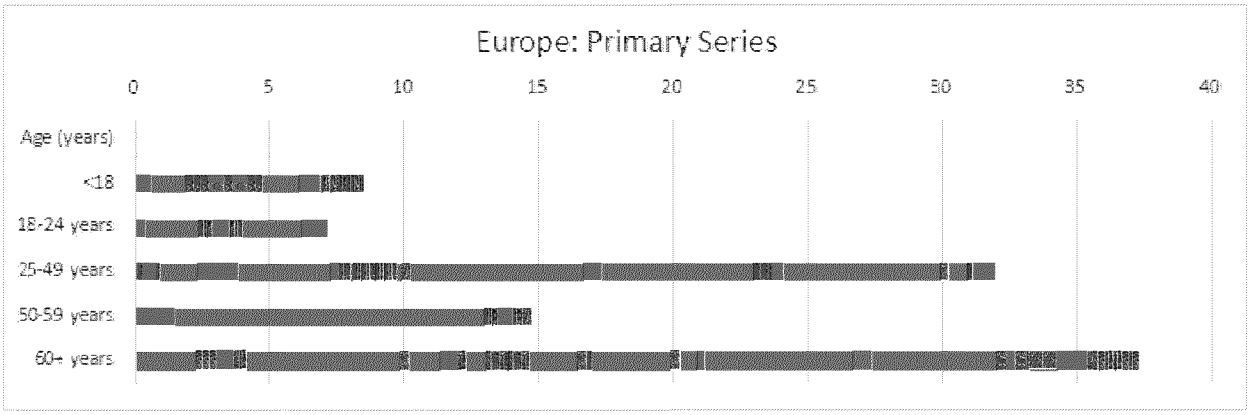


Data as of 10 May 2023 from CDC COVID-19 Data tracker [6].

Available demographic characteristics of vaccine recipients (primary series boosters and elasomeran/imelasomeran and elasomeran/davesomeran) are shown for the European Economic Area (EEA) (Figure 5-4, Figure 5-5, Figure 5-6 and Figure 5-7) and Canada (Figure 5-8 and Figure 5-9). In the EEA, the highest proportion of vaccinated individuals were among 25-49 years of age for primary series and 60 years and older for booster doses. In Canada, the highest

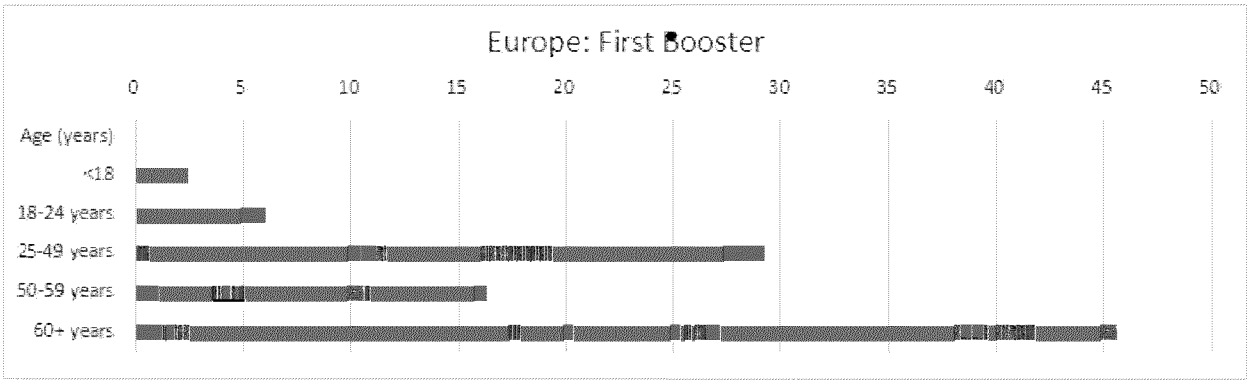
proportion of vaccinated individuals were among 18-29 years for primary series and 60-69 years for booster doses. Information on distribution by gender was not published by European Center for Disease Prevention and Control (ECDC) at the time that the data were accessed (https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab Accessed on June 18th, 2023).

Figure 5-4 EEA Recipients of All COVID-19 Vaccine Products for Primary Series by Age



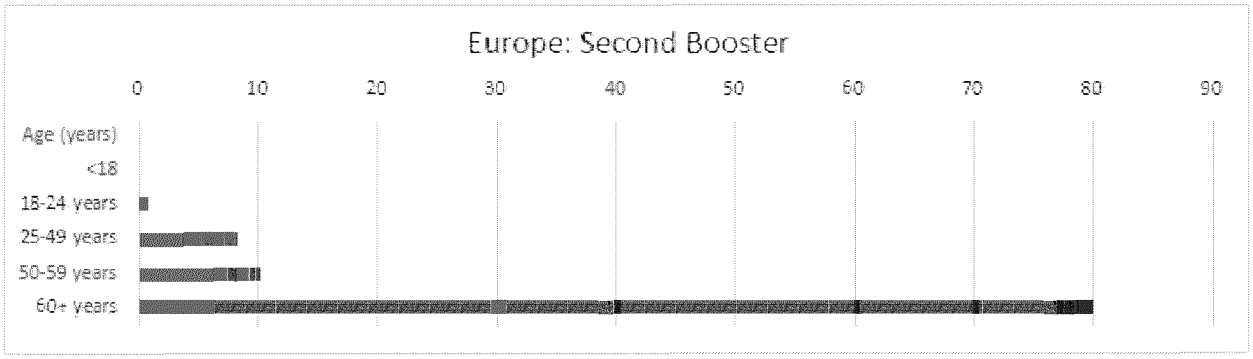
Data as of 16 Jun 2023 from ECDC [7].

Figure 5-5 EEA Recipients of All COVID-19 Vaccine Products for First Booster by Age



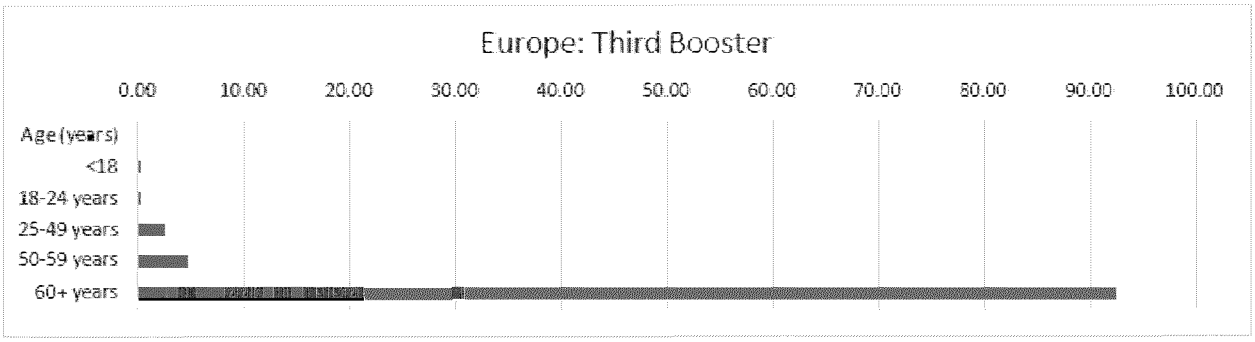
Data as of 16 Jun 2023 from ECDC [7].

Figure 5-6 EEA Recipients of All COVID-19 Vaccine Products for Second Booster by Age



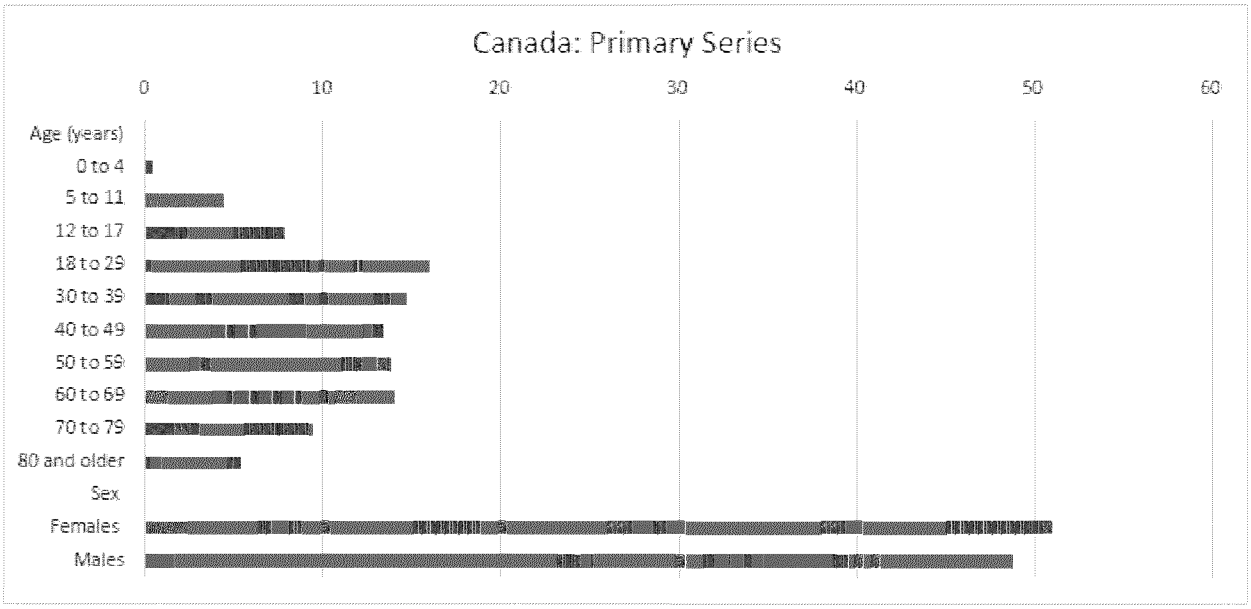
Data as of 16 Jun 2023 from ECDC [7].

Figure 5-7 EEA Recipients of All COVID-19 Vaccine Products for Third Booster by Age



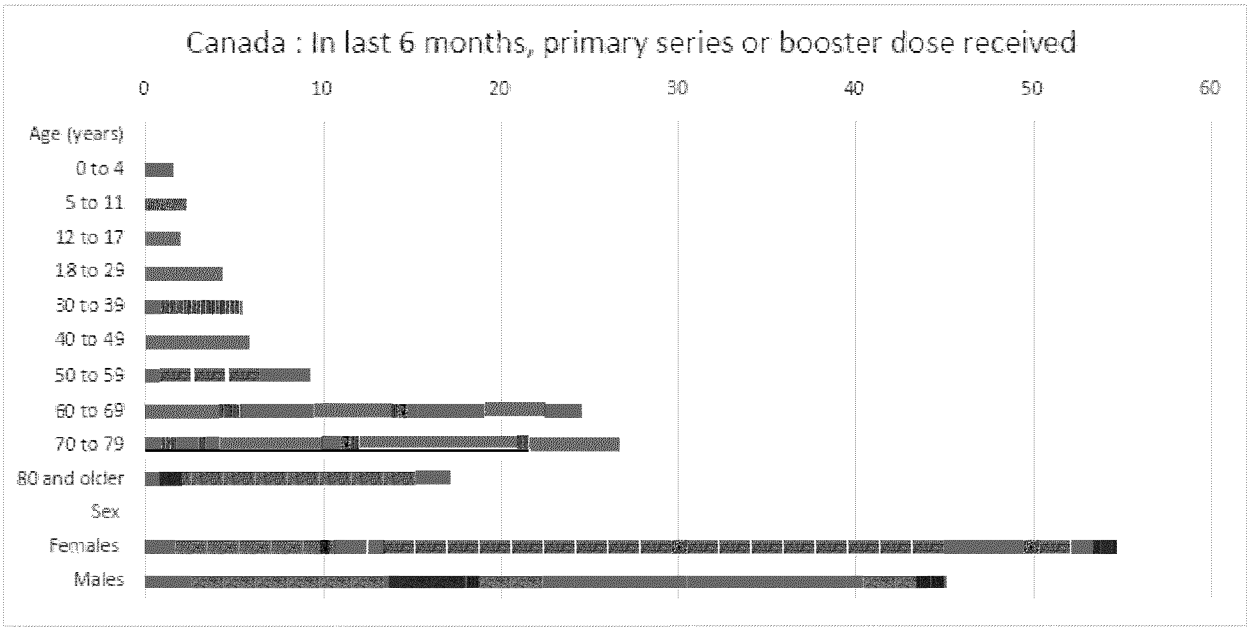
Data as of 16 Jun 2023 from ECDC [7].

Figure 5-8 Canadian Recipients of All COVID-19 Vaccine Products for Primary Series by Age and Sex



Data as of 18 Jun 2023 from Government of Canada: COVID-19 vaccination website [8].

Figure 5-9 Canadian Recipients of All COVID-19 Vaccine Products for Primary Series and booster doses by Age and Sex



Data as of 18 Jun 2023 from Government of Canada: COVID-19 vaccination website [8].

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

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

- Placeholder space for name of vaccine;
- Vaccine brand name and manufacturer name;
- Placeholder space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the

vaccine;

- QR code that links to a website with additional information on product use; and
- Adverse event reporting information.

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

5.2.2 Post authorization use in Special Populations

5.2.2.1 Use in Elderly

Evaluation of information received during the PBRER reporting period relating to use of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeranin the elderly populationhas not identified any additional clinically relevant new safety information for this subpopulation. The number of cases received during this reporting period and the associated Marketing Authorization Holder (MAH) comment are presented by product in Table 5.10. Refer to Appendix 12.3 for more information.

Table 5.10 Case Reports and MAH Comment by Product

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	3,430	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/ Imelasomeran	>65 years of age	2,324	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.
Elasomeran/ Davesomeran	>65 years of age	772	The MAH will continue to monitor events for Elderly using routine surveillance. The benefit-risk evaluation remains positive.

5.2.2.2 Use in Children

Evaluation of information received during the PBRER reporting interval relating to use of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in children, has not

identified any additional clinically relevant new safety information for this subpopulation. The number of cases received during this reporting period and associated MAH comment are presented by age group in Table 5.11. Refer to Appendix 12.4 for additional information.

During the reporting period, the MAH received 745 cases (121 serious, 685 medically confirmed, 6 fatal) with 1,749 events (275 serious) for children <18 years of age who received elasomeran as primary series, or booster with elasomeran/imelasomeran or elasomeran/davesomeran. When gender was known, no significant difference was noted in cases involving males (318, 42.7%) and females (350, 47.0%), with small proportion of cases (77, 10.3%) having no gender reported. The mean patient age was 6.9 years (standard deviation: 5.9) and median age of 4.0 (range: 0.0 to 17.0 years). The majority of these reports were spontaneous (429, 57.6%), with highest number of cases reported in United States (410, 55.0%) followed by Latin America (112, 15.0%) and Asia (97, 13.0%).

During the reporting period, when dose number and time to onset could be determined, events were most often reported after Dose 2 (250, 14.3%) followed by Dose 1 (214, 12.2%) and Dose 3 (171, 9.8%), typically within 7 days of vaccination.

As requested by a health authority, the MAH reviewed cases of Arrhythmia for children <18 years of age. The search retrieved one (1) case of Arrhythmia. For case details and MAH comments refer to Section 15.2.1.

The most frequently reported events in children were non-serious and often involved product use issues (Expired product administered (193, 11.0%), Wrong product administered (114, 6.5%) and Product storage error (80, 4.6%)) with no associated adverse events (AEs) reported. It should be noted that there were 393 (22.5%) events of Preferred term (PT) No adverse event.

Table 5.11 Case Reports and MAH comment by Age group

Exposed Populationby 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:17 Cases (seven serious, two fatal). Elasomeran/imelasomeran: 1 non-serious case Elasomeran/davesomeran: 4 non-serious cases	Two fatal cases described congenital birth defects in confounded cases with no plausible association to elasomeran. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children (6	Elasomeran: 243 Cases (15 serious, 0 fatal)	The three fatal cases had insufficient

Exposed Population by Age groups	Number of Case Reports Received	MAH Comment on Benefit and/or Risk (any observed differences from overall population)
months to 5 years)	Elasomeran/imelasomeran: Four cases (three serious, one fatal). Elasomeran/davesomeran: 139 cases (2 serious, 2 fatal)	evidence of a causal association with vaccination. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Children 6-11 years	Elasomeran: 59 cases (three serious, 0 fatal) Elasomeran/imelasomeran: No cases reported during this reporting period. Elasomeran/davesomeran: 54 cases (24 serious, 0 fatal)	The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.
Adolescents (12 to 17 years)	Elasomeran: 139 Cases (35 serious, one fatal) Elasomeran/imelasomeran: 13 non-serious cases. Elasomeran/davesomeran: 72 cases (32 serious, 0 fatal)	There was one fatal report of myocarditis, which is an important identified risk for elasomeran. The MAH will continue to monitor events for children using routine surveillance. The Benefit-risk evaluation remains positive.

Table 5.12 Source of new information

Source of New Information	• Moderna Global Safety Database (GSDB) • Literature Sources- See Appendix 13.4 • New and Significant Safety Information: None (0)

Overall, the events reflected reactogenicity or those known to occur following vaccination with elasomeran, elasomeran/imelasomeran, and/or elasomeran/davesomeran. Other reported events did not show any new or unusual patterns.

No new safety concerns were identified in these reports.

5.2.3 Other clinical topics

5.2.3.1 Overdose

Table 5.13 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 all the VAERs reports received from 2007-2018, more than three-fourths of the reports of an excess dose of vaccine did not describe an AE. Among reports where an AE was reported, most of the common events included expected conditions such as pyrexia, injection site erythema, pain, and headache. Although most of the reports were of other vaccines (e.g., trivalent inactivated influenza, varicella, hepatitis A, and measles, mumps, rubella, varicella), the percentage of the AEs among these vaccine reports were comparable to all reports submitted to VAERS during the same period [9].
Methods	The MAH queried the GSDB for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. The search criteria applied for identification of Overdose cases included the following terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.
Results	***Overdose Cases Involving use of Elasomeran*** During the review period, the MAH received 11 cases (11 events) of Overdose with 4 serious cases (1 serious event), and 1 case with a fatal outcome. All 11 cases were medically confirmed. The fatal outcome was due to the multiple underlying conditions including an aggravated small cell lung cancer. Additionally, the single serious overdose event in the fatal case was unrelated to elasomeran but associated with irbesartan. The reported events were "Accidental overdose" (6; 54.5%) and "Overdose" (5; 45.5%). There were 5 medically confirmed cases (5 events) involving booster dose with elasomeran, and there were no fatal cases. The reported events were "Accidental overdose" (4, 80%) and "Overdose" (1; 20%). ***Overdose Cases Involving use of Elasomeran/Imelasomeran*** During this review period, the MAH received 2 cases (2 events) of Overdose with no serious cases, and no fatal outcomes in patients who received elasomeran/imelasomeran. Both cases were medically confirmed. The reported events were "Overdose" (2; 100%). ***Overdose Cases Involving use of Elasomeran/Davesomeran*** During the review period, the MAH received 10 cases (10 events) of Overdose with no serious cases and no cases with a fatal outcome. There were 10 medically confirmed cases involving elasomeran/davesomeran. The reported events were "Overdose" (6; 60%) and "Accidental Overdose" (4; 40%).
Discussion	A review of the data received during the reporting period of this PBRER, showed that overall numbers of overdose were relatively small, ranging from 2 to 11 cases for the elasomeran original and bivalents (elasomeran/imelasomeran and elasomeran/davesomeran). All events of overdose were non-serious. One serious case for the elasomeran original reported a serious overdose event for irbesartan but not for the vaccine. Furthermore, in one serious case there was no causal relation between the elasomeran original and fatal outcome, which was due to multiple underlying conditions

	including an aggravated small cell lung cancer. 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 on 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, and elasomeran/davesomeran did not raise any safety issue of concern. The MAH will continue to monitor events of overdose using routine surveillance. The benefit-risk evaluation remains positive.

Refer to Appendix 12.5 for more detailed information.

5.2.3.2 Off-Label use

Table 5.14 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 authorization. Examples include the intentional use of a product in situations other than the ones described in the authorized product information, such as a different indication in terms of medical condition, a different group of patients (e.g., a different age group), a different route or method of administration or a different posology. The reference terms for off--label use are the terms of marketing authorization in the country where the product is used." (EMA Good Pharmacovigilance Practices Annex 1 – Definitions [Rev 4]) [10].
Methods	The search criteria applied for identification of Off-label use cases included the following terms: Off-label use, Off-label use of device, Intentional dose omission, Intentional product misuse, Intentional product misuse to child, and Intentional product use issue. If warranted, the Company causality assessment is provided utilizing the World Health Organization-Uppsala Monitoring Center (WHO-UMC) standardized case causality assessment for serious cases classified as meeting the definition of Off-label use.
Results	***Off-label Use Cases Involving use of Elasomeran*** During the review period, the MAH received 43 cases (45 events) of Off-label use with 35 serious cases (30 serious events), and 1 case with a fatal outcome. Of note, the patient with a fatal outcome had aggravated lung cancer, also reported the event of intentional product misuse (misuse of irbesartan, aminophylline, carbocisteine, methotrexate and others), and had no description of off-label use for elasomeran. There were 22 medically confirmed cases involving elasomeran. Most cases involved females (28 cases, 65.1%), males (14 cases, 32.6%); gender information missing in 1 case (2.3%). The mean age

	was 54.1 years (Standard deviation: 14.1) and median age was 52.5 years (range: 24.0 to 82.0 years). The country with the most frequent cases of Off-label use was Canada (21; 48.8%) followed by Germany (11; 25.6%). The events reported were "Off-label use" (42; 93.3%) and "Intentional product misuse" (3; 6.7%). ***Off-label Cases Involving use of Elasomeran/Imelasomeran*** During this review period, the MAH received 1 non-serious case (1 event) of Off-label use. The case involved a 63-year-old female. The case was received from Canada (1; 100%) and the event reported was "Off-label use" in elasomeran/imelasomeran. ***Off-label Cases Involving use of Elasomeran/Davesomeran*** During the review period, the MAH received 3 cases (3 events) of Off-label use with 1 serious case (1 serious event) and no case with a fatal outcome. There were 2 medically confirmed cases involving elasomeran/davesomeran. There were 2 cases reported in females (66.7%), and 1 case reported in males (33.3%). The mean age was 28.7 years (SD: 35.8) and median age was 28.7 years (range: 3.3 to 54.0 years). The country with the most cases of Off-label use was the United States (2; 66.7%) followed by Canada (1; 33.3%). The events reported were "Off-label use" (3; 100%).
Discussion	During the reporting period, the total number of off-label use cases decreased compared with last review period (60 vs 47 cases) as well as the number of medically confirmed cases (37 vs 25 cases). Same as the last review period, "off-label use" was the most frequently reported PT. Only isolated non-serious cases of off-label use were received from both elasomeran/imelasomeran and elasomeran/davesomeran boosters during the review period. One fatal case was reported by a consumer for elasomeran administration during this review period. Of note, the fatal outcome was most likely due to underlying aggravated lung cancer based on the information provided. Furthermore, the patient also reported the events of intentional product misuse and drug abuse of multiple other medications, but there was no description of off-label use for elasomeran. Off-label use observed during the review period did not change the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran exposure. The MAH will continue to monitor events for off-label use using routine surveillance. The benefit-risk evaluation remains positive.

Refer to Appendix 12.6 for more detailed information.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 was used for the coding of AEs/adverse drug reactions (ADRs) presented in this report. The line listings and summary tabulations are first arranged alphabetically by primary MedDRA System Organ Class (SOC) and then by the PT.

6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative (18 Dec 2020 to 17 Jun 2023) summary tabulation of Serious Adverse Events (SAEs) from Company-sponsored CTs is provided in Appendix 3. Inclusion requirement parameters for the incorporation of data from Company sponsored-CTs are that the SAE occurred during active treatment, the SAE originated from a clinical study with mRNA-1273, mRNA-1273.214, mRNA-1273.222, mRNA-1273.815 and mRNA-1273.231, the event was assessed as serious, and the active treatment was mRNA-1273 or placebo.

6.3. Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

A cumulative (18 Dec 2020 to 17 Jun 2023) and interval (18 Dec 2022 to 17 Jun 2023) summary tabulation of ADRs (serious and non-serious) is provided in Appendix 4. The ADRs presented in this tabulation were derived from spontaneous sources (healthcare professionals [HCPs], consumers, scientific literature, and regulatory authorities [RAs]) as well as serious ADRs from non-interventional studies and non-interventional solicited sources.

7. SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS IN THE REPORTING INTERVAL

7.1. Completed Clinical Trials

There were no ModernaTx, Inc. sponsored CTs which were completed during the reporting period.

7.2. Ongoing Clinical Trials

There was a total of 12 ModernaTx, Inc. sponsored CTs ongoing (mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P305, mRNA-1283-P101, mRNA-1283-P201, mRNA-1273-P206,

mRNA-1273-P306, mRNA-1283-P301, and mRNA-CRID-001), during the current reporting period. Of these 12 ongoing CTs, four trials (mRNA-1283-P101, mRNA-1283-P201, mRNA1283-P301 and mRNA-CRID-001) included mRNA-1273 treatment arms. Cumulative exposure by study- has been presented in Table 7.1.

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

Table 7.1 Summary of Cumulative Subject Exposure by Study[a]

Study ID	Total subjects exposed
mRNA-1273-P203	4,321
mRNA-1273-P204	11,915
mRNA-1273-P205	5,163
mRNA-1273-P206	54
mRNA-1273-P301	30,346
mRNA-1273-P304	234
mRNA-1273-P305	3,548
mRNA-1273-P306	930
mRNA-1283-P101[b]	27
mRNA-1283-P201[b]	57
mRNA-1283-P301	7,771
mRNA-CRID-001[b]	60

[a]=The total count of 53,983 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) and hence the total of all studies varies from the total unique subjects exposed.
[b]=The counts from these studies do not include Investigational Product other than mRNA-1273, Comparator or Placebo.

Refer to Appendix 6 for further details of all the ongoing and completed studies during the reporting period.

7.3. Long-term Follow-up

The Phase 3 study mRNA-1273-P301 includes a total of 24 months follow-up; no long-term safety concerns have been identified for the two-dose mRNA-1273 100 mcg primary series based on an interim analysis that includes 16,818.4 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). Participants completing CTs mRNA-1273-P101 (Division of Microbiology and Infectious Diseases [DMID] 20-0003), mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, and mRNA-1273-P306 are followed up for safety for 12 months.

In the adolescent Phase 3 Study mRNA-1273-P203, participants from the age of 12 through 17 years had a median follow-up of 342 days after Dose 1 and 312 days after Dose 2. In the pediatric Phase 3 Study mRNA-1273-P204, participants 6 months through 11 years had a median follow-up ranging between 254 and 267 days across age groups.

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

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

7.4. Other Therapeutic Use of Medicinal Product

Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran have not been investigated for any other therapeutic use during the reporting period.

7.5. New Safety Data Related to Fixed Combination Therapies

For elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, there were three combination therapies in which elasomeran, elasomeran/imelasomeran and/or elasomeran/davesomeran are part of the fixed combinations: mRNA-1073, mRNA-1230 and mRNA-1083. There are separate Development Safety Update Reports (DSURs) for each of these fixed combination therapies. No new safety information has been identified from the fixed combination therapies that are in development.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

The following non-interventional study was completed during the reporting period:

mRNA-1273-P902

Title: Moderna mRNA-1273 Observational Pregnancy Outcome Study.

Status: Enrolment for this prospective pregnancy registry began in Oct 2021. Enrolment proceeded slowly and the study was replaced in the EU RMP by the ongoing study mRNA-1273-P905 and study mRNA-1273-P919 (planned), a US administrative claims-based study of pregnancy safety. No safety findings have yet been identified.

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

mRNA-1273-P901

Title: Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the US.

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

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

Prior analyses conducted from the P901 study assessing relative vaccine effectiveness of receipt of a single booster dose of the monovalent mRNA-1273 (following receipt of 2 doses of monovalent mRNA COVID vaccine) between 20 Oct 2021 and 31 Dec 2021 demonstrated rVE against hospitalization, SARS-CoV-2 infection and death to be 89.0% (95% Confidence Interval [CI]: 86.2%-91.2%), 61.3% (95% CI: 60.5% – 62.2%), and 96% (95% CI: 68.0%-99.5%),

respectively among 431,328 immunocompetent adults receiving a single booster dose of mRNA-1273 (and a similar number of matched comparators who received a 2 dose mRNA monovalent COVID vaccine only) [11]. In addition, an analysis conducted between 01 Jan 2022 and Jun 30, 2022 among 30,809 SARS-CoV-2 cases and 92,427 matched controls looking at Omicron variant specific relative vaccine effectiveness of a booster dose of mRNA-1273 against hospitalization for COVID-19 demonstrated the rVE against BA.1, BA.2, and BA.4/5 Omicron sub-variants to be 88.8% (95% CI: 83.3-92.5); 75.0% (95% CI: 47.6-88.1); and 87.5% (95% CI: 51.8%-96.8%) [12].

mRNA-1273-P903

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

Status: This retrospective observational cohort study used secondary, de-identified individual level medical and pharmacy claims data provided by HealthVerity. Components of active vaccine surveillance via a historically controlled comparator and signal refinement using a SCRI design were implemented, and a final study report was submitted 30 Jun 2023.

Statistical Analyses:

In the screening stage, incidence rates (IR) were calculated per 100,000 person-years following vaccination and were compared to IR calculated during two historical periods using incidence rate ratios (IRR). Where unadjusted IR >2.0 and ≥5 events, observed versus expected (O/E) ratios and 95% CIs comparing the number of events after vaccination to the expected number of events based on the historic rates were estimated. Where the lower bound of O/E ratio > 1, SCRI analyses were performed among vaccinated cases where ≥10 total cases were observed. All analyses were presented for any dose (referenced as dose-agnostic analysis) and for doses 1, 2 or 3 with stratification by age and sex. Analyses were presented separately for persons with immunocompromised conditions identified prior to the index date, for heterologous booster dose recipients, and for elasomeran bivalent recipients as feasible. Pregnancy outcomes were presented separately with age strata limited to plausible values for women of childbearing age.

Results: The pre-COVID and COVID era cohorts included 50,015,708 individuals meeting study entry criteria. Of these individuals, 38,686,912 were at least 18 years of age and 11,328,796 were under 18 years of age. Among the historical comparator populations, there were 939,115 and 928,955 immunocompromised adults and 34,686 and 36,698 immunocompromised children in the

pre-COVID and COVID eras, respectively. Among females of childbearing age (12-55 years) in the historical populations, after applying study inclusion criteria, there were 94,244 and 83,390 pregnant women in the pre-COVID and COVID eras, respectively. Within the pre-COVID comparator population, 5,276,278 adults and 1,803,180 individuals <18 years of age were vaccinated for influenza.

There were 6,824,063 adults and 9,046 children vaccinated with elasomeran who met study entry criteria through 31 Aug 2022 with 1-year of continuous medical and pharmacy enrolment prior to their elasomeran administration. Primary analyses among children (<18 years) were restricted to vaccinations occurring between 17 Jun 2022 and 31 Aug 2022 reflecting authorization of elasomeran in this age range in US children and adolescents. Among individuals receiving at least one dose of elasomeran, 70.1% of adults and 40.9% of children received a second dose. Among individuals who received a second dose, 38.4% of adults and 0.7% of children also received a third dose. There were 262,276 immunocompromised adults who were vaccinated with elasomeran, of which 68.6% received a second dose; 46.0% of immunocompromised adults with a second dose also received a third dose. Slightly more immunocompromised adults received a non-elasomeran COVID-19 vaccine during follow-up than the general population (4.8% vs. 4.3%). There were 23,713 pregnant women 12-55 years who received elasomeran and met study entry criteria to be included in the pregnancy-specific analyses, and 55.1% received a second dose of elasomeran. Of these, 4.2% also received a third dose.

Myocarditis: There were 276 cases of myocarditis included in dose-agnostic SCRI analyses considering a 7-day risk and 42-day control window; 56.1% occurred after the second dose of elasomeran. Dose-agnostic, dose 1, dose 2 and dose 3-specific SCRI analyses indicated an elevated rate of myocarditis within 7 days of vaccination, driven particularly by young adults (Dose 2 Event rate ratio [ERR] 8.47, 95% CI 4.55 – 15.77). The association was strongest for males 18-29 years of age following dose 2 (ERR 9.50, 95% CI 4.61–19.57), noting that increased risk was also present in other subgroups. Estimates after dose 3 showed numerical elevations that reached statistical significance in sensitivity but not primary analyses. In SCRI analyses among heterologous vaccine recipients and children, counts were too low to support meaningful inference.

The signal evaluation results for myocarditis were consistent with known safety profile of elasomeran vaccine.

Pericarditis: Among adults, there were 413 cases of pericarditis identified through 31 Aug 2022, most (55.7%) after the second dose of elasomeran. Dose-agnostic and dose 2-specific SCRI analyses indicate an elevated rate among males 18-29 years of age in the 7 days following

elasomeran vaccination, primarily driven by the second dose (ERR 3.40, 95% CI 1.51 – 7.66). SCRI analysis following a third or a heterologous dose was conducted, however counts were too low to support any meaningful inference. In children, no pericarditis events were observed following elasomeran administration.

The signal evaluation results for pericarditis were consistent with known safety profile of elasomeran vaccine.

Other Adverse Events of Special Interest (AESI): SCRI analyses were also indicated for the following AESI: acute kidney injury, acute respiratory distress syndrome, anaphylaxis, anosmia/ageusia, arrhythmia, Bell's palsy, chilblain-like lesions, cerebral venous sinus thrombosis, coagulation disorders, erythema multiforme, immune thrombocytopenia, meningoencephalitis, narcolepsy/cataplexy, non-hemorrhagic stroke, seizures/convulsions, single organ cutaneous vasculitis, thrombosis with thrombocytopenia, Guillain-Barré syndrome (GBS), myositis, and transverse myelitis. SCRI analyses could be conducted for these AESI are reported where the threshold of ≥10 cases was met.

Anosmia/ageusia: There were 2,709 anosmia/ageusia cases observed among adults in the 28-day risk and 42-day control windows following elasomeran administration through 31 Aug 2022. An increased event rate of questionable clinical significance was observed in the 28-day risk window following all doses among adults (ERR 1.10, 95% CI 1.02 – 1.19 in dose-agnostic analysis). In SCRI analyses following a heterologous dose, no increase in risk window event rates were observed. Similarly, sensitivity analyses not censoring on COVID-19 diagnosis and washing out for history of COVID-19 led to similar conclusions as the primary analysis. Results for another sensitivity analysis using a 14-day risk window led to more varied event rate ratios but were genuinely attenuated. Only 3 events were observed for estimating the rate of anosmia/ageusia following the Omicron-containing bivalent booster, limiting interpretation. There were 14 children included in the dose-agnostic SCRI. No elevated rates of anosmia/ageusia were observed in analyses performed.

Anaphylaxis: There were 719 cases of anaphylaxis within the risk and control periods following elasomeran administration observed among adults through 31 Aug 2022. Increased event rates in the 2-day risk window following elasomeran vaccination were observed in the dose-agnostic and dose-specific analyses for most age and sex strata, with a larger ERR for females (e.g., ERR 4.70, 95% CI 3.79-5.84 in dose-agnostic analyses). Analyses following dose 3 were less interpretable given low counts. Dose-agnostic SCRI analysis excluding cases with allergen immunotherapy and separately not censoring on COVID-19 diagnoses led to similar conclusions as the primary

analysis. Only 4 events were observed among adults when estimating the rate of anaphylaxis following the Omicron-containing bivalent booster, thus limiting interpretation. SCRI analyses of anaphylaxis among children were not conducted given the threshold of ≥10 events was not met.

The signal evaluation results for anaphylaxis were consistent with known safety profile of elasomeran original vaccine.

Myositis: There were 7,006 cases included in the dose-agnostic SCRI analysis, which did not show elevated rates overall (ERR 0.99, 95% CI 0.93-1.05) or in subgroups by age and gender. In dose specific analyses, elevated rates were observed isolated subgroups – males ages 18-29 after dose 1 (ERR 1.77, 95% CI 1.02-3.10) and males 30-39 after dose 2 (1.73, 95% CI 1.02-2.93). Low case counts did not allow for interpretable analyses of myositis following a heterologous dose or an Omicron-containing bivalent booster. In the adult immunocompromised population, there were 599 cases included in the dose-agnostic SCRI analysis (ERR 1.05, 95% CI 0.85-1.30). In this subgroup, elevated rates were observed in adults ≥75 years (ERR 2.37, 95% CI 1.11–5.06). In the dose 1- specific SCRI analyses, an increase in rates was observed among IC adults 18-29 years (ERR 3.82, 95% CI 1.25-11.67) and females 18-29 years (ERR 3.49, 95% CI 1.02-11.91). On the dose 2-specific SCRI analyses, an imprecise numerical elevation in rate was observed among IC males 40-49 years (ERR 3.00, 95% CI 0.90-9.96). No heterologous dose SCRI analysis was conducted given the threshold of ≥10 events were not met.

Given this extent of multiple testing and the absence of a consistent pattern in other subgroups, interpretation of this finding is unclear. For further details on signal evaluation, please refer to Section 16.2.4.

Single organ cutaneous vasculitis (SOCV): Among the 485 events among adults included in the dose-agnostic SCRI analysis, an elevated rate of SOCV was not observed (ERR 0.91, 95% CI 0.76-1.09). Within the dose 3-specific SCRI analysis, an elevated rate of SOCV was suggested in the 28-day risk window among males overall (ERR 2.37, 95% CI 1.12-5.02) and within males 50---64 years (ERR 3.22, 95% CI 1.12-9.23), however event counts were low and should be interpreted with caution. The dose 1- and 2-specific SCRI analyses yielded no observed elevated rates, nor in a dose-agnostic sensitivity analysis not censoring on COVID-19 diagnosis. Only 2 events were observed among adults for estimating the rate of SOCV following the Omicron -containing bivalent booster, thus limiting interpretation. SCRI analyses within adults with a heterologous dose and within children were not conducted due to insufficient event counts.

Acute kidney injury, Arrhythmia, cerebral venous sinus thrombosis, Chilblain-like lesions, erythema multiforme GBS, immune thrombocytopenia, narcolepsy, seizure, and transverse myelitis: No significantly elevated event rate ratios were observed.

Discussion

Results of this final report for study mRNA-1273-P903 are largely consistent with findings from the interim reports and its known safety profile, particularly for labeled events such as myocarditis and anaphylaxis. Additional monitoring of potentially artifactual increases isolated to specific subgroups for myositis and SOCV will be subject to continued monitoring in studies mRNA--1273--P904 and mRNA-1273-P920.

mRNA-1273-P904

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

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

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

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

10 signals for each country. Most signals were detected in Spain (Information System for Research in Primary Care).

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

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

Discussion

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

mRNA-1273-P905

Title: Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries.

Summary: For this observational cohort study carried using large administrative databases in Denmark, Norway, Italy, Spain, and the UK, with feasibility counts were described in the Mar 2023 interim study update. At this time, no safety findings have yet been identified given the early stage of the study.

mRNA-1273-P911

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

Summary: The overarching goal of this study is to characterize presentation, clinical course, and long-term outcomes of myocarditis temporally associated with administration of mRNA-1273 (elasomeran). The first interim feasibility report was completed 31 Oct 2022. Cases of myocarditis

identified in routine clinical practice meeting the CDC case definition, including those occurring following administration of elasomeran as well as cases not secondary to vaccines targeting SARS-CoV-2. At this time, no safety findings have yet been identified given the early stage of the study.

mRNA-1273-P915

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

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

A report for this database survey was submitted to Pharmaceuticals and Medical Devices Agency (PMDA) on 17 May 2023. Based on the analysis of 13,309 individuals, the occurrence of hypersensitivity in individuals at high risk for COVID-19 infection was consistent with the known safety profile of elasomeran.

mRNA-1273-P916

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

Status: The overarching goal of this PMS activity is to identify the incidence of specified AEs in the acute phase observed after vaccination in subjects with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. A report for this database survey was submitted to PMDA on 17 May 2023. Based on the analysis of 8,844 individuals, the occurrence of solicited AEs, particularly, reactogenicity had an occurrence of > 1% within 8-days of vaccination in individuals at high risk for COVID-19 infection.

mRNA-1273-P917

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

Status: The overarching goal of this PMS activity is to identify hypotheses for the safety evaluation of this product by confirming the occurrence status of non-acute hospitalization associated serious events observed after vaccination in persons with underlying diseases considered to be at high risk of aggravation of COVID-19 in Japan. The study is ongoing; however, no safety findings have been identified to date.

mRNA-1273-P918

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

Summary: The overarching goal of this PMS activity is to follow-up subjects who are vaccinated early after the marketing approval of this product in Japan for 11 months from the day after the day following the last day of the last vaccination with this drug as the primary immunization (the last day of the observation period in the health status investigation of preceding vaccinees) to 12 months after the last vaccination with this drug as the primary immunization, and to collect information on SAEs observed during the follow-up period and COVID-19. Enrolment for this survey ended in Dec 2022. There were 8,637 individuals in the safety and efficacy analysis set. At this time, no safety findings have yet been identified. The observation of the final subject was completed in Apr 2023, and final analyses are ongoing.

mRNA-1273-P922

Title: DisCOVEries II: An Observational Study to Evaluate the Immunogenicity of a COVID-19 Bivalent Booster as the Second Booster Dose Against Omicron BA.4/5.

Status: A six-month observational prospective study (with an optional long-term follow-up of up to 12 months), to investigate antibody levels with respect to time since receiving a bivalent COVID-19 booster dose. The protocol was approved on 06 Dec 2022. At this time, no safety findings have been identified.

mRNA-1273-P928

Title: Relative Effectiveness of mRNA-1273 in Adults with At-Risk Clinical Conditions.

Status: This is an Observational retrospective cohort study.

Part I: To determine the rVE of 2 doses of the mRNA-1273 vaccine vs. 2 doses of the BNT162b2 vaccine and 2 doses of the mRNA-1273 vaccine vs. 1 dose of the Ad26.COV2.S vaccine in individuals aged 18 years and older who have at least one underlying medical condition (endpoints: medically-attended COVID-19 illness/COVID-19 illness in outpatients/ COVID-19 illness requiring hospitalization).

Part II: To determine the rVE of a single homologous booster dose of the mRNA-1273 vaccine vs. a single homologous booster dose of the BNT162b2 vaccine in adults aged 18 years and older who have at least one underlying medical condition associated with higher risk for severe COVID-19

(endpoints: medically-attended COVID-19 illness/ COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization). Protocol was approved on 02 Mar 2023 and interim updates were done on 12 May 2023. At this time, no safety findings have been identified.

mRNA-1273-P930

Title: Relative effectiveness of the BNT162b2, mRNA-1273, and Ad26.COV2.S COVID-19 Vaccines in adults in the US.

Status: This is an Observational retrospective cohort study.

Part I: To determine the rVE of 2 doses of the mRNA-1273 vaccine vs. 2 doses of the BNT162b2 vaccine and 2 doses of the mRNA-1273 vaccine vs. 1 dose of the Ad26.COV2.S vaccine in individuals aged 18 years and older (endpoints: medically-attended COVID-19 illness/COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization).

Part II: To determine the rVE of a single homologous booster dose of the mRNA-1273 vaccine vs. a single homologous booster dose of the BNT162b2 vaccine in adults aged 18 years and older (endpoints: medically attended COVID-19 illness/ COVID-19 illness in outpatients/COVID-19 illness requiring hospitalization). Accepted for publication (Open Forum Infectious Diseases).

This retrospective observational study follows a cohort during two distinct periods that reflect vaccination guidelines. The first period began in Feb 2021, when COVID-19 vaccines become available, until booster doses were recommended in Oct 2021. The second period began in Oct 2021, when individuals started receiving their booster dose until the end of Jan 2022, when the omicron variant wave was rapidly progressing throughout the United States. P930 was approved by Patient Review and Coordination in Apr 2022. At this time, no safety findings have yet been identified given the early stage of the study.

mRNA-1273-P931

Title: Comparative Effectiveness of the Bivalent COVID-19 mRNA Vaccines (ORIGINAL AND OMICRON BA.4/BA.5) in Adults in the US.

Status: The goal of this study is to determine the rVE between the two mRNA Bivalent vaccines against COVID-19-related hospitalization/outpatient visits in adults 18 years or older. The protocol was approved on 11 May 2023 and first interim updates were done on 22 May 2023. At this time, no safety findings have been identified given the early stage of the study.

mRNA-1273-P932

Title: Real-world comparative effectiveness of a third dose of mRNA-1273 versus BNT162b2 among immunocompromised adults in the US.

Status: The goal of this retrospective database study is to compare the real-world effectiveness of a third dose of the Spikevax vaccine vs. a third dose of the Comirnaty vaccine against breakthrough COVID-19 hospitalizations among immunocompromised adults in the US. This protocol for this study was approved on 01 Mar 2023, and analyses were initiated in Jun 2023. Analyses are ongoing with final completion expected by 21 Oct 2023. At this time, no safety findings have been identified given the early stage of the study.

mRNA-1273-P933

Title: Real world comparative effectiveness of a booster dose of Spikevax versus Comirnaty among adults age 65+ in the US.

Status: The goal of this retrospective database study is to compare the real-world effectiveness of a 1st booster dose of the Spikevax vaccine vs. a 1st booster dose of the Comirnaty vaccine against breakthrough COVID-19 hospitalizations among adults age 65+ who have completed a primary series of an mRNA-based COVID-19 vaccine. This protocol for this study was approved on 01 Mar 2023, and analyses were initiated in Jun 2023. Analyses are ongoing with final completion expected by 21 Oct 2023. At this time, no safety findings have been identified given the early stage of the study.

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

mRNA-1273-P910

Title: Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2.

Summary: The overarching goal of this study is to characterize the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with elasomeran and elasomeran bivalent vaccination. Startup activities including creation of the case adjudication system are currently in progress.

mRNA-1273-P919

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

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

mRNA-1273-P920

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

Status: The overarching aim of this study is to characterize the safety of the Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine as used in routine clinical practice. Preliminary analyses are ongoing.

mRNA-1273-P921

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

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

mRNA-1273-P923

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

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

mRNA-1273-P924

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

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

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

9.1.1 Investigator-sponsored Studies

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

Short Title: Vaccine in chronic lymphocytic leukaemia (CLL).

Title: Vaccine responsiveness in patients with CLL.

Summary: In this prospective study, 60% of patients with CLL developed SARSCoV-2 antibodies and 80% developed functional T-cell responses after vaccination. For this study enrolment has been completed, first patient first visit dated 01 Sep 2020 and final CSR was completed on 07 Mar 2023. The total number of subjects enrolled was 36. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short tittle: COVERALL Initial

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: The objective for this study was to have a head-to-head comparison BNTI 62b2 and mRNA-1273. The start date for this study was Dec 2021 and end date was Jun 2022. The total number of subjects enrolled till DLP was 601 subjects. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

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

Short Tittle: T-Cell immunity

Title: T-Cell immunity

Description for T-Cell immunity: Recently, two mRNA vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have become available, but there is also an emergence of SARS-CoV-2 variants with increased transmissibility and virulence. A major concern is whether the available vaccines will be equally effective against these variants. The vaccines are designed to induce an immune response against the SARS-CoV-2 spike protein which is required for viral entry to host cells. Immunity to SARS-CoV-2 is often evaluated by antibody production, while less is known about the T-cell response. Here we developed, characterized, and implemented two standardized, functional assays to measure T-cell immunity to SARS-CoV-2 in uninfected, convalescent, and vaccinated individuals. The MAH found that vaccinated individuals had robust

T-cell responses to the wild type of spike and nucleocapsid proteins, even more so than convalescent patients. The MAH also found detectable but diminished T-cell responses to spike variants (B.1.1.7, B.1.351, and B.1.1.248) among vaccinated but otherwise healthy donors. Since decreases in antibody neutralization have also been observed with some variants, investigation into the T-cell response to these variants as an alternative means of viral control is imperative. Standardized measurements of T-cell responses to SARS-CoV-2 are feasible and can be easily adjusted to determine changes in response to variants. Estimated completion date is 25 Feb 2024.

Summary: Enrolment is complete, first patient first visit dated in 2022 and planned final report date is Sep 2023. The total number of subjects enrolled was 50. No AEs have been reported and no significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: 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 dated 26 Oct 2022 and planned final report date is 31 Dec 2023. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: SCQM

Title: N/A

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

Short Tittle: CoviBoost 2

Title: AP-HA

Summary: For this study enrolment was complete, first patient first visit was 22 Aug 2022 and planned final report date is Aug 2023. The total number of subjects enrolled was 414. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: SCQM Extension

Title: N/A

Summary: For this study enrolment was complete, first patient first visit was 03 Apr 2021 and planned final report date is Sep 2023. The total number of subjects enrolled was 917. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: MIViral

Title: N/A

Summary: For this study enrolment was complete, first patient first visit was in Oct 2022 and planned final report date is Dec 2023. The total number of subjects enrolled was 180. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: N/A

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

Summary: Objective of this study is to identify predictors of hospitalization for fully vaccinated patients presenting to an emergency department (ED) and identify predictors of severe outcomes in fully vaccinated hospitalized patients. No subjects have been enrolled/exposed for this study at DLP of this PBRER. This study started on 15 Jun 2023 and the projected end date for this study is Jan 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

Short Tittle: VI

Title: VI

Summary: Objective of this study is to determine the correlation of pre-existing antibodies against influenza or COVID with the kinetics of infectious viral load. No subjects have been enrolled in this study at DLP for this PBRER. This study started in Feb 2023 and the projected end date for this study is in Jun 2024. No AEs were reported. No significant safety findings have been identified for this study during the reporting period of this PBRER.

9.1.2 License partner studies

9.1.2.1 Completed trials

Sponsored by Glaxo SmithKline (GSK):

Protocol or Study Number: 217670 (ZOSTER-091)

A Phase 3, randomized, open-label, controlled, multicenter study to evaluate the immune response and safety of both herpes zoster subunit vaccine in healthy adults aged 50 years and older and the influenza virus vaccine in healthy adults aged 18 years and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.

Country-US

Dosing details: mRNA-1273 50 µg per dose (embedded in SM-102 LNPs); water for injections q.s. 0.5 mL.

- Flu D-QIV: Flu Quadrivalent Influenza vaccine 15 µg per strain/dose;
- HZ/su: Varicella-Zoster Vaccine gE (50 µg) and AS01B: QS-21 (50 µg), MPL (50 µg), liposomes; water for injections q.s. 0.5 mL.

Summary: Total enrolment was 2,013 subjects and actual subjects exposed to mRNA-1273 was 1,534. Start date for this study was 07 Oct 2021 and end date was 28 Feb 2023 (Date of final CSR). No safety, efficacy, or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons.

9.1.2.2 Ongoing trials

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

Protocol or Study Number: mRNA-1273-P102/21-0002/NCT04785144

A Phase 1, open-label, randomized study to access the safety and immunogenicity of a SARS-CoV-2 variant vaccine (mRNA-1273.351) in naïve and previously vaccinated adults.

Country-US

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

1. ARM 1A: 50 µg 1273.35,
2. ARM 1B: 25 µg 1273+25 µg 1273.351,

3. ARM 2A: 100 µg 1273/100 µg 1273/50 µg 1273.351,
4. ARM 2B:50 µg 1273/50 µg 1273/50 µg 1273.351,
5. ARM 2C: 100 µg 1273.351/100 µg 1273.351,
6. ARM 2D: 50 µg 1273.351/50 µg 1273.351,
7. ARM 2E: 100 µg 1273/100 µg 1273.351,
8. ARM 2F:50 µg 1273/50 µg 1273.351,
9. ARM 2G:50 µg 1273 + 50 µg 1273.351/50 µg 1273 + 50 µg 1273.351,
10. ARM 2H:25 µg 1273 + 25 µg 1273.351/25 µg 1273 + 25 µg 1273.351.

Summary: Planned enrolment was 210 subjects and actual subjects exposed to mRNA-1273 was 135. Start date for this study was 29 Mar 2020 and end date was in Apr 2023. The estimated completion date for the CSR is late 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.

Protocol or Study Number: mRNA-1273-P101/20-0003/NCT04283461

A Phase 1, open-label, dose-ranging study to access the safety and immunogenicity of 2019-nCov Vaccine (mRNA-1273) in Healthy Adults.

Country-US

Dosing details: In this study doses were divided into below mentioned groups and all groups had option of booster dose 100 µg.

1.	Cohort 1	ages 18-55	25 µg mRNA-1273
2.	Cohort 2	ages 18-55	100 µg mRNA-1273
3.	Cohort 3	ages 18-55	250 µg mRNA-1273
4.	Cohort 4	ages 56-70	25 µg mRNA-1273
5.	Cohort 5	ages 56-70	100 µg mRNA-1273
6.	Cohort 6	ages 56-70	250 µg mRNA-1273
7.	Cohort 7	ages ≥71	25 µg mRNA-1273
8.	Cohort 8	ages ≥71	100 µg mRNA-1273

9. Cohort 9	ages ≥71	250 µg mRNA-1273
10. Cohort 10	ages 18-55	50 µg mRNA-1273
11. Cohort 11	ages 56-70	50 µg mRNA-1273
12. Cohort 12	ages ≥71	50 µg mRNA-1273

Summary: Planned enrolment was 140 subjects and actual subjects exposed to mRNA-1273 was 120. Start date for this study was 16 Mar 2020 and end date was 26 Apr 2023. The estimated completion date for the CSR is Oct 2023. No safety concerns were reported. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. Dose of 250 µg was not well tolerated (previously reported). Immunogenicity data was submitted to FDA and published. ModernaTx, Inc. has all the immunogenicity data and papers generated. Preliminary CSR was published in Feb 2021. Follow-up for booster is still ongoing.

Protocol or Study Number: 21-0012

A Phase 1/2 study of delayed heterologous SARS-CoV-2 vaccine dosing (Boost) after receipt of EUA vaccines.

Country-US

Dosing details: mRNA-1273 - 100 µg; mRNA-1273-50 µg, 1273-211-100 µg.

Summary: Planned enrolment was 433 subjects and actual subjects exposed to mRNA-1273 were 423. Start date for this study was 28 May 2021 and projected end date is 14 Dec 2023. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons. ModernaTx, Inc. has all the immunogenicity data and papers generated. Immunogenicity reports have been submitted to the FDA. This study has additional manufacturers to ModernaTx, Inc.; for this reason, total enrolment exceeds that noted here.

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

Phase 2 Clinical Trial to Optimize Immune Coverage of SARS-CoV-2 Existing and Emerging Variants-COVID-19 Variant Immunologic Landscape Trial (COVAIL Trial).

Country-US

Dosing details: In this study, dosing was conducted in 6 different arms as follows:

1. Arm 1: 1 Dose Prototype mRNA-1273, = (99);

2. Arm 2: 1 Dose Beta (B.1.351) + Omicron (B.1.1.529) = (100);
3. Arm 3: 2 Dose Beta (B.1.351) + Omicron (B.1.529) = (102);
4. Arm 4: 1 Dose Delta (B.1.1529) = (101);
5. Arm 5: 1 Dose Omicron (B.1.1.529) = (100);
6. Arm 6: 1 Dose Omicron (B.1.1.529) + Prototype 1273 = (100).

Summary: Planned enrolment was 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. One hundred ninety-four breakthrough infections to date, sequencing of the variants is ongoing, as well as correlates of protection study being conducted. Manuscript reporting on serological data through day 91, for stages 1-3, being prepared.

Sponsored by National Cancer Institute (NCI):

Study or Protocol Number 000115

A Trial of the Safety and Immunogenicity of the COVID-19 Vaccine (mRNA-1273) in Participants with Hematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumors on PD1/PDL1 Inhibitor Therapy, Including Booster Doses of Vaccine.

Country: US

Dosing details: The vaccine is administered in 2 doses, 28 days apart. Participants receive an IM injection (0.5 mL) of mRNA-1273 on Day 1 and Day 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394).

Summary: Up to 120 participants will be enrolled, 1) 60 participants with solid tumour malignancies who have initiated programmed cell death 1(PD1)/programmed cell death ligand 1 (PDL1) inhibitor therapy as part of standard of care and are deemed to have a stable regimen without the need for any immunosuppressive therapy or corticosteroids; 2) Sixty participants with leukaemia, lymphoma, multiple myeloma and participants post-allogeneic stem cell transplant will be enrolled based on their perceived risk of immunosuppression. As of 17 Jun 2023, 17 subjects were exposed to mRNA-1273. Start date for this study was 27 Apr 2021 and estimated study completion date is 25 Feb 2024. No significant safety findings in this ongoing CT have been identified during the reporting period.

Sponsored by the University of California, Los Angeles (UCLA):

Study or Protocol Number: COVID-19 Version 2.0

Phase I/II, Open-label Dose-Escalation Trial of High Dose mRNA-1273 Booster for Lung Transplant Recipients.

Country: US

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

Summary: Planned enrolment was 60 subjects and number of subjects enrolled and exposed to mRNA-1273 were 19. Start date for this study was in Mar 2022, enrolment has been completed, and the end date was 27 Feb 2023. Data analysis is currently ongoing. No safety concerns were reported. No safety and efficacy or effectiveness information was identified during the reporting period. In addition, there were no regulatory actions taken due to safety reasons.

Sponsored by South Africa Medical Research Council (SAMRC):

Study or Protocol Number: Sisonke 4 (SHERPA)/mRNA-1273-P508

Sisonke Heterologous mRNA-1273 boost after prime with Ad26.COV2.S (SHERPA study). Open-label, phase 3 study to evaluate the effectiveness of heterologous mRNA-1273 boosting of the single or two dose Ad26.COV2.S COVID-19 vaccine among health-care workers in South Africa.

Country: South Africa

Dosing details: 50 ug.

Summary: Planned enrolment was 15,000 subjects and number of subjects enrolled and exposed to mRNA-1273 was 12,340 subjects. Actual recruitment end date was 12 Nov 2022 and last subject visit was on 09 May 2023. One hundred and six AEs have been reported, of which 18 were Grade 1 Related Adverse events and 4 were Grade 2 Related Adverse events. Fifteen SAEs have been reported, all of which were not Related to the study product. Eight AESIs have been reported, 4 of which were Related to study product. Five hundred and eighty-two cases of Reactogenicity have been reported, none of which were Grade 3 or higher. Forty-six breakthrough infections have been reported, 1 of which resulted in death. The remaining breakthrough infections were mild or asymptomatic infections. There are no safety concerns, new efficacy/effectiveness information or regulatory actions taken for safety reasons.

Sponsored by Merck, Sharp and Dohme (MSD):

Study or Protocol Number: V110-911-00

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of the Concomitant Administration of Either 23-Valent Pneumococcal Polysaccharide Vaccine or 15-Valent Pneumococcal Conjugate Vaccine with a Booster Dose of SARS-CoV-2 mRNA Vaccine in Healthy Adults 50 Years of Age or Older.

Country: US, including Puerto Rico

Dosing details: Participants enrolled in the concomitant groups will receive either 23-Valent Pneumococcal Polysaccharide Vaccine (V110) or 15-Valent Pneumococcal Conjugate Vaccine (V114) (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive placebo (blinded) in the left arm 30 days later at Visit 3 (Day 30). Participants enrolled in the non-concomitant groups will receive placebo (blinded) in the left arm and mRNA-1273 (open-label) in the right arm on Day 1, and then will receive V110 or V114 (blinded) in the left arm 30 days later at Visit 3 (Day 30).

Summary: Planned enrolment was 850 subjects and total subjects enrolled were 850 subjects and all 850 subjects enrolled were exposed to mRNA-1273. Start date for this study was 12 Jan 2022 and last participant last visit was on 21 Feb 2023. Database lock is targeted for Oct 2023. The CSR is targeted for finalization in Jan 2024. No safety concerns were reported. No new efficacy or effectiveness information has been obtained. No regulatory actions were taken for safety reasons.

Study or Protocol Number: V503-076-00

A Phase 3, Multicenter, Open-Label Study to Evaluate the Safety and Immunogenicity of 2-dose Regimens of 9v Human papillomavirus and mRNA-1273 SARS-CoV-2 Vaccines Where the First Dose of Each Vaccine Are Given Concomitantly in Boys and Girls 9 to 11 Years of Age.

Country: US

Dosing details: 50 μg primary series (2 doses of 50 μg 28 days apart).

Summary: Planned enrolment was 160 subjects and total number of subjects enrolled were 165 and out of which 162 subjects were exposed to mRNA-1273. Start date for this study was 28 Mar 2022 and projected end date is 14 Jun 2024. No new safety concerns, and no regulatory actions taken for safety reasons during the reporting period. There is no information that would affect the safety profile of the product through the reporting period. There is no new efficacy, effectiveness, or immunogenicity information.

Sponsored by the University of Southampton (CoV Boost):

Study or Protocol Number: RHM MED1781

A randomized, phase II UK multicenter study to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2.

Country: UK

Dosing details: mRNA-1273.529 50 µg and mRNA-1273.214 50 µg

Summary: For mRNA-1273.529 50 µg, planned enrolment is 205 subjects and the number of subjects enrolled and exposed to mRNA-1273 were 209. Start date for this study was 18 Feb 2022 and projected end date is 30 Nov 2023. No SAEs have been reported to ModernaTx, Inc. Interim analysis is not yet complete for efficacy and effectiveness information. No regulatory actions have been taken for safety reasons.

For mRNA-1273.214 50 µg, planned enrolment is 100 subjects and number of subjects enrolled and exposed to mRNA-1273 were 96. Start date for this study was 25 Jul 2022 and project end date is 31 Mar 2024. No SAEs are reported to ModernaTx, Inc. Interim analysis is not yet complete for efficacy and effectiveness information. No regulatory actions have been taken for safety reasons.

9.2. Medication Errors

Table 9.1 Medication errors

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 0 ○ 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. European Union legislation requires information on medication errors to be collected and reported through national pharmacovigilance systems.
Methods	The ModernaTx, Inc. GSDB was searched using the SMQ *Medication errors*, with a broad scope. The results were reviewed to exclude cases describing scenarios of off-label use and intentional product use issues.
Results	Refer to Appendix 9.g for additional information. **Medication Errors Involving Elasomeran** During this review period, the MAH received 2,745 cases (8,995 events) of Medication

	errors with 402 serious cases (1,164 serious events), and 11 cases with a fatal outcome. There were 2,512 medically confirmed cases involving elasomeran. The most frequently reported PTs were "Expired product administered" (1163; 12.9%), followed by "Interchange of vaccine product" (565; 6.3%), and "COVID-19 Immunization" (454; 5.0%). It should be noted that the PT "No adverse event" (1665; 18.5%) had the highest number of events. During the review period, there were 798 cases (3,183 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (258;8.1%), followed by "Headache" (78; 2.5%) and "Vaccination site pain" (70;2.2%). The number of case reports are listed below by age group exposed: • **<6 months of age:** 6 cases (9 events) of medication errors were reported. None of the medication error reports noted an associated AE. • **Infants and toddlers (6 months to 23 months):** 86 cases (130 events) of medication errors were reported. 5 cases (5 non-serious events; 1 serious event) reported AEs. • **Children (2 years to 5 years):** 117 cases (173 events) of medication error were reported. 4 cases (4 non-serious events) reported AEs. • **Children (6 years to 11 years):** 47 cases (53 events) of medication error were reported. 3 cases (6 non-serious events) reported AEs • **Adolescents (12 to 17 years):**31 cases (36 events) of medication error were reported. 4 cases (3 non-serious events; 1 serious event) reported AEs. **<u>Medication Errors Involving Elasomeran/Imelasomeran</u>** During the review period, the MAH received 349 cases (474 events) of Medication errors with 28 serious cases (25 serious events), and no cases with a fatal outcome. There were 308 medically confirmed cases involving elasomeran/imelasomeran. The most frequently reported PTs were Expired product administered" (192; 40.5%), followed by "Underdose" (70; 14.8%), and "Product storage error" (48; 10.1%). During the review period, there were 88 cases (216 events) of medication error reported with an associated AE. The most frequent AE reported were "Adverse drug reaction" (21; 9.7%), followed by "Pain in extremity" (13; 6.0%), and "Headache" (10; 4.6%). **<u>Medication Errors Involving Elasomeran/Davesomeran</u>** During the review period, the MAH received 2,742 cases (3,897 events) of Medication errors with 5 serious cases (1 serious event), and no cases with a fatal outcome. There were 2,728 medically confirmed cases involving elasomeran/davesomeran. The most frequently reported PTs were "Expired product administered" (1,405; 36.1%), followed by "Product storage error" (715, 18.3%), and "Underdose" (386; 9.9%). During the review period, there were 113 cases (261 events) of medication error reported with an associated AE. The most frequent AE reported were "COVID-19" (17; 6.5%), followed by "Pyrexia" (16; 6.1%), "Myalgia" (10; 3.8%) and "Pain" (10; 3.8%).
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 elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccine beyond the primary series or any interchange of other COVID-19 vaccine products. There seemed no difference for the nature of reported

	medication errors and importantly associated AEs among the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeranin general. AEs associated with reported medication errors were usually known to the elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran safety profile, and no events were associated with significant harm to the patient due to the medication error. There were no significant changes in the frequencies and types of medication error events in general from this review period and the last review period.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would suggest medication errors associated with administrations of elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran impact the benefit--risk profile for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. The benefit-risk evaluation remains positive. Medication errors reported to ModernaTx, Inc. will continue to be monitored using the routine pharmacovigilance measures implemented for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

9.3. Medical device incidents

A review of reports of device related issues from elasomeran/imelasomeran did not reveal any patterns or other safety information relevant to the benefit-risk assessment for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

10. NON-CLINICAL DATA

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

11. LITERATURE

A global literature search and analysis were performed utilizing Embase, Medline and PubMed databases for abstracts for the reporting period 18 Dec 2022 to 17 Jun 2023. The literature search was performed for the publications related to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran 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). Find the complete global literature search strategy used for Medline and Embase search under Appendix 13.1 and search strategy used for PubMed underAppendix 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. Please find the journal list under Appendix 13.3. Literature search strategy for medical topics can be found under Appendix 13.4.

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

Response: The MAH has implemented a series of improvements to the literature retrieval process. While routine global literature reviews were previously conducted weekly using Medline and Embase in screenings elasomeran-related literature articles. The MAH recognizing vast literature on Covid-19, expanded its literature screening to the comprehensive PubMed database (rather a part covered through Medline). Consequently, PubMed is now searched at the product level without specific AE filters. This strategic addition has introduced an additional 30,000 articles/hits for retrospective review since IBD compared to the previous methodology. This upgraded literature screening process involved retrospective identification of previously missed articles that were then assessed for Individual Case Safety Reports (ICSRs), signal detection and aggregate reporting and submitted accordingly. Thus, MAH is confident in the thoroughness of the literature retrieval process, ensuring minimal likelihood of overlooking pertinent articles, as evidenced by MAHs comprehensive representation in the PBRERs.

During the reporting period, there were a total of 71,091 abstracts retrieved and upon removal of duplicates 23,574 abstracts were reviewed from the global search. There were 7,745 local journal searches performed and 236 abstracts were reviewed. From all the searches performed, two articles were identified with new safety relevant information and are summarized below. For more detailed information and full text articles please refer to Appendix 13.5.

Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study [13].

Ljung et al. performed a nationwide, register based cohort study from Swedish national and regional registers RECOVAC and SCIFI-PEARL to check the risks of any menstrual disturbance and bleeding following first, second and third dose of SARS-CoV-2 vaccination (BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19) in premenopausal or postmenopausal women. A total of 2,946,448 Swedish women aged 12-74 years were included in the vaccination analyses. Pregnant women, women living in nursing homes, and women with history of any menstruation or bleeding disorders, breast cancer, cancer of female genital organs, or who underwent a hysterectomy

between 01 Jan 2015 and 26 Dec 2020 were excluded. The following observations were made from the study: The highest risks for bleeding in women who were postmenopausal were observed after the third dose in one to seven days risk window (hazard ratio 1.28 [95% CI=1.01 to 1.62]) and in the 8-90 days risk window (1.25 [1.04 to 1.50]). The impact of adjustment for covariates was modest. An increased risk of postmenopausal bleeding suggested 23 to 33 percent after 8-90 days window with BNT162b2 and mRNA-1273 after the third dose, but the association with ChAdOx1 nCoV-19 was less clear. During the analyses for menstrual disturbance or bleeding in women who were premenopausal, an adjustment for covariates almost completely removed the weak associations noted in the crude analyses. The premenopausal bleeding estimates were more imprecise compared with the other outcomes because of the fewer observed events. The strongest associations observed in premenopausal bleeding after vaccination were not significant and noted a 14% increased risk during one to seven days window after the first dose (1.14 [0.86 to 1.50]) and the third dose (1.14 [0.77 to 1.70]). There was no increased risk observed after the second dose (0.96 [0.71 to 1.30]) in the corresponding risk window. The authors observed a weak and inconsistent associations between SARS-CoV-2 vaccination and healthcare contacts for bleeding in women who are postmenopausal, and even less evidence was recorded of an association for menstrual disturbance or bleeding in women who were premenopausal. The study findings did not provide substantial support for a causal association between SARS-CoV-2 vaccination and healthcare contacts related to menstrual or bleeding disorders.

Morphologic and molecular analysis of liver injury after SARS-CoV-2 vaccination reveals distinct characteristics [14].

The article by Uzun et al, 2023, is presented in Section 11, as this event of Vaccine Induced Liver Injury (VILI) was reported for the first time during the PBRER#5 review period and after thorough medical review of such cases and the article, do not provide sufficient information to establish a causal relationship with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

The following article by Uzun et al, describes six (6) Swiss elasomeran patients with reported VILI and nine (9) with the initial diagnosis of Autoimmune Hepatitis. Formalin fixed liver biopsies for both were examined using immunofluorescence, immune repertoire histomorphology, whole -transcriptome and spatial transcriptome sequencing. The article had no information on the PMH, family history or medication for the subjects with Autoimmune Hepatitis, except 4 had stage 1 fibrosis. For the subjects with presumed VILI the age ranged from 21-85 years and the medical histories of the patients are limited except for one patient, a 21-year-old female is said to have "polymyalgia" and antibodies to thyroid peroxidase; another, a 78 y/o male with significant HBP

and a third, a 63 y/o male with Type 2 Diabetes Mellitus and elevated lipids. Only 3/6 Antinuclear Antibody+, both SMA and anti-Liver Abs Negative, Immunoglobulin G (IgG) levels normal in 4/6. Two females/4 males, time to onset (TTO) 2 to 28 days. There is no information on any previous liver issues or on the medications received by these for the other subject. For the presumed VILI subjects, one was untreated and the other 5 given steroids with all achieving drug free remission for the 12 to 18 months of follow-up.

The results of the extensive histomorphology studies were similar for both the presumed VILI and autoimmune hepatitis (AIH) cohorts. However, for the subjects with presumed VILI, the gene expressions profiling showed that mitochondrial metabolism and oxidative stress-related pathways were more and interferon response pathways less enriched. In addition, in these subjects, the multiplex analysis revealed that inflammation was dominated by CD8+ effector T-cells. In contrast, for the Autoimmune Hepatitis subjects, there was a predominance of CD4+ effector T--cells and CD79a+B and plasma cells. T-cell receptor (TCR) and B-cell receptor sequencing demonstrated- the T- and B-cell clones were more dominant in the presumed VILI than the Autoimmune Hepatitis subjects. In addition, many T-cell clones detected in the liver were also found in the blood. Finally, analysis of TCR beta chain and Ig heavy chain variable-joining gene usage showed that TRBV6-1, TRBV5-1, TRBV7-6 and IgHV1-24 genes were used differently in the presumed VILI than Autoimmune Hepatitis subjects.

The authors concluded that the liver injury in the presumed VILI subjects is related to AIH but demonstrated distinct differences in histomorphology, pathway activation, cellular immune infiltrates, and TCR usage. They further note that these 6 patients appear more closely like drug-induced autoimmune-like hepatitis. The extensive data presented in this article is based upon a selected cohort of subjects who developed liver injury within 30 days of the first (3) or second (3) vaccination with elasomeran in comparison to cohort of initial Autoimmune Hepatitis. Both cohorts have limited medical histories which are important in assessing the etiology of liver injury in patients. The presumed VILI subjects either required no treatment (1) or a limited course of steroids with continued remission for 12-18 months. The article presents an interesting concept which at this point is a diagnostic concept based upon an extensive assessment of a limited group of patients with liver injury post elasomeran vaccination out of over 80 cases reported in the literature. Using the Simplified Criteria for Autoimmune Hepatitis, 2 met Definite, 2 Probable and 2 did not meet Simplified Criteria for Autoimmune Hepatitis. Similar to the conclusions of assessment of Autoimmune Hepatitis, the reports in this article are rare, confounded, lack a clinically well-characterized representative comparison group and do not provide sufficient

information to establish a causal relationship with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

12. OTHER PERIODIC REPORTS

No other PBRERs have been written for elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran.

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

During the reporting period, no new data emerged that indicated a lack of efficacy from interventional, non-interventional, retrospective studies or from the review of literature articles.

14. LATE-BREAKING INFORMATION

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

15. OVERVIEW OF SIGNALS: NEW, ONGOING OR CLOSED

15.1. Validated signals during the reporting period

ModernaTx, Inc. has an established signal management process that includes signal detection, validation, prioritization, and assessment. During signal detection, data sources are screened for new safety information related to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. 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, vaccine AEs reporting system [VAERS]), and communications from external sources, including regulatory agencies, and (if applicable) business partners. As part of the ModernaTx, Inc.'s routine pharmacovigilance activities, weekly to monthly signal detection analyzes are performed on the following data sources: ModernaTx, Inc. global pharmacovigilance database (Argus platform) using a defined signal detection methodology (both qualitative and quantitative aggregated analyzes), signals of

disproportionate reporting from regulatory databases (e.g., Eudravigilance, VAERs), published literature that involves targeted keyword searches in widely recognized databases (i.e., Medline, Embase), health authority websites screening, review of publicly available competitors' labels, as well as social media.

This routine aggregate review also includes O/E analyzes, which are performed as described in Appendix 12.2.

During the reporting period of this PBRER, 4 signals were closed as refuted, and 2 signals were ongoing. The list of ongoing/closed signals as of DLP of this report is presented in Table 15.1 below and detailed summary tabulation of all signals is included in Appendix 5.1.

Table 15.1 Status of Validated Signals

Signal	Cross reference to the corresponding procedure for which a safety evaluation or regulatory request has been closed during the reporting period	Status (Ongoing/ Closed)	Outcome (Refuted / Substantiated)	Assessed in another regulatory procedure (Safety summary report or a variation)
Amenorrhea (re-evaluation)	NA (Re-evaluation signal was triggered internally by Moderna following PRAC request to provide an updated analysis in PBRER#4, as an outcome of closed EPITT 19781)	Closed	Refuted	PBRER#4 (signal ongoing) The updated analysis requested by PRAC was submitted to PRAC separately. PBRER#5 (signal closed, presented in Section 16.2.1, signal evaluation report appended to PBRER [same content as the updated analysis submitted separately to PRAC]).
Pemphigus and pemphigoid	PRAC Signal procedure (EPITT No. 19860)	Closed	Refuted	PBRER#5 MSSR#19 MSSR#20
Diarrhea (re-evaluation)	NA (Signal was triggered internally by Moderna)	Closed	Refuted	PBRER#5 MSSR#20 MSSR#21 MSSR#22
Idiopathic inflammatory myopathy/ Myositis	PRAC Signal procedure (EPITT No. 19884)	Closed	Refuted	PBRER#5 MSSR#19 MSSR#20 MSSR#21
IgA nephropathy flare-up*	EMEA/H/C/PSUSA/00010897/202112	Ongoing	Pending	PBRER#5 MSSR#22
Sensorineural	TGA request	Ongoing	Pending	PBRER#5

Signal	Cross reference to the corresponding procedure for which a safety evaluation or regulatory request has been closed during the reporting period	Status (Ongoing/ Closed)	Outcome (Refuted / Substantiated)	Assessed in another regulatory procedure (Safety summary report or a variation)
hearing loss**				MSSR#24

*IgA nephropathy was ongoing till the DLP (17 Jun 2023) and was considered closed and refuted by MAH after the DLP i.e., on 22 Jun 2023.
**Sensorineural hearing loss was ongoing till the DLP (17 Jun 2023) and was considered closed and refuted by MAH after the DLP i.e., on 14 Aug 2023. The evaluation of this signal has been presented in Section 16.2 and signal evaluation report (SER) has also been appended in Appendix 5.2e as per TGA request.

15.2. Requests from Health Authorities or regulatory bodies

15.2.1 Arrhythmias

Table 15.2 Arrhythmias

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 157 New and Significant Safety Information: None (0)
Background	The MAH received a Health Authority request to perform for PBRER#4 (DLP 17 Dec 2022) a cumulative review of all cases concerning elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran associated with arrhythmias from all sources, including any relevant articles from literature. For the current PBRER#5, a Health Authority requested that the MAH re-evaluate cumulatively the WHO-UMC classification of all serious cases of Arrhythmias, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e., Possible vs Probable and Probable vs Certain), and to discuss the result in the context of the totality of evidence on the subject.
Methods of Evaluation	The MAH queried the GSDB cumulatively as of 17 Jun 2023, for valid case reports of arrhythmia received from HCPs, HAs, consumers, and literature worldwide reported for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran using the following MedDRA version 26.0 "SMQ Cardiac Arrhythmia (Narrow scope)." There is no SPEAC or Brighton Collaboration case definition available for arrhythmias, therefore the MAH has created a case definition for evaluation of the arrhythmia cases. Cardiac arrhythmia is characterized by abnormal or irregular rhythm of heartbeat which could be either too slow (<60 beats/min) or too fast (>100 beats/min) and can happen at any age [15]. Cardiac arrhythmias can be classified according to the site of origin (e.g., atria, atrioventricular junction, or ventricles) and whether the response is abnormally fast and early (tachycardia or premature beats), or abnormally slow and delayed (bradycardia

	or escape beats) [16]. Arrhythmia reports were classified into four categories as: 1. **Confirmed case**: has less than 60 beats/min (Bradycardia) or more than 100 beats per min (tachycardia) and ee lectrocardiogram(ECG) identifying irregular heart rhythm 2. **Possible case**: Only has information on the irregular rhythm or number of beats per minute (pulse rate, heart rate) and no diagnostic confirmation (no info on ECG) 3. **Not a case**: Case has normal rhythm 4. **Unassessable**: Has no information on heart rate or pulse rate or ECG The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [17]. *Methodology Implemented to Review the Post-marketing Data* The MAH performed the cumulative search as of 17 Jun 2023 in the GSDB, using the MedDRA (v 26.0) SMQ "Cardiac arrhythmias" (Narrow scope.) The search retrieved reports that were then screened for information on ECG and that were further screened for Arrhythmia related information using the following key words (*Bradycardia, Heartbeat, Irregular heartbeat, Tachycardia, irregular rhythm, ventricles, Premature beats, and Atrioventricular junction*). The reports retrieved were separated with Tachycardia confirmed reports and the rest of the serious reports with Tachycardia alone with other key terms were medically reviewed for Arrhythmia confirmed cases.

Results:

Results for Cardiac arrhythmias are summarized below. Refer to Appendix 12.7 for additional information.

Cumulatively, as of 17 Jun 2023, the MAH received 9,453 reports (10,793 events) of Cardiac arrhythmias with 6,765 serious reports (7,282 serious events) and 261 reports with a fatal outcome. There were 4,358 medically confirmed reports (involving elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran). Most of the reports involved elasomeran: 9,240 reports (10,558 events) of Cardiac arrhythmias with 6,578 serious reports (7,083 serious events) and 254 reports with a fatal outcome. There were 4,300 medically confirmed reports. Most reports involved females (5,317 reports, 57.5%) compared to males (3,786 cases, 41.0%); 137 (1.5%) cases did not include gender information. The mean age was 53.4 years (SD: 17.2) and median age was 54.0 years (range: 0.1 to 121 years). For events (7,089 events) associated with a known dose number, 4,546 (64.1%) had an onset of <7 days from the time of vaccination with any dose. Of note, a total of 3,469 (32.9%) events were reported with insufficient information to determine dose number.

During the review period, the MAH received 590 reports (681 events) of Cardiac arrhythmias with 503 serious reports (539 serious events), and 13 reports with a fatal outcome. There were

153 medically confirmed reports (involving elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran). Most of the reports involved elasomeran: 460 reports (534 events) of Cardiac arrhythmias with 379 serious reports (403 serious events) and 8 reports with a fatal outcome. There were 108 medically confirmed reports. Most reports involved females (261 reports, 56.7%) compared to males (191 reports, 41.5%); 8 reports did not include gender information. The mean age was 48.5 years (SD: 15.9) and median age was 48.0 years (range: 0.3 to 90.0 years). For events associated with a known dose number (231 events), 122 (52.8%) had an onset of < 7 days from the time of vaccination with any dose. Of note, a total of 303 (56.7%) events were reported with insufficient information to determine dose number.

Compared to the PBRER#4, the distribution of reports in this PBRER#5 was similar with respect to sex, age, reporting source, region, and TTO.

As per the methodology described above, the MAH performed the review period search for 18 Dec 2022 to 17 Jun 2023 in the GSDB, using the MedDRA (v 26.0) Standard MedDRA Query (SMQ) "Cardiac arrhythmias" (Narrow scope), and retrieved 590 reports (681 events). These 590 reports were screened for information on electrocardiogram (ECG), which identified 117 reports. These 117 reports were further analysed for Arrhythmia related information with the following key words (Bradycardia, Heartbeat, Irregular heartbeat, Tachycardia, irregular rhythm, ventricles, Premature beats, and Atrioventricular junction). The analysis of the 117 cases with the key terms found 54 reports. Of these, all Tachycardia confirmed reports (37) with no other associated symptom were eliminated. Tachycardia is an increased heart rate for any reason. It can be a usual rise in heart rate caused by exercise or a stress response such as sinus tachycardia. Sinus tachycardia is considered a symptom, not a disease. Of the remaining 17 reports, 1 was non-serious and another report was a duplicate. Thus, 15 unique serious reports from this reporting period were further reviewed in detail, to identify and assess true cases of Arrhythmia. Details of these reviews are presented below in MAH re-evaluation of cumulative data.

A Health Authority requested for this PBRER that the MAH re-evaluate cumulatively the WHO-UMC classification of all serious cases of Arrhythmias, explicitly listing the official WHO-UMC criteria used to include/exclude cases in/from adjacent causality categories (i.e., Possible vs Probable and Probable vs Certain), and to discuss the result in the context of the totality of evidence on the subject. As requested, the serious cases as of PBRER#4, 134 cases, and 15 cases during the current PBRER#5 were combined and re-evaluated for the WHO-UMC causality criteria. Overall, 149 serious cases were re-evaluated for WHO causality and categorized as

follows, Possible (62), Unlikely (46), Unassessable (39), and Conditional (2). There were no cases of positive rechallenge.

Cases with age < 18 years. There was 1 case in a person < 18 years of age. A consumer reported that an infant with congenital transposition of the great arteries, who was exposed to vaccine *in utero* by maternal vaccination, experienced supraventricular tachycardia beginning one month before death at age 3 months; cause of death was transposition of the great arteries and supraventricular tachycardia, and an autopsy was not done. WHO-UMC causality for arrhythmia unlikely due to the congenital defect.

Please refer to Appendix 12.7 for detailed MAH comment and categorization of the 149 cases.

Discussion

Cumulatively 10,793 events (9,453 reports) were reported for elasomeran (9,240 reports), elasomeran/imelasomeran (185 reports) and elasomeran/davesomeran (31 reports) (*Note: there is overlap of two reports, as the following case#* [redacted] *was reported in Elasomeran and Elasomeran/imelasomeran; similarly another case#* [redacted] *was reported in Elasomeran/imelasomeran and Elasomeran/davesomeran*) of which 149 serious reports were identified as Arrhythmia cases using the methodology explained above. Of these 149 serious cases, 134 were presented during the PBRER#4 and 15 are reported during this PBRER#5. Overall re-evaluation of all 149 serious cases was performed. The WHO-UMC classification was provided for the serious 149 cases as follows: Possible (62), Unlikely (46), Unassessable (39), and Conditional (2). The clinical spectrum of events in this reporting period was similar to that reported in the previous PBRER.

No cases qualified for classification as "Probable" or "Certain," according to the WHO-UMC classification. Although some cases had a plausible temporal relationship from time of vaccine administration to development of reported cardiac arrhythmia, other data in the case reports provided reasons that weighed against both probable and certain causality by vaccine. Such countervailing data include medical history of arrhythmia; concomitant medical conditions, medications or diseases that are associated with arrhythmia; SARS-COVID-19 illness; excessive TTO of arrhythmia from vaccination; and lack of necessary medical/clinical detail. There was also a lack of clear positive rechallenge. In addition, there is no proven pathophysiological mechanism to explain how elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran causes arrhythmia; similarly, there is no pathognomonic sign of vaccine-induced arrhythmia. Further, many of the AE reports lack information on important factors such hydration, stress/anxiety/panic, drug use, alcohol use, non-prescription cold and allergy medications, dietary supplements,

SARS-COVID-19 infection, etc. Finally, the medical literature, taken together, including a small number of epidemiologic studies that have been reviewed in detail in previous submissions, does not demonstrate that arrhythmia is associated with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran.

Based on the analysis of all the safety data available as of 17 Jun 2023, the totality of the evidence does not indicate that arrhythmia is causally associated with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran. This evidence includes the post-marketing, post-approval, and post-authorization information (including literature) noted above, as well as CT data previously submitted, that do not show an association.

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 arrhythmia events and administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of Arrhythmia, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety issue of concern, and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events of Arrhythmia using routine surveillance. The benefit-risk evaluation remains positive.

15.2.2 Chronic Urticaria

In the final assessment report for PBRER #4, the following was noted by a Health Authority:

"Chronic urticaria" – literature

The publication by Drivenes et al [18] is claimed by the MAH to be a ModernaTx, Inc CT and has not been further commented upon by the MAH. The MAH should comment upon this paper in the next PSUR, both on the content regarding elasomeran and occurrence of urticaria-related events, in particular the events concerning chronic urticaria, and to explain the stated relationship to a ModernaTx, Inc's CT.

The MAH is requested to comment upon the publication by Duperrex et al [19] in the next PSUR.

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

Drivenes et al [18]

The Drivenes article featured a Letter to the Editor which presented a case series describing sixteen patients (10 female/6 male, median age of 33 years [range: 20 to 73 years]) who experienced events of delayed onset urticaria. Thirteen patients had no prior medical history of urticaria and developed inducible urticaria and/or spontaneous urticaria post-vaccination. The remaining three patients developed an exacerbation of their pre-existing urticaria with two of those three patients experiencing newly developed symptomatic dermographism. All patients developed symptoms within 1 day to 3 weeks following booster vaccination with a median time of 14 days. Most patients had severe symptoms with six requiring acute doctor visits and four patients being admitted to the emergency room. All patients were treated with high-dose antihistamines, and four patients received treatment with systemic corticosteroids. A total of five patients received further treatment with omalizumab. Events of delayed onset urticaria were more commonly observed after vaccination with a booster dose of Moderna (12; 75.0%), despite only 13.5% of Danes receiving Moderna as booster vaccines. In all cases, the onset of delayed urticaria and symptomatic dermographism was temporally associated with the administration of the vaccine.

MAH Comment: The MAH erroneously stated that the cases described in this article were from a Moderna CT and would not necessitate the creation of post market ICSRs. The MAH regrets this misstatement and has undertaken creation of ICSRs.

Duperrex et al [19]

Chronic spontaneous urticaria (CSU) is a common medical condition and has a wide range of causes. The background rates of CSU from population-based observational studies prior to the era of COVID-19 reported ranged from 80 to 150 per 100,000 population per year in Europe [20], [21], [22]. The authors did not perform a comparison between the estimated incidences of CSU after receipt of the third dose of mRNA COVID-19 vaccine and the background rates.

Using passively reported CSU cases nationwide from Swissmedic, the authors extracted 607 CSU cases reported to Swissmedic after the third Moderna dose during 21 Jan 2021 to 31 Aug 2022 and reported the incidence rate being 30.8 per 100,000 persons (95% CI=28.4, 33.4) during one and half years. Using the lower bound of background rates (80 per 100,000 person per year) as a

conservative reference rate and a risk window of six weeks based on the clinical definition of CSU, the crude O/E is 2.08 (95% CI=1.92 to 2.25), implying the observed number of cases was higher than the expected signaling an excess of risk [23]. However, spontaneous reporting systems detect signals that could be due to factors other than the vaccine itself, and the signal requires further investigation and confirmation from formal epidemiologic studies. It is unclear whether these CSU reported cases underwent a clinical review and whether there was stimulated reporting or under-reporting of CSU cases to the Swissmedic system during the case accrual period. The O/E ratio was crude without adjustment for demographics and risk factors for CSU. Misclassification of the risk window could over- or under-estimate O/E ratios; analyses assuming that cases could be reported at any time after vaccination did not suggest an increased risk.

Based on a convenience sample of CSU in the canton of Vaud of Switzerland, the authors included 69 patients with CSU after the third Moderna dose and reported an incidence rate of 43.9 per 100,000 persons (95% CI=34.5-56.0) during approximately four months of follow-up. Using the lower bound of background rates (80 per 100,000 person per year) to be conservative and a risk window of six weeks based on the clinical definition of CSU, the crude O/E ratio is 15.04 (95% CI=11.70, 18.80), implying the observed number of cases were higher than the expected signaling an excess of risk. However, this estimate requires cautious interpretation. First, misclassification of the cause of CSU is possible. The case definition or eligibility of CSU that allergists used, and attributable causes of CSU were not reported. Most CSU patients had risk factors (75% taking daily antihistamine, 14% with previous urticaria, 29% had hay fever, and 11% had drug allergies) that put them at a higher risk to develop CSU for a wide range of causes. Second, as the authors acknowledged in the Discussion, "there is a selection bias for patients with CSU in relation to COVID-19 vaccines". The questionnaire and characteristics of those who did not participate are not available. Over 80% of the patients had active CSU at data collection and were more likely to report their recent COVID-19 vaccination history when it was asked. Other alternative causes for CSU may not be elucidated. Third, the case accrual period was much shorter than the national analysis, rendering approximately five expected cases and imprecise estimate of the ratio. The O/E ratio was crude without adjustment for demographics and risk factors for CSU. Misclassification of the risk window could over- or under-estimate O/E ratios.

Comparisons between vaccine brands were limited by confounding and potential selection bias for both analysis in Vaud and Switzerland nationwide. Firstly, the authors acknowledged in the Discussion, "we could not adjust IR because individual data on vaccination by brand, age, and sex were not available", yet demographics and risk factors for CSU of CSU patients secondary to Pfizer-BioNTech vs Moderna recipients may differ. A formal head-to-head comparison with

proper adjustment for confounding is needed for a fair interpretation of risk differences, if any. Secondly, in the analysis in Vaud using a convenience sample, it is unclear whether the institutes where the 16 allergists had access to CSU cases had higher proportion of Moderna receipts, compared with the brand distribution of the whole Vaud area. Also, it is unclear whether factors affecting patients' participation in the questionnaire differ between two brands (80/97 participated). In the analysis in Switzerland nationwide, it is unclear whether reports following Moderna vaccination were simulated during 21 Jan 2021 to 31 Aug 2022, compared with Pfizer vaccination, which could contribute to differential reporting rates.

MAH Conclusion:

The MAH considers that the information presented in these two articles does not offer compelling evidence of any new or emerging safety concern to warrant further evaluation for the topic of chronic urticaria. The current safety information adequately reflects the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran and an amendment of the Product Information is not warranted.

15.2.3 Idiopathic Inflammatory myopathies (IIM)/Myositis

Table 15.3 Idiopathic Inflammatory Myopathies (IIM)/Myositis

Source of New Information	o Moderna GSDB o Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 48 o New and Significant Safety Information: None (0)
Background	In response to a request from a Health Authority on 12 Jan 2023, the MAH performed a signal evaluation for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran regarding IIM/myositis. The Health Authority agreed with the MAH's assessment that a causal association between Moderna COVID-19 mRNA vaccine and myositis could not be concluded. The following were further requested by the Health Authority: *1. The MAH should continue to monitor IIM/myositis and their flares through routine pharmacovigilance in the upcoming PSURs. Any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms should be presented.* *2. The MAH should include and follow-up on IIM/myositis in the final Study report of EU Post authorization safety study (PASS) mRNA-1273-P904 to be submitted in Dec 2023.*
Methods of Evaluation	In 2017, European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) developed and validated classification criteria for IIMs and their major subgroups. The EULAR/ACR criteria employ easily accessible and operationally defined elements including age, muscle weakness, skin/other clinical manifestations, laboratory measurements, and muscle biopsy features for the classification of "definite", "probable", and "possible" IIM. The MAH adopted the EULAR/ACR criteria for classification of IIMs, and given the nature of spontaneous reports, added two categories: 1) "Unassessable" for case reports lacking critical information needed to complete IIM case classification (e.g., lack of data on objective signs of weakness, skin manifestations, myositis antibody panel, liver or muscle enzymes, muscle, or skin biopsy results); and 2) "Not a case" for case reports that do not meet the EULAR/ACR "definite," "probable," or "possible" classification and clearly have an alternate diagnosis for the reported events. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

Results:

Results for IIM/myositis are summarized below. Refer to Appendix 12.9 for additional information, including summary tables of cases and events, case evaluations, and additional analyses.

The MAH performed an updated review of reports received after 17 Feb 2023, the DLP of the signal evaluation, to cover the period 18 Feb 2023 through 17 Jun 2023, the DLP of PBRER #5. During this period, the MAH received 17 cases (16 serious) of IIM/myositis. No cases had a fatal outcome. There were 7 medically confirmed cases. (Note: Medically confirmed case reports are reports provided by a medically qualified patient, friend, relative or caregiver of the patient. In the same way, where one or more suspected ARs initially reported by a consumer are subsequently confirmed by a healthcare professional, the ICSR should be considered medically confirmed.) The majority of cases involved females (11 cases, 64.7 %) compared to males (6 cases, 35.3%). The mean patient age was 54.6 years (SD: 11.9) and median age was 57.0 years (range: 31.0 to 71.0 years). The reporting of events is consistent with the natural history of IIM/myositis which occurs more commonly in women and in the older age groups.

Of the total 17 cases, 14 cases (13 serious) with 15 events (11 serious) were reported for elasomeran and 3 serious cases (3 serious events) were reported for elasomeran/imelasomeran. There were no cases reported for elasomeran/davesomeran. [redacted] and [redacted] are serious cases with elasomeran with non-serious IIM events reported.

Most reports were from regulatory authorities (13, 76.5%), followed by spontaneous reports (3, 17.6%) with one (5.9%) report originating from the literature (non-study report). Most of the cases were received from the EEA (9 cases, 52.9%), followed by the United Kingdom and United States (3 cases, 17.6% from each).

Dose number and TTO could not be determined for 12 of the 18 events and given the low case/event counts, no meaningful pattern in dose number or TTO was appreciable.

Out of the 17 cases identified in the reporting period, 9 were unassessable, 4 were unlikely, 3 were not cases of IIM (note however, [redacted] indicated potential rechallenge), and 1 case ([redacted]) was a possible case of IIM according to the modified EULAR/ACR criteria adopted by the MAH.

The MAH considers [redacted] and [redacted] as relevant new cases (including those reporting re-challenge information) to present as requested by the Health Authority.

[redacted] **(WW Identifier** [redacted]**)** is a literature non-study case concerning a 71-year-old female reported to have no significant medical history, who started having gradual onset of proximal lower extremity weakness 2 weeks after the second dose of mRNA-1273 COVID-19 vaccine. Over the next 9 months, she reported persistent

weakness and leg pain. Blood work revealed aspartate aminotransferase 126 unit/L, normal alanine transaminase, creatinine kinase level 541 IU/dL, and a positive Antinuclear Antibody test. The patient was evaluated by outpatient rheumatology and found to have objective proximal muscle weakness. Electromyography and nerve conduction study reportedly showed evidence of myopathic disease. She was admitted for inpatient workup and found to have proximal muscle weakness with preservation in distal muscle groups. A routine myositis antibody panel was negative. Brain, cervical, and thoracic Magnetic Resonance Imaging (MRI) showed findings that were chronic and not compatible with her symptoms. Muscle biopsy revealed frequent necrotic muscle fibres undergoing myophagocytosis and patchy endomysial macrophage, which supported the diagnosis of immune-mediated necrotizing myopathy. Given the high association of immune-mediated necrotizing myopathy to underlying malignancy, computed tomography of the chest, abdomen and pelvis was performed which did not show malignancy or metastatic disease but did show a mildly thickened endometrium. Endometrial biopsy could not be performed due to cervical stenosis, and the patient declined colonoscopy for colon cancer screening. She had persistent muscle weakness despite being on high-dose prednisone for a month. Intravenous immune globulin (IVIG) and rituximab were added as steroid-sparing agents, and the patient continued to be monitored closely. According to the authors malignancy was not completely excluded given the patient's refusal to undergo further colonoscopy and endometrium biopsy.

MAH Comment: Based on the temporal association, clinical presentation, high Creatinine Kinase, positive Antinuclear Antibody (presumably anti-Jo-1), and muscle biopsy results, this is assessed as a possible case of IIM. Based on the confounding possibility of associated malignancy, this case is considered possible according to WHO causality assessment.

[redacted] **(WW Identifier** [redacted] is a regulatory authority case from a consumer of a 56-year-old male, with diabetes and asthma, and COVID-19 (SARS-CoV-2) infection 54 days after receiving the second dose of the CHADOX1/NCOV-19 vaccine, who experienced first episode myositis 44 days after dose 1 CHADOX1/NCOV-19, and a second episode of myositis 72 days after elasomeran as third vaccination. The patient experienced sharp pain in the muscle of the upper arms for which he went for physiotherapy and after about 6 weeks was recommended to have steroid injection. Patient had loss of strength in both arms. No further information regarding risk factors, relevant medical history, concurrent conditions, investigations, and additional treatment received were provided. The outcome of myositis was reported as not recovered.

MAH Comment: While the events were reported as myositis, the clinical presentation is inconsistent with myositis, likely representing reactogenicity events occurring after vaccine interchange. Additionally, this report is heavily confounded by the reporting of the first episode after dose 1 of the CHADOX1/NCOV-19 vaccine, as well as the reported COVID-19 (SARS-CoV-2 infection) 54 days after dose 2 of the CHADOX1/NCOV-19 vaccine. This is not considered a case of IIM.

Discussion

In this reporting period, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported IIM, no consistent or independent risk factors were identified in any of the cases that would support a causal association with administration of elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran.

A focused literature review did not identify articles that provided any new information on possible pathogenic mechanisms on the occurrence of IIM.

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 elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of IIM/myositis reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events for IIM/myositis using routine surveillance and present new relevant cases in PBRERs. The benefit-risk evaluation remains positive.

As per request from a health authority, the MAH will include myositis as an AESI for the final study report for the EU PASS study mRNA-1273-P904 to be submitted in Dec 2023.

15.2.4 Pemphigus and Pemphigoid

Table 15.4 Pemphigus and Pemphigoid

Source of New Information	o Moderna GSDB o Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 27 o New and Significant Safety Information: None (0)
Background	During the review period covered by this report, the MAH received a request from a Regulatory Authority followed by Responses to Queries (RTQ) to the preliminary Health Authority Assessment Report for this safety topic (EPITT ref. no. 19860). The Health Authority subsequently concluded that '*…the current evidence is insufficient to establish a causal relationship between Spikevax and pemphigus or pemphigoid*'. Further, it noted: • *The MAH for COVID-19 mRNA vaccine Spikevax (Moderna Biotech Spain, S.L.) should continue to monitor these topics in PSURs.* • *In the next PSUR (DLP 17 Jun 2023), the MAH should perform a review all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid (separately) after exposure to Spikevax, including data from clinical trials, post-marketing exposure and new scientific literature. The MAH should perform the assessment of causality, an O/E analysis and provide all case narratives within this review.* • *The MAH is requested to clearly state if cases identified using the MedDRA High level term (HLT) "bullous conditions" fulfil the definitions of bullous pemphigoid or pemphigus, and group them accordingly.*
Methods of Evaluation	Moderna GSDB was searched for all new cases reported from 18 Dec 2022 to 17 Jun 2023 for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran using the previously established customized MedDRA SMQ (as detailed in PBRER#4). This also included the MedDRA HLT 'Bullous conditions.' There is no universal case definition for Pemphigus or pemphigoid, therefore MAH developed a working case definition (see Appendix 12.10). The Company causality assessment is provided utilizing the WHO-UMC causality assessment.

Results:

Results for pemphigus and pemphigoid reports are summarized below. Refer to Appendix 12.10 for additional information, including summary of cases and events, case evaluations, and additional analyses.

During the review period, the MAH retrieved a total of 118 new cases (120 events) included in the HLT of 'Bullous conditions'; 95 cases were reported for elasomeran, 14 cases for elasomeran/imelasomeran and 10 cases for elasomeran/davesomeran (Note: there is overlap of one report, as the following case#[redacted] was reported after elasomeran and elasomeran/imelasomeran), with 74 serious cases (74 serious events), and no cases with a fatal outcome. There were 44 medically confirmed cases. The majority of cases involved females (76 cases, 64.4%) than males (35 cases, 29.7%); 7 cases did not include gender information. The mean age was 52.2 years (SD: 18.1) and median age was 53.0 years (range: 19 to 94 years). For events associated with a known dose number (34 events), 17 (50%) had an onset of < 7 days (other than events on Dose-4, reported events > 7 days) from the time of vaccination on any dose. Of note, a total of 85 (70.8%) events were reported with insufficient information to determine dose number.

All the 118 cases (120 events) were medically reviewed to identify potential cases of Pemphigus or pemphigoid and to differentiate them. There were 58 events reported as Blister, 42 events as Autoimmune disorder, 13 events as Pemphigoid, 3 events as Pemphigus, 2 events as Dermatitis bullous, one event as Immune-mediated adverse reaction, and one event as Acquired epidermolysis bullosa.

Summary of cases identified for Pemphigus:

A total of 3 cases with the reported PT of pemphigus were identified during the reporting period. The WHO causality was assessed as unlikely in two cases: A long latency (6 months or more) following the vaccination with elasomeran was noted in two cases. In one other case, insufficient clinical and laboratory details were provided for a detailed causality assessment (see Appendix 12.10).

Review of the cases from HLT of Bullous Conditions did not identify any other relevant cases that fulfil the definitions of pemphigus.

Summary of cases identified for Pemphigoid:

A total of 13 new cases (13 events) with the reported PT of Pemphigoid were identified during the reporting period. Of these, 11 cases were reported for elasomeran and 2 cases for elasomeran/imelasomeran. There were no pemphigoid cases reported for elasomeran/davesomeran during the interval period. There have been no cases with a fatal outcome. There were 8 medically confirmed cases. Most cases involved males (6 cases, 46.2 %) compared to females (5 cases, 38.5%); 2 (15.4%) cases did not include gender information. The mean age was 68.8 years (SD:

15.2) and median age was 69.0 years (range: 44 to 94 years). Of the 13 cases, 9 cases had a missing TTO and rest of the 5 cases, no specific pattern was observed on TTO. Similarly, majority of cases had unknown dose (11 cases, 11 events) and two cases with known dose were reported one each on Dose-2 and Dose-4.

All 13 cases were medically reviewed using the MAH case definition criteria and were accordingly classified as: 'confirmed' for 2 cases; and 'possible' for 6 cases; 'unassessable' for 4 cases as these cases were lacking in sufficient clinical information details and supportive laboratory diagnostic information for pemphigoid. One another case was assessed as 'not a case' since the event reported as a pemphigoid occurred >3 months after vaccination, the laboratory findings for immune serology returned negative. Refer to Appendix 12.10.

Out of the 13 cases reported during the reporting period:

Summary of Reports on Elasomeran (11 cases):

- There were 4 cases that were considered new onset cases based on the information provided. The WHO-causality in two (2) of these cases were considered as possible: Alternative etiology is suspected in this case as the concurrent medical history of chronic urticaria which could be suggestive of a potential underlying autoimmune disorder (predisposing risk factor); the second case with limited diagnostic confirmatory data for pemphigoid described event onset >1 month in an 87-year-old (risk factor) patient who was receiving polypharmacy (bullous dermatitis is listed for Cordarone). The WHO-causality in one other literature case was deemed unlikely as the event of pemphigoid (onset >3 months post vaccination) was attributed to a preceding COVID-19 infection and not vaccine related by the authors. One case was assessed as not a case (described above).
- Three cases described a flare-up of pre-existing pemphigoids. The WHO-causality was assessed as unlikely in two cases: the TTO in one case was >3 months after vaccination and in the other 140 days post vaccination, and unassessable in one case where the latency information was unavailable for a complete case assessment.
- In 4 other cases, the status of pemphigoid was unclear from the available information. The WHO-causality in one case was assessed as possible in a 94-year-old patient (advanced age is a risk factor) while the complete information regarding the patient's medical history, co-morbidities including COVID-19 status and concomitant medications were unavailable, limiting the causality assessment. The second case was deemed unlikely related as the

event onset was >6 months after vaccination. Two other cases were unassessable due to insufficient case information.

Summary of Reports on Elasomeran/Imelasomeran (2 cases):

- There was 1 case which was considered new onset case based on the information provided. The WHO-causality in this case was considered as possible which described blisters affecting the soles of the feet (atypical presentation) in a 72-year-old patient with concurrent asthma (risk factor) and who concomitantly received spironolactone (risk factor; severe skin reactions including Stevens–Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms listed). No confirmatory diagnostic laboratory data (biopsy/Direct Immunofluorescence/serology) for pemphigoid were provided.
- The WHO-causality assessment in one (1) other case was unassessable due to lack of sufficient clinical or diagnostic laboratory details confirming diagnosis of pemphigoid, including information on medical history/comorbidities, concomitant medications were reported.

There were no other relevant cases identified from the medical review of cases from the MedDRA HLT bullous conditions that fulfilled the definition of pemphigoid (see Appendix 12.10).

Discussion

The MAH conducted a review of cases for pemphigus and pemphigoid in the GSDB, CTs data and in literature for the interval period covered by this PBRER (18 Dec 2022 to 17 Jun 2023) for elasomeran, elasomeran/ imelasomeran and elasomeran/ davesomeran.

For the review period, a total of 3 cases (3 events) contained the reported PTs of pemphigus. The WHO-causality was unlikely in 2 cases with onset of events >6 months following vaccination with elasomeran. One other case contained insufficient details for causality assessment. There were no cases with a reported fatal outcome.

Overall, the observed post-marketing safety data from the cases containing relevant PTs of pemphigus revealed no new significant safety information. The events were generally manageable in clinic with appropriate treatment.

For the review period, a total of 13 cases (13 events) containing the reported PTs of Pemphigoid were retrieved: 11 cases for elasomeran (4 new onset; 3 flare-ups, where the relevant information was available) and 2 for elasomeran/imelasomeran (1 new onset).

Overall, in four cases (3 cases for elasomeran; 1 elasomeran/imelasomeran), the WHO-causality was assessed as possible. In these cases, alternative etiologies provided a more likely explanation of the reported pemphigoid event such as involving concomitant usage of medications for which pemphigoid or a related dermatological event are listed (e.g. spironolactone, Cordarone, etc), having known pre-disposing risk factors including a history of allergy (e.g. bronchial asthma, having potential association with pemphigoid [24], underlying chronic autoimmune condition) or involving patients of advanced ages (>70 years old). In two of these cases, the confirmatory laboratory diagnostic information for pemphigoid were not provided.

Overall, the observed post-marketing safety data from the cases containing relevant PTs of Pemphigoid revealed no new significant safety information. There were no cases with a reported fatal outcome.

No new significant safety information of relevance for this topic became available from the ongoing CTs for elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran during the period of this report.

The clinical presentation of events in this reporting period was similar to that reported in the previous PBRER. Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported pemphigus or pemphigoid, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Conclusion

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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of pemphigus/ pemphigoid reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran,

elasomeran/davesomeran exposure. The MAH will continue to monitor for events of pemphigus and pemphigoid using routine surveillance. The benefit-risk evaluation remains positive.

15.2.5 Heavy menstrual bleeding (Bivalent Only)

Table 15.5 Heavy menstrual bleeding (Bivalent Only)

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 117 ○ New and Significant Safety Information: 1. Refer to Section 11 for additional information on this article by Uzun et al, 2023 [14].
Background	Heavy Menstrual Bleeding (HMB) following bivalent vaccination was triggered by a request received from a Health Authority on 27 Apr 2023 (see below). *"ModernaTx, Inc. is requested to submit the following:* *1. Information reviewed to date regarding HMB following Spikevax COVID-19 vaccination contained limited discussion of bivalent vaccines. In addition, long-term outcomes, reporting rates, and risk factors have not yet been characterized. Provide an updated review of Heavy Menstrual Bleeding in the next PSUR/PBRER including:* *a. Cumulative review of post-market cases, with a focus on reports following bivalent vaccination.* *An updated review of any new literature (e.g., prospective cohort studies) on the risk of HMB following monovalent and/or bivalent Spikevax COVID-19 vaccination. Any relevant feasibility assessment documents on implementing new or amending ongoing PASS that were prepared for other regulatory agencies (e.g., EMA). A discussion on the need to update the RMP to better characterize the risk of HMB following Spikevax vaccination."*
Methods of Evaluation	**Identification of Case Reports in ModernaTx, Inc. GSDB**: Search Criteria Applied: Cases of heavy menstrual bleeding associated with elasomeran/imelasomeran and elasomeran/davesomeran were retrieved from the company safety database using the following three MedDRA PTs: "Heavy menstrual bleeding," "Menometrorrhagia," and "Polymenorrhagia" with a DLP date of 17 Jun 2023 using MedDRA version 26.0.
Results	Refer to Appendix 12.12 for additional information, including summary tables of cases and events, case evaluations, and additional analyses. ***A. Cumulative review of post-market cases, with a focus on reports following bivalent vaccination.*** Cumulatively, the MAH received 86 cases (9 serious cases) with 117 events

	(8 serious) which reported symptoms of heavy menstrual bleeding in individuals who received a booster dose of elasomeran/imelasomeran or elasomeran/davesomeran. No cases reported a fatal outcome, and 5 cases were medically confirmed. The MAH received more cases with events of heavy menstrual bleeding for individuals who received elasomeran/imelasomeran than those who received elasomeran/davesomeran. For individuals who received elasomeran/imelasomeran, the MAH received 83 cases (114 events) with 8 serious cases (7 serious events). No cases reported a fatal outcome, and 4 cases were medically confirmed. For individuals who received elasomeran/davesomeran, the MAH received 3 cases (3 events) with 1 serious case (1 serious event). No cases reported a fatal outcome and 1 case was medically confirmed. Cumulatively, the majority of the reported events (77 events; 89.5%) were non-serious. The most reported PTs were heavy menstrual bleeding (85) and polymenorrhoea (17). Of the 86 case reports, none of the cases required hospitalization or blood transfusions for heavy menstrual bleeding. Treatment information was provided in 2 cases which included hormone replacement therapy and tranexamic acid. Cumulatively, 83 (96.5%) reports were from regulatory authorities and 3 (3.5%) reports were spontaneously reported to the MAH. Most of the cases were received from the EEA (71; 82.6%) and UK (11; 12.8%). As expected, most cases were reported among women of reproductive age (18 to 49 years of age). When age was reported, 38 cases (60.3%) were reported among women 25 to 49 years of age. There were no reports received in the adolescent group of 12-17 years of age. The mean age was 48.1 years, and the median age was 48.0 years (range: 29.0 to 61.0). Of the 86 cases received, 36 cases reported medical history with pre-existing conditions including COVID-19 infection (32 cases), endometriosis (1 case), polycystic ovaries (1 case), menopause (1 case), rheumatoid arthritis (1 case), epilepsy (1 case), unspecified lung disorder (1 case), and asthma (1 case). In 44 cases (51.2%), the patients had received prior COVID-19 vaccinations with Pfizer-BioNTech COVID-19 vaccine and/or Janssen COVID-19 vaccine. Cumulatively, when the dose number immediately preceding the event was known, more events were reported after Dose 4 (5 events; 83.3%) than Dose 3 (1 event; 16.7%). This data should be interpreted with caution as dose number was not reported in the majority (111 events; 94.9%) of events; and the global vaccine administration/exposure data are limited for the various doses. When time to onset and dose number was known, the average TTO was 8.2 days (SD: 9.4) with a median TTO of 5 days (range: 0 to 30 days). Cumulative data does not present clustering of cases by dose and TTO; however, it is difficult to interpret the TTO without putting it into context of the menstrual cycle including what phase of menstrual cycle vaccination occurred. Most events reported an outcome of Not recovered/ Not resolved"

	(71 events: 60.7%). The remaining events reported outcomes as "Recovered/Resolved" (21 events; 17.9%), "Recovering/Resolving" (12 events; 10.3%), "Unknown" (12 events; 10.3%), and "Recovered/Resolved with Sequelae (1 event; 0.9%). No events reported a fatal outcome. In many cases, key missing information included medical history, concomitant medications, duration of bleeding, number of pads, onset of the event, clinical course, gynaecologic examination, treatment, dechallenge/rechallenge information, and diagnostic studies. According to the WHO-UMC causality assessment, 86 cases were assessed as follows: "Unassessable" (85 cases) and "Unlikely" (1 case). *Serious Events of Heavy Menstrual Bleeding* Cumulatively, 9 serious cases (8 serious cases for elasomeran/imelasomeran and 1 serious case for elasomeran/davesomeran) were reported with events of heavy menstrual bleeding. However, only 7 cases reported the PT "Heavy menstrual bleeding" as a serious event. Two of the serious cases [redacted] and [redacted]) reported the event of "post-menopausal haemorrhage" as the only serious event (both individuals were 51 years of age). The remaining 7 serious cases ([redacted], and [redacted]) reported the PT "Heavy menstrual bleeding" as serious. Of these 7 serious cases, no cases were fatal or medically confirmed. In cases where age was reported, all patients were female between the ages of 29 and 61 years old [median age: 45.0 years old; mean age: 45.4 years (SD: 12.4)]. In the 4 cases that reported medical history, concurrent conditions included COVID-19 infection (4 cases), menopause (1 case), asthma (1 case), and rheumatoid arthritis (1 case). The reported outcomes for these serious events were as follows: "Not Recovered/ Not resolved" (4 events; 50.0%), "Recovered/Resolved" (2 events; 25.0%), "Recovering/Resolving" (1 event; 12.5%), and outcome "Unknown" (1 event; 12.5%). According to the WHO-UMC causality assessment, all 7 serious cases reporting the specific event of heavy menstrual bleeding as serious were assessed as "Unassessable" due to insufficient information. ***B. An updated review of any new literature (e.g., prospective cohort studies) on the risk of HMB following monovalent and/or bivalent Spikevax COVID-19 vaccination.*** Please refer to *Source of New Information* section above. ***C. Any relevant feasibility assessment documents on implementing new or amending ongoing PASS that were prepared for other regulatory agencies (e.g., EMA). A discussion on the need to update the Risk Management Plan to better characterize the risk of HMB following Spikevax vaccination.*** To date, no PASS has been planned for any regulatory agencies. The MAH

	has comprehensively evaluated the topic of HMB previously using all MAH data source as well as the published literature. In the Monthly Summary Safety Report (MSSR) #8, the MAH reviewed all data sources including CT data to investigate the topic of menstrual disorders including HMB. Another comprehensive review was performed in response to the validated signal of "Heavy menstrual bleeding" (EPITT No. 19780). Having considered all the data submitted by MAH for both evaluations, PRAC concluded that the current evidence was insufficient to warrant an update to the produce information at present. Menstrual cycle disorders are challenging to study even in CTs for several reasons. The basic biology of the menstrual cycle is not so basic; it is a complex, coordinated sequence of events involving the hypothalamus, anterior pituitary, ovary, and endometrium. Variation in menstrual cycle duration, timing, and intensity is expected under normal conditions and measures of "heavy menstrual bleeding" are subjective and imply comparison to an individual's baseline. In the absence of consistent capture of data over a pre-vaccination and post-vaccination interval to form a basis for comparison, data following a vaccination event would be difficult to interpret. From a perspective of practicality, these data were not collected in existing trials. Given the serious ethical concern because of the availability of approved vaccines targeting SARS-CoV-2, the existing trials do not have a placebo ann. In setting of expected natural variation in menstruation and the high prevalence of HMB, a control arm is critical because data from an uncontrolled cohort will be difficult to interpret. Concerning the feasibility of including heavy menstrual bleeding in subsequent SARS-CoV-2 clinical studies, the aforementioned concerns remain. Although, HMB is currently captured via unsolicited reporting, sensitivity of the capture of heavy menstrual bleeding could be enhanced by soliciting this adverse event during follow-up. However, it is expected that the impact of solicited reporting might disproportionately increase this subjective measure. In the context of trials, only very large-scale studies capturing a high number of women of childbearing age at points in time that correspond to an etiologically relevant time frame influencing menstrual bleeding could be informative, however, studies of this size no longer have a placebo. Collection of additional placebo-controlled data would present a serious ethical concern given the availability of approved vaccines targeting SARS-CoV-2, and it is unclear how uncontrolled CT data could be interpreted. The MAH considers that there is no need to include HMB in the RMP for Spikevax. The MAH will continue to monitor heavy menstrual bleeding through routine surveillance as well as the ongoing prospective cohort studies that are designed to study heavy menstrual bleeding as an outcome after SARS-CoV-2 vaccination, being conducted by independent by third party investigators (e.g., NIH funded studies conducted by Boston University, Harvard Medical School, John's Hopkins University, Michigan State University, and Oregon

	Health and Science University; (https://www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation) which may yield more timely evidence.
Discussion	The clinical spectrum of events for elasomeran/imelasomeran and elasomeran/davesomeran were similar to data previously reported for elasomeran. Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported heavy menstrual bleeding, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of elasomeran/imelasomeran and elasomeran/davesomeran. Evaluation of the risks of any menstrual disturbance and bleeding following SARS-CoV-2 vaccination in women who are premenopausal or postmenopausal has been discussed in the literature. A nationwide register-based cohort study in Sweden conducted by Ljung et al. concluded that "weak and inconsistent associations were observed between SARS-CoV-2 vaccination and healthcare contacts for bleeding in women who are postmenopausal, and even less evidence was recorded of an association for menstrual disturbance or bleeding in women who were premenopausal. These findings do not provide substantial support for a causal association between SARS-CoV-2 vaccination and healthcare contacts related to menstrual or bleeding disorders" [13]. Of note, Health Canada stated in the Jul 2023 publication of Health Product InfoWatch (received after the DLP of this PBRER) that there were no scientific or medical evidence that vaccination with monovalent mRNA vaccines (Comimaty [Pfizer-BioNTech COVID-19 Vaccine], Spikevax [COVID-19 Vaccine Moderna]) increased the risk of HMB [25].
Conclusion	Information presented in this report does not differ from the known safety profile of elasomeran. elasomeran/imelasomeran and elasomeran/davesomeran. Published clinical literature has not provided substantial evidence for a causal association between SARS-CoV-2 vaccination in relation to menstrual or bleeding disorders and has not described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in regard to the topic of heavy menstrual bleeding. Based on the analysis of all the safety data received cumulatively, the MAH considers that cases included under the medical topic of heavy menstrual bleeding, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran did not raise any new safety issue of concern. The MAH will continue to monitor events for heavy menstrual bleeding using routine surveillance. The benefit-risk evaluation remains positive.

15.2.6 Retinal Vein Occlusion

Table 15.6 Retinal Vein Occlusion

Source of New Information	o Modema GSDB o Literature Sources

	o Search Criteria Applied: Appendix 13.4 o Retrieved: 152 o New and Significant Safety Information: None (0)
Background	During the review period covered by this report, the MAH received a request from a Health Authority regarding the interim CSR for the ongoing mRNA-1273-P304 study, which is a Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls. The request from the health authority stated, "*In the next PSUR, the MAH is requested to provide a cumulative review of retinal vein occlusion, based on data from all sources including the literature.*"
Methods of Evaluation	The Moderna GSDB was queried cumulative from 18 Dec 2020 to 17 Jun 2023 for cases of retinal vein occlusion after elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran using the MedDRA (v.26.0) PTs: retinal vein occlusion, retinal vascular occlusion, retinal occlusive vasculitis, central retinal vein occlusion and branch retinal vein occlusion. There is no Brighton Collaboration case definition for retina vein occlusion (RVO). Therefore, the MAH used the Guidelines for the Management of Retinal Vein Occlusion by the European Society of Retina Specialists (EURETINA) [26] to establish a case definition for RVO. Diagnosis of retinal vein occlusion is based on the retinal examination findings of the following: • Intraretinal hemorrhages • Dilated vein • Cotton wool spots that have been described as a "blood and thunder appearance" for central retina vein occlusion (CRVO). • Macular edema may also be present. Evaluated cases reported for RVO were further graded as: • Level 1: Case of RVO • Level 2: Not a case of RVO • Level 3: Reported case of RVO with insufficient evidence to meet Level 1 or Level 2 of the case definition. The Company causality assessment was conducted using the WHO-UMC standardized case causality assessment.

Results:

Results of the analysis of cases reported for retinal vein occlusion are summarized below. Refer to Appendix 12.13 for additional information.

Cumulatively, the MAH retrieved a total of 146 cases (148 events) of retinal vein occlusion with 140 (95.9%) serious cases (141 serious events) after vaccination with elasomeran. No case had a fatal outcome. There were 89 medically confirmed cases. (Note: A medically confirmed case is a report that is provided by a medically qualified patient, friend, relative or carer of the patient. In

the same way, where one or more suspected ARs initially reported by a consumer are subsequently confirmed by a healthcare professional, the ICSR should be considered medically confirmed.) There were more cases reported in females (79, 54.1%) than males (66, 45.2%), with 1 case (0.7%) having no gender reported. Most of the patients (109; 74.6%) were older than 50 years. The median patient age was 58.0 years (range: 26.0 to 94.0 years). Three cases did not report age.

The majority of case reports were received from regulatory authorities (130, 89.0%), with most of the cases reported from France (27, 18.5%), United States (24, 16.4%), and Germany (18;12.3%).

The most frequently reported events were retinal vein occlusion (134, 90.5%), retinal vascular occlusion (12, 8.1%), and retinal occlusive vasculitis (2, 1.4%).

When dose number and TTO were reported, 82 events reported dose number, with most events occurring after Dose 2 (42, 51.2%) and Dose 3 (22, 26.8%) and most often event typically occurred within 2 weeks of vaccination. For events reported after Dose 3, there were no observed shorter TTO suggesting sensitization. Also, there were no clustering or trends observed. Of note, a total of 66 (44.6%) events were reported without dose number. The average TTO was 26.7 days (SD: 42.1 days) with a median number of days of 10.0 (range: 0 to 300 days).

Of the total 146 reported cases, 100 cases (68.5%) reported medical histories and 41 of these cases reported medical conditions that are risk factors for retinal vein occlusion, including hypertension, diabetes mellitus, oral contraception and smoking, cancer, hyperlipidemia, glaucoma, hypothyroidism, and atheroma.

Cumulatively, as at the time of report, 6 events (4.1%) had resolved, 29 events (19.6%) were resolving, and 77 events (52.0%) were not resolved. Of note, 19 events (12.8%) did not report an outcome.

Of the 146 case reports for retinal vein occlusion, 128 cases (87.7%) did not report funduscopic examination results, making a comprehensive assessment challenging. Two cases without funduscopic results had comorbidities that were confounders including Susac's syndrome (autoimmune endotheliopathy), retinal vascular occlusion, and chorioretinitis.

According to the MAH described case classification, out of the 146 case reports, there were 14 cases (9.6%), all of which provided fundoscopic results, that were classified as Level 1; 1 case (0.7%) was classified as Level 2 as this was not a case of RVO but rather a case of bilateral uveitis and panuveitis with associated occlusive vasculitis in the context of inflammatory bowel disease; and there were 131 cases (89.7%) classified as Level 3, given that there was insufficient information for meet Level 1 or Level 2.

According to the WHO causality assessment the 14 cases classified as Level 1, five cases were assessed as possible, based on temporal association with the use of the product; 5 other cases were assessed as unlikely due to long/short TTO (ranging from 41 to 187 days), pre-existing RVO, (with a long TTO of 41 days and confounded by hypertension and chorioretinopathy) and alternate etiologies that provided plausible explanation for the occurrence of the event. Three cases were assessed as conditional due to missing relevant information including medical histories and clinical course of events needed for proper causality assessment; and one case was assessed as unassessable due to insufficient information, that cannot be complemented. Reported medical conditions that were confounders/risk factors included hypertension, hyperlipidemia, diabetes mellitus, glaucoma, cancers, COVID-19 infection, smoking, hypothyroidism, and atheroma.

There were no cases of retinal vein occlusion reported for elasomeran/imelasomeran and elasomeran/davesomeran.

Discussion

Overall, majority (130; 89.0%) of case reports for RVO had insufficient information for proper assessment. Since most of the reports were by regulatory authorities, information could not be complemented or verified. The median patient age of 58 years is consistent with that reported in the general population. Over two-third of reported cases had medical conditions that are risk factors for retinal vein occlusion, including hypertension, diabetes mellitus, oral contraception and smoking, cancer, hyperlipidemia, glaucoma, hypothyroidism, and atherosclerosis.

A causal relationship could not be established between the cases reported for RVO and elasomeran, due to either insufficient relevant information for proper assessment, pre-existing RVO with a long TTO, comorbidities that were risk factors, and provided alternate etiologies.

While few cases had a temporal relationship from time of vaccine administration to development of reported retinal vein occlusion, these cases were confounded by comorbidities including atherothrombosis, myocardial infarction, atrial fibrillation, diabetes mellitus, previous smoking history and hypothyroidism, that provide plausible alternate etiologies.

Literature search results did not provide evidence of a causal association between retinal vein occlusion and elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran.

Conclusion

Cumulative evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events of retinal vein occlusion and administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in

those reports does not differ from the known safety profile of elasomeran., elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received, the MAH considers that cases included under the medical topic of retinal vein occlusion reported in temporal association with the administration of elasomeran did not raise any new safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events for retinal vein occlusion using routine surveillance. The benefit-risk evaluation remains positive.

15.2.7 Single Organ Cutaneous Vasculitis (SOCV)

The following was noted by a Health Authority:

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

The cases of elasomeran/imelasomeran, [redacted] and [redacted] are both Regulatory Authority cases. The MAH searched the Regulatory Authority database, and no new updated information was available as of the DLP of this PBRER. Please refer to Section 8 for results from the PASS study mRNA-1273-P903 on SOCV.

15.2.8 Haemophagocytic lymphohistiocytosis (HLH)

Table 15.7 Haemophagocytic Lymphohistiocytosis with Possible Involvement of Epstein-Barr Virus (EBV) Reactivation

Source of New Information	o Moderna GSDB o Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 267 o New and Significant Safety Information: None (0)
Background	The MAH received a request from a Health Authority to analyse the topic of HLH: "*It has come to our attention on accumulating literature articles on HLH with COVID-19 vaccines, and more particularly on a new hypothesis of a possible involvement of EBV reactivation. Some case reports describing EBV-positive HLH after COVID-19 vaccination have been recently published [27] [28] [29] [30]. We would like Moderna to discuss HLH in the next PSUR in view of the mentioned literature, but also any other literature/data available on this topic.*"
Methods of Evaluation	A focused search of published literature from PubMed was performed that identified articles including the terms HLH and EBV and any COVID-19 vaccine. In addition, the Moderna GSDB was searched cumulatively for literature reports of HLH and for adverse event reports that noted vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran and involved the MedDRA PT of Hemophagocytic lymphohistiocytosis, as well as EBV infection. This review focused on the hypothesis of a possible involvement of EBV reactivation in HLH, with attention to the HLH-2004 Diagnostic and Therapeutic Guidelines [31].

Scientific Background on HLH and EBV:

Hemophagocytic lymphohistiocytosis is a rare and potentially life-threatening disorder characterized by hyperinflammation caused by uncontrolled activation of immune cells, such as macrophages and lymphocytes [32]. Hemophagocytic lymphohistiocytosis can be triggered by various factors, including infections, genetic mutations [33], or autoimmune diseases. HLH can involve widespread inflammation and tissue damage. It can be classified into primary and secondary HLH. Primary HLH involves genetic mutations affecting the immune system; defects in transport, processing, and function of cytotoxic granules in natural killer cells and cytotoxic T lymphocytes play a role. Secondary HLH can be triggered by various factors, including infections, of which EBV (independent of vaccination) is the most common. In addition, secondary HLH is observed as a complication of malignancies, metabolic disturbances, and rheumatic diseases, such as juvenile arthritis or systemic lupus erythematosus [34]. Patients with HLH often present with persistent fever, hepatosplenomegaly (enlargement of the liver and spleen), and cytopenias (abnormal low levels of blood cells) [35]. This disease can lead to severe organ damage and

multi-organ failure if left untreated. Diagnosing HLH can be challenging due to its heterogeneous presentation and rarity. The HLH-2004 Diagnostic and Therapeutic Guidelines include clinical and laboratory features that were developed to address diagnostic and other challenges [31].

Epstein-Barr virus, also known as human herpesvirus 4, is a common virus belonging to the herpesvirus family. It is one of the most prevalent viruses in humans, having infected about 95% of adults worldwide. Epstein-Barr Virus infects and replicates in B lymphocytes, which are critically important to the immune response. Most people initially infected with EBV will not experience any symptoms or have mild flu-like symptoms, including self-limited infectious mononucleosis. After initial infection, the virus can remain dormant in the body's cells for a lifetime without causing any harm. In a minority of infected persons, EBV and its reactivation may cause, or be associated with, several illnesses including certain types of cancers and HLH. In some cases, especially in individuals with weakened immune systems, EBV infection can lead to severe complications, including death.

Role of EBV in HLH (apart from vaccination)

Epstein-Barr virus is known to play a significant role in some cases of HLH, specifically in the context of secondary or reactive HLH [35]. Epstein-Barr Virus is linked to a greater proportion of HLH cases than any other pathogen. In the case of secondary HLH associated with EBV, the virus can be involved in the triggering of a hyperimmune response. The pathophysiological mechanism of HLH is related to defective function of natural killer (NK) cells and cytotoxic T lymphocytes, resulting in uncontrolled activation of lymphocytes and macrophages that induce excessive production of cytokines, that cause the inflammatory response and characteristic inflammation seen in HLH [36] [37]. The exact mechanisms by which EBV is associated with HLH are not fully understood. The vast majority of EBV infections do not lead to HLH; however, in individuals with a predisposition or underlying immune dysfunction, such as genetic susceptibility to HLH, EBV infection can be a triggering factor for the development of HLH [32].

Results:

Results for hemophagocytic lymphohistiocytosis with possible involvement of EBV reactivation are summarized below. Refer to Appendix 12.14 for additional information, including summary tables of cases and events.

Results from Published Literature

A focused search of published literature from PubMed (see Appendix 13.4) retrieved 267 articles (including the 4 articles noted by the Health Authority). Besides those 4 articles, no new and

significant safety information was noted from the search results. Below please find discussions of the four literature reports noted by the Health Authority.

- **Arand et al [27]:** This brief Letter to the Editor concerns a previously healthy 17-year-old male who had onset of headache, nausea and fever around 7 days after dose 2 of an mRNA vaccine (not further specified.) He tested "negative rapid EBV antibody and COVID antigen" on day 14 after dose 2 and was discharged home. By day 21 he was admitted to hospital and had developed symptoms consistent with HLH, meeting the 2004 HLH definition with fever, splenomegaly, cytopenia, positive bone marrow biopsy with prominent hemophagocytosis without evidence of malignancy, elevated ferritin and low fibrinogen. He also had new onset neck stiffness, dark urine, listlessness, tachycardia and hypotension. His EBV Immunoglobulin M (IgM) assay was highly positive at 54,000 (WNL <500) at hospital admission, indicating primary infection with EBV. Multisystem Inflammatory Syndrome in Children was considered, but there was no recent COVID exposure. Initially suspected to have cold autoimmune hemolytic anemia, he was treated with immune globulin and methylprednisolone; he then clinically stabilized on day 3 of admission. On day 10, his condition worsened with symptom recurrence, splenomegaly, bilateral pleural effusions, worsening cytopenia's, decreased fibrinogenand elevated ferritin. Laboratory testing related to HLH found elevated soluble IL-2, CXCL9, IL18 and CD163, consistent with immune dysregulation. Consequently, treatment was changed to the HLH2004 protocol: oral dexamethasone and IV etoposide. At 4 weeks of therapy EBV levels were undetectable; however, for 6 weeks there was alternation between clinical and laboratory remission and reactivation. Following 8 weeks of etoposide and 12 weeks of steroid treatment, the patient was asymptomatic and in remission.
  MAH Comment: Familial HLH was unlikely due to the whole-exome sequencing finding no causative mutations. Negative COVID-19 antigen test early in the illness and history of lack of recent COVID exposure do not fully rule out COVID-19 infection. The highly positive EBV IgM assay indicated that this case of EBV infection was primary and not a reactivation. Primary infection with EBV, as occurred in this case, can by itself elicit HLH. The authors did not suggest that the mRNA vaccine caused the HLH in this patient but rather that the vaccine may "drive a more complex, protracted clinical course" and that further studies are needed. For this vaccination with an unspecified mRNA vaccine, WHO-UMC assessment for causality of HLH triggered by reactivation of EBV is unlikely because this case involved primary infection with EBV. Primary infection with EBV is a known cause of HLH and can be considered an alternate explanation of the disease in this

case.

- **Lin et al [29]:** This literature case report involves a 14-year-old female with onset of fever, headache and nausea 11 days after dose 1 of BNT162b2; she was hospitalized on day 15 after vaccination. Substantial progression of disease and symptoms then occurred, meeting the 2004 HLH definition with fever, splenomegaly, cytopenia, decreased fibrinogen, elevated ferritin, and positive bone marrow biopsy demonstrating hemophagocytosis. She was initially treated with a dose of IVIG. Although the patient tested positive for EBV, the multiple different types of laboratory assays of EBV were not conclusive with regard to the timing of the infection, and the authors concluded that "Both acute and past infection would be possible according to this serological profile." The nasal swab for the SARS-CoV-2 polymerase chain reaction (PCR) was negative. On day 17 after vaccination, HLH was confirmed, and IVIG and methylprednisolone pulse therapy were given. Venoarterial extracorporeal membrane oxygenation was performed for 3 days due to hypotension, with intubation continuing 5 more days. Intracranial and subarachnoid hemorrhages were observed. The hemogram and the inflammatory biomarkers gradually returned to normal without chemotherapeutic medications. Patient was released from hospital on day 28. Steroid therapy duration was about 5 weeks. Laboratory tests to assess the possibility of familial HLH were not done due to their not being available at the authors' hospital.

  MAH Comment: With regard to treatment, it is unclear why this patient's fulminant HLH was not treated with the addition of more aggressive therapy, such as etoposide, rather than only steroids and IVIG. Also unclear is whether the patient's EBV infection was primary or reactivation; although the authors performed multiple laboratory tests for EBV, the test results did not permit them to determine this important information. The observed serological profile was consistent with either primary or reactivation of EBV. In addition, the authors stated that they could not exclude the possibility that their patient had familial HLH because they were unable to perform the necessary tests. For reasons of missing important information, WHO-UMC causality assessment is unassessable for BNT162b2 causing HLH with EBV reactivation.
- **Tanaka et al [28]:** This article concerns a 79-year-old male with a history of Hodgkin lymphoma (EBV RNA positive) ten years prior that was treated with chemotherapy and resulted in remission. Past history also included schistosomiasis. He was admitted to hospital about 2 weeks after dose 1 of BNT162b2, with fever since the day after vaccination. During his hospital course he met the 2004 HLH definition with fever,

splenomegaly, high soluble IL2R, high ferritin and low neutrophils. "Hypoplastic marrow was observed on bone marrow examination, but there were no findings suggestive of lymphoma infiltration or leukemia, and only marginally hemophagocytosis images were observed". This bone marrow biopsy report does not strongly support the diagnosis of HLH, and the authors noted the patient's condition was similar to EBV-NK-LPD and CAEBV (EBV in CD56+ NK cells). The authors noted that identification and analysis of infected cells in peripheral blood suggested monoclonal proliferation because EBV was only present and proliferated in CD56-positive NK cells. The patient was treated with prednisolone starting day 8 of hospitalization with defervescence, but on day 20 fever recurred and high dose IVIG was added, with no improvement. On hospital day 31 the chemotherapeutic agent etoposide was added with some benefit, but neutropenia led to discontinuation of etoposide and to starting of filgrastim. After blood cell count recovery, etoposide was restarted on day 44, but the primary disease was not controlled, and the patient died 10 days later with Acute Respiratory Distress Syndrome (ARDS).
MAH Comment: The past medical history of Hodgkin lymphoma positive for EBV RNA is a strong confounder in this case. In this regard, the authors stated "even after remission, a constant, subclinical amount of EBV-infected cells was observed." In addition, age-related immune senescence is likely to have played some role in this AE. Moreover, the authors did not rule out malignant disease in this case. WHO-UMC causality is possible for a BNT162b2 role in this case of HLH-like illness with EBV reactivation. The confounding factors noted above do not permit an assessment of probable causality.

- **Tang and Hu [30]:** This Letter to the Editor reported a 43-year-old female [redacted] who developed "malaise, vomiting, and persistent high fever (up to 39.7 °C) shortly after receiving the first dose of the inactivated [not mRNA] SARS-CoV-2 vaccine." Treatment with antibiotics and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) was ineffective. The patient was reported as having been healthy, with no remarkable medical history or recent medication intake. She was admitted to hospital on day 8. She met the 2004 HLH definition with cytopenia, fibrinogen, low NK cell activity, positive bone marrow biopsy showing hemophagocytosis and elevated ferritin. Laboratory testing showed EBV reactivation and elevated levels inflammatory factors hsCRP, sCD25, IL-1beta, IL-6, IL-8 and IL-10. Testing for genes related to familial HLH identified none. She was immediately treated with dexamethasone, and the signs and abnormal laboratory results resolved gradually; the patient was discharged on hospital day 17.

MAH Comment: This case does not involve mRNA vaccination against Covid-19, but rather inactivated SARS-CoV-2 vaccine. The specific antibiotics and NSAIDS which the patient was prescribed were not reported. The medications were taken at a time when the patient may have had a viral illness or reactogenicity to the vaccine. Given this missing information concerning medication just prior to the diagnosis of HLH, the WHO-UMC causality for this inactivated SARS-Cov-2 vaccine is possible, but not probable, due to temporal association.

Considering together the articles summarized above, with regard to reactivation of EBV the two adult patients had reactivation; in contrast, one of the adolescents had primary EBV infection, and the testing of the other adolescent patient did not clearly indicate primary infection or reactivation. In addition, in the elderly patient with reactivation, the history of treated Hodgkin lymphoma that was positive for EBV RNA provides an important potential contributory factor to his reactivation of EBV. In addition, these four cases taken together do not demonstrate a clear pattern about age, gender, or reactivation of new EBV infection vs primary infection. Further, the vaccines involved were BNT162b2 (two patients), an unspecified mRNA vaccine and inactivated [not mRNA] SARS-CoV-2 vaccine; none of these literature case reports noted vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran.

Literature Reports of HLH in ModernaTx, Inc GSDB

In an additional step, the MAH searched its own GSDB for literature reports of HLH. Five literature case reports of HLH were identified in the GSDB; none of these case reports noted the presence of EBV infection.

Review of Individual Case Safety Reports from ModernaTx, Inc GSDB

Cumulatively, the MAH received reports of 36 cases (36 events) of HLH involving elasomeran (35 cases) and elasomeran/imelasomeran (1 case;) no cases involving elasomeran/davesomeran were reported. A total of 36 serious cases (36 serious events) and 4 cases with a fatal outcome were reported. There were 34 medically confirmed cases. Of these 36 reports of HLH, presence of EBV infection was noted in only 3 HLH case reports. Descriptions of these 3 cases follow.

[redacted] **(WWID#** [redacted]**:** This case concerns a 53-year-old male with no reported past medical history or reported concomitant medications. Concurrent medical conditions were Hepatitis B core antibody positive. The day of his second vaccination (4 to 6 hours later), the patient developed fever, fatigue, cough, abdominal discomfort, and shortness of breath. Eight to 14 days later there was progression to thrombocytopenia, encephalopathy, renal failure,

hypertriglyceridemia, hepatosplenomegaly, respiratory failure, and EBV-viremia. Laboratories demonstrated elevated cytokines, normal NK cells, high ferritin level and bone marrow biopsy which showed rare evidence of what looked like erythrocytes in the cytoplasm of cells (type not reported). Because of the EBV-viremia, the patient was treated with rituximab and steroids. Because of worsening condition with renal and respiratory failure, the patient was intubated and received dialysis. He was treated with Anakinra and ultimately extubated but was still on dialysis as of this report with encephalopathy of unknown origin. MRI of head was normal. The cause of HLH and other events was not reported. The patient met 2004 criteria for HLH with 5/8 met (fever, hepatosplenomegaly, high ferritin, hypertriglyceridemia, and rare hemophagocytosis "concerning for HLH.").

MAH Comment: Interpretation of this case is hindered by the lack of information on medications, past medical history and possibility of Hep B infection. The temporal association with vaccination, but the lack of the information noted directly above, lead to WHO-UMC causality assessment: possible.

[redacted] **(WWID#** [redacted]**:** This case concerns an 80-year-old male with a medical history that included EBV associated lymphoproliferative disorder in Aug 2014 and Angioimmunoblastic T-cell lymphoma (Stage 4B) treated and reported in complete remission in Aug 2018. At an unspecified time after an unspecified vaccine, the patient had EBV-associated lymphoproliferation after an infection. Current medical conditions only reported as GERD with no reported concomitant medications. On 21 Jan 2021 and 18 Feb 2021, the patient received the 1st and 2nd doses of elasomeran After the 1st dose there was slow deterioration of reported condition that became worse after the 2nd with hospitalization on 27 Mar 2021 (66 days post-first and 39 days post-second vaccination). The diagnosis was macrophage activation/HLH with EBV-positive proliferation. The 2004 HLH criteria [31] were met with fever, splenomegaly, cytopenia, hypertriglyceridemia, and hyperferritinemia (5/8). There was no bone marrow exam reported. The patient was treated with rituximab and high dose methylprednisolone with positive results resulting in the steroids being stopped but rituximab as maintenance therapy was continued.

MAH Comment: The case is confounded by age (possible immune senescence), the past history of angioimmunoblastic T-cell lymphoma and past history of EBV associated lymphoproliferation. WHO Causality Assessment is possible. It is not considered probable because of these confounders.

[redacted] **(WWID#** [redacted]**:** This case concerns a 19-year-old male with a medical history of graft rejection and kidney transplant in 02 Jul 2016

without any other information on past medical history, current medical history, past medications, or present medications. On 02 Apr 2021, he received the 1st dose of elasomeran and on 15 Apr 2021, he developed HLH and EBV reactivation and was hospitalized. There are no reports of laboratories or treatments. However, as of 10 Mar 2023, the patient had recovered from both HLH and EBV reactivation. No further information is available. There is not enough information to confirm HLH criteria, and causality cannot be determined. Assessment of this case is hindered by the lack of past medical history, especially the kidney transplant and graft rejection. Given the history of kidney transplantation and graft rejection, it is likely that at the time of vaccination the patient was receiving immunosuppressive medications that may predispose to EBV reactivation; however, there is neither concurrent medical history nor concomitant medications reported.

MAH Comment: The critically important missing information noted directly above leads to WHO-UMC causality assessment: Unassessable.

Overall assessment of the HLH case reports from GSDB involving EBV

All three cases involved elasomeran, as is clear from the vaccination dates. All were male, and their ages varied widely: 19, 53 and 80 years. No clear pattern in TTO or dose number prior to the AE was observed. Drawing inferences from these cases is challenging due to the limited information in the reports and the small number of events. In addition, the history of angioimmunoblastic T-cell lymphoma in the 80-year-old male; and the history of graft rejection and kidney transplantation in the 19-year-old male; and the possibility of Hep B infection in the 53-year-old provide evidence of non-vaccine explanations for the patients' illnesses. These cases do not together constitute a clinical pattern supporting correlation between EBV-related HLH and elasomeran.

Discussion

The literature reports reviewed above, as well as the small number of ICSRs in the MAH's GSDB that involve HLH and EBV, do not support the hypothesis that mRNA vaccination against Covid-19 promotes HLH with reactivation of EBV. The small number of AE reports in the MAH's GSDB that note both HLH and EBV infection provide limited information and are confounded by important pre-existing medical conditions that can predispose to HLH with EBV; in addition, none of these reports involved bivalent vaccine. Moreover, there is an absence of direct evidence of a mechanism to explain the hypothetical association of vaccination against Covid-19, EBV reactivation and HLH. In any event, given the billions of doses of mRNA vaccines administered worldwide, such AEs are extremely rare occurrences.

Conclusion

Evaluation of the cumulative data does not suggest an association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran. Information presented in those reports does not change the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Based on the analysis of all the safety data received during the reporting period, the MAH considers that cases included under the medical topic of HLH, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran did not raise any safety issue of concern, and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events for HLH using routine surveillance. The benefit-risk evaluation remains positive.

15.3. Other Safety Topics

15.3.1 Postural orthostatic tachycardia syndrome (POTS)

Table 15.8 Postural orthostatic tachycardia syndrome

Source of New Information	o Moderna GSDB
	o Evaluation of cases of POTS is presented in this PBRER, cumulative as of 17 Jun 2023, given that the observed number of cases was higher than the expected number of cases. In the observed to expected analyses, the lower bound of 95% confidence interval of rate ratio was > 1 for the 40-49 years and the 50-64 years subgroups.
	o Literature Sources
	  o Search Criteria Applied: Appendix 13.4
	  o Retrieved: 96 articles
	  o New and Significant Safety Information: None (0)

Background	Postural orthostatic tachycardia syndrome is a chronic and often disabling disorder characterized by orthostatic intolerance with excessive heart rate increase without hypotension during upright posture. Patients often experience a constellation of other typical symptoms including fatigue, exercise intolerance and gastrointestinal distress. A typical patient with POTS is a female of child-bearing age, who often first displays symptoms in adolescence. The onset of POTS may be precipitated by immunological stressors such as a viral infection. A variety of pathophysiologies are involved in the abnormal postural tachycardia response; however, the pathophysiology of the syndrome

	is incompletely understood and undoubtedly multifaceted [38]. The prevalence of POTS is based largely on clinical experience, ranging from 0.2% and 1% of the US population, which would suggest approximately 1–3 million affected persons [39] [40] [41]. Most patients present with POTS between the ages of 12 to 50 years old and more than 75% are female (F:M ratio > 4:1). POTS is also common in patients with chronic fatigue syndrome [41]. The cause of this condition remains unclear. Although there is a consensus clinical definition for POTS, misdiagnosis is common. The syndrome is heterogeneous in the sense that the spectrum of clinical features varies among patients, multiple etiologies may produce similar clinical phenotype and there is overlap with other clinically defined syndromes. The clinical evaluation of patients with suspected POTS is not standardized, nor are treatment approaches. There is a lack of familiarity with POTS in the medical community, and the epidemiology of the disorder and natural history are not known [42]. According to Sheldon et al., POTS is a clinical syndrome usually characterized by (1) frequent symptoms that occur with standing, such as light-headedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue; (2) an increase in heart rate of ≥30 beats per minute (bpm) when moving from a recumbent to a standing position (or ≥40 bpm in individuals 12 to 19 years of age); and (3) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure). The symptoms associated with POTS are those that occur with standing, such as light-headedness and palpitations; not associated with particular postures, such as bloating, nausea, diarrhea, and abdominal pain; and systemic, such as fatigue, sleep disturbance, and migraine headaches. The standing (or orthostatic) heart rate of individuals with POTS is often ≥120 bpm and undergoes greater increases in the morning than in the evening. The increases in orthostatic heart rate gradually decrease with age and not abruptly at age 20. Many patients with POTS faint occasionally, although presyncope is much more common. It is important to note that the diagnoses of POTS and vasovagal syncope are not mutually exclusive. In addition, POTS has been found to overlap with or occur in certain conditions such as migraine, hypermobile Ehlers-Danlos syndrome (hEDS), mast cell activation syndrome (MCAS) or chronic fatigue syndrome (CFS), inappropriate tachycardia syndrome and some other forms of orthostatic intolerance such as neurocardiogenic syncope [43]. Amyloidosis, Sjogren's syndrome, multiple sclerosis, mast cell activation disorders and hypermobility syndrome (Ehlers-Danlos syndrome type III) are other diseases associated with or thought to cause POTS. This subset of POTS patients commonly reports episodes of flushing, urticaria, dyspnea, headache, excessive diuresis, and gastrointestinal symptoms such as diarrhea, nausea, and vomiting, which may be accompanied by elevated urine methylhistamine or 11-ß-Prostaglandin F2 excretion or elevation of other mast cell mediators [44]. Some researchers have suggested that there is a neuropathic basis underlying at least half of patients with POTS and found that about 1:7 of patients studied had ganglionic acetylcholine receptor antibodies suggesting an autoimmune etiology for this proportion of patients with POTS. Several mechanisms have been described in patients with POTS, including autonomic

	denervation, hypovolemia, hyperadrenergic stimulation, deconditioning, and hypervigilance, which is a careful and at times unusual focus on bodily sensations. These mechanisms often appear to co-exist in patients with POTS. The onset of POTS may be precipitated by a typical immunological stressor such as viral syndrome (often upper respiratory or gastrointestinal and for example, with EBV), physical trauma (such as concussion), menarche, pregnancy, or surgery and autoimmunity as with paraneoplastic conditions in small cell lung and pancreatic cancers as well as with autoimmune autonomic neuropathy. An antecedent history of suspected viral infection is reported in 20–50% of patients [45]. The presentation seems to have two patterns – acute onset after one of the above triggers or with slowly progressive symptoms over a longer period of time [46]. Significant symptomatic recovery has been reported by a subset of patients, but a majority report chronic symptoms with recurrent exacerbations. POTS is now known as one of many possible features of post-acute COVID-19 syndromes that can develop after SARS-CoV-2 infection. While the acute impacts of COVID-19 were the initial focus of concern, it is becoming clear that in the wake of COVID-19, many patients are developing chronic symptoms that have been called Long-COVID. Some of the symptoms and signs include those of POTS [47]. Commonly described symptoms of Long-COVID include some combination of breathlessness, palpitation, chest discomfort, fatigue, pain, cognitive impairment ("brain fog"), sleep disturbance, orthostatic intolerance, peripheral neuropathy symptoms (pins and needles, and numbness), abdominal discomfort, nausea, diarrhea, joint and muscle pains, symptoms of anxiety or depression, skin rashes, sore throat, headache, earache and tinnitus. These symptoms, when combined with excessive orthostatic tachycardia, can lead to a diagnosis of POTS post-COVID-19 [47]. The United Kingdom National Institute for Health and Care Excellence (NICE) has defined various symptomatic phases of COVID-19 [48]. These include: • "Acute COVID-19" which includes signs and symptoms up to 4 weeks following onset of illness • "Ongoing symptomatic COVID-19" for signs and symptoms of COVID-19 from 4 to 12 weeks after the onset of illness • "Post-COVID-19 syndrome" for signs and symptoms that develop during or after an infection consistent with COVID-19, continue for> 12 weeks and are not explained by an alternative diagnosis • "Long-COVID" that includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Given that SARS-CoV-2 infection can trigger POTS and other cardiovascular dysautonomia's, it has been hypothesized that COVID-19 infection might be a potent immune trigger that evokes an autoimmune response in susceptible individuals [49]. The post-COVID-19 cardiovascular autonomic dysfunction can affect global circulatory control, producing not only a POTS-like pattern but also tachycardia at rest, blood pressure instability with both hypotension and hypertension, and local circulatory disorders such as migraine, coronary microvascular dysfunction, or Raynaud-like symptoms. Microvascular dysfunction with inadequate regional microvascular and

	macrovascular responses, such as vasospasm and circulatory mismatch between local oxygen demands and supply, and venous retention leading to pooling and reduced venous return after standing, might explain the plethora of symptoms that are frequently observed in POTS. There are sparse reports suggesting that microvascular dysfunction is an important mechanism of post-COVID-19 complications. All these dysautonomic phenotypes might coexist, and, more importantly, they preferentially affect young and middle-aged women, possibly suggesting a genetic predisposition and/or a mechanistic role for sex hormones. Of note, POTS is extremely rare among either prepubertal girls or postmenopausal women. There have been reports of POTS in the medical literature, from Japan, Korea, and the US, about new onset POTS in previously healthy people who had recently received a messenger RNA (mRNA) COVID-19 vaccine. A large cohort study [50] identified a possible association between COVID-19 vaccination and POTS as well as a much stronger link between SARS-CoV-2 infection and POTS. Kwan AC et al. used a retrospective cohort of patients who received at least one dose of COVID-19 vaccine in the Cedars-Sinai Health System in US from 2020 to 2022, to compare odds of POTS diagnosis identified by International Classification of Diseases (ICD) codes in the outpatient encounters within 90 days post the first dose of COVID-19 vaccine with odds of POTS 90 days pre-vaccination in a sequence symmetry analysis (SSA). Similar analyses were conducted for myocarditis, common primary care (CPC) diagnoses, and post Dose 2 in the vaccinated cohort and another retrospective cohort of patients with SARS-CoV-2 infection. The authors found the post-Dose 1 odds of new POTS-associated diagnoses (1.33, 95% confidence interval=1.25–1.41) was slightly higher than for CPC diagnoses (odds=1.21, 95%CI=1.18–1.23) in the vaccinated cohort, and post-infection odds of new POTS-associated diagnoses (1.52, 95%CI=1.33–1.72) was slightly higher than that for CPC diagnoses (odds = 1.40, 95%CI=1.31–1.50) in the infected cohort. Although this single medical center study identified a slightly elevated risk of receiving a POTS diagnosis after COVID-19 vaccination, the interpretation of the results requires caution given the following limitations, and additional studies are required to verify the association as the authors recommended. First, the primary analysis was restricted to vaccinated persons and consequently may have had bias away from the null because people who experienced POTS may have delayed or may not have received a COVID-19 vaccine, violating a key assumption of the SSA analytic methodology (i.e., the event of interest [POTS] does not alter the probability of subsequent exposure [vaccination]). No distribution of POTS diagnoses pre- and post-vaccination is presented to evaluate. Healthy vaccinee effect, however, was reflected by the also elected OR for CPC diagnoses. The authors attempted to address this bias by reporting the crude ratio of ORs between POTS diagnosis and CPC diagnosis (1.10, 95%CI 1.03–1.17). However, such estimate was likely confounded, and the significance was likely driven by the large sample size. Second, the authors acknowledged that "the lack of a standard single ICD code for capturing a formal diagnosis of POTS can lead to overlap with other medical conditions and variation in the application of available ICD codes". Moreover, POTS

	diagnoses were not fully adjudicated and are subject to outcome misclassification, as the author mentioned "a significant degree of non-POTS diagnoses were captured within our ICD codes". The degree of misclassification pre- and post-vaccination may not necessarily be non-differential because diagnostic vigilance of POTS may be intensified after vaccination, biasing the association away from the null; moreover, symptoms associated with common vaccine reactogenicity such as fever and fatigue might lead to patient complaints that overlap some POTS criteria. Furthermore, it was unclear how "new diagnosis" of POTS was identified and whether patients with a previous code related to POTS were included in the analysis and whether the distribution differed in the pre- and post-vaccination events, biasing the association in either direction depending on the distribution of prevalent events. Third, the OR estimates and ratios of ORs were crude without adjustment for confounding. The confounding distribution, such as risk factors for POTS, may be different in events that occurred pre and post vaccination. Fourth, diagnosis of POTS, as noted above, requires a three-month duration of symptoms; however, the authors did not confirm this important temporal aspect, relying instead on ICD codes that are not specific for POTS and may only represent acute diagnoses. In summary, POTS is a chronic multi-system disorder involving the autonomic nervous system that is characterized by an exaggerated sinus tachycardia, and symptoms upon standing. POTS primarily affects females starting around puberty and through their child-bearing age and is associated with significant functional disability, such as decreased ability to participate in education, limited ability to work and generate an income, and decreased quality of life. The pathophysiology is incompletely understood, which is likely responsible for limited data on effective treatments. Postural tachycardia syndrome cases associated with COVID-19 infection have been reported, as well as cases occurring after COVID-19 vaccination.
Methods of Evaluation	The Moderna GSDB was queried cumulative to 17 Jun 2023 for valid case reports received from HCPs, HAs, consumers, and literature worldwide, for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, using the MedDRA PT of "Postural orthostatic tachycardia syndrome". Identified cases were evaluated according to the latest case definition presented by Vernino et al., [38] as part of the National Institute of Health Expert Consensus meeting of 2019, based on the different previous definitions by major international neurologic, autonomic, cardiac and pediatric societies [51], [52], [41] as requiring: • **Confirmed**: o A sustained HR increment of not less than 30 beats/minute within 10 min of standing or head-up tilt. For individuals who are 12 to 19 years old, the required HR increment is at least 40 beats/minute; **and** o An absence of orthostatic hypotension (i.e., no sustained systolic blood pressure drop of 20 mmHg or more); **and** o Frequent symptoms of orthostatic intolerance during standing, with rapid

	improvement upon return to a supine position. Symptoms may include light-headedness, palpitations, tremulousness, generalized weakness, blurred vision, and fatigue; and o Duration of symptoms for at least 3 months; **and** o Absence of other conditions explaining sinus tachycardia such as anorexia nervosa, primary anxiety disorders, hyperventilation, anemia, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, use of cardioactive drugs (e.g., sympathomimetics, anticholinergics) or severe deconditioning caused by prolonged bed rest. • **Unassessable**: A reported event of POTS with insufficient evidence to meet the case definition. • **Not a Case**: Alternative diagnosis for the described events. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.

Results:

Refer to Appendix 12.15 for additional information, including summary tables of cases and events, case evaluations, and additional analyses.

Cumulatively, through 17 Jun 2023, a total of 157 cases (159 events), 105 serious cases (81 serious events) with the reported term of POTS have been received for all the elasomeran vaccines, including the two bivalents. A total of 96 cases were medically confirmed, and no case report noted a fatal outcome. The majority of cases involved females (121 cases, 77.1%) than males (34 cases, 21.7%); 2 cases (1.3%) did not include gender information. Of these, 151 cases were reported for elasomeran (mean age: 38.5 years old [SD 12.8]; median age: 36 years old [16 to 82 years old]) and 3 cases each for elasomeran/imelasomeran (mean age 27 years [SD 0]; median age 27 years old) and elasomeran/davesomeran (mean age: 44.5 years old [SD 29]; median age: 44.5 years old [24 to 65 years old]). Of note, a total of 85 events (53.5%) events were reported with insufficient information to determine dose number. Most of the events (67; 42.9%) were reported within 7 days after vaccination regardless of dose number.

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

Out of the 157 cases reported cumulatively as of 17 Jun 2023:

- For Elasomeran (151 cases):
  - There were 12 cases that were considered new onset cases (including one case for possible new onset) based on the information provided. Out of those, there were

5 reports considered possibly related to the vaccine due to temporal association, as well as the absence of other conditions that may explain the symptoms presented by the patients; however, some important information was missing including full clinical course and information on any confirmatory testing that may have been conducted. There were 4 reports considered unlikely, two based on a TTO of hours after the 1st dose of elasomeran (TTO too short), as well as concurrent medical history of Long-COVID in two of the reports. There were 3 cases that were unassessable based on the lack of important information regarding medical history, final test results, etc.

- There were 17 cases that were considered as possible flares of POTS given their previous medical history of POTS. Out of those, 1 case was considered possibly related to vaccination, given the recurrence of symptoms the same day after receiving a 3rd dose with elasomeran. In this report, most of the POTS symptoms experienced by the patient can also be confounded by expected reactogenicity events like nausea, pyrexia, dizziness, etc. There were 11 reports that were considered unlikely related to the vaccine given a recent history of COVID-19 infection, ongoing Long-COVID, other autoimmune conditions, including CFS, Ehlers-Danlos syndrome, among others; a short TTO (same day after vaccination) and concurrent amphetamine use and polypharmacy. There were 3 reports that were unassessable due to missing important information needed to perform causality assessment. The causality in 2 other reports was not applicable as these were not representative of true POTS cases based on the available details (one case described symptoms likely of anaphylaxis and the other for vaccine reactogenicity).
- There were 13 reports that were not considered new onset cases based on the description of the symptoms, but previous medical history of POTS was missing. Out of those, 3 were considered unlikely related to the vaccine due to concurrent medical history that provided a more plausible explanation for the occurrence of the reported events, including COVID-19 infection, Ehlers-Danlos syndrome; one case was diagnosed as an atypical case of GBS. In 5 reports, causality was unassessable due to important missing information. The causality in 5 other reports was not applicable as these were not true POTS cases.
- In a further 23 reports, the causality was assessed as unlikely related to the vaccine as alternative etiologies were suspected that provide a more plausible explanation of the reported events (post/Long-COVID setting, concurrent EBV, RSV other acute viral

infections, co-morbidities some having known association with POTS, migraine, celiac disease, mast cell activation syndrome, concomitant use of lurasidone [orthostatic hypotension, tachycardia, syncope, dizziness are listed events; Latuda (lurasidone) SmPC], polypharmacy), etc. Few of these cases involved a time to drug intake which makes the causal relationship improbable (short TTO, same day of vaccination or delayed latency (5 months or more)) or involved a misdiagnosis.

- There were another 85 cases that were unassessable based on the lack of information including medical history, clinical course of the condition, any testing (laboratory or diagnostic) conducted, and in some instances dose number and TTO, important to establish causal association with the vaccine.
- The causality in 1 another case was not applicable as this was not a true POTS case (hyperthyroidism in a patient with recent chemotherapy).

- For elasomeran/imelasomeran (3 cases)
  - There were 3 reports, and all were considered unassessable as a case according to the case definition as well as causality assessment. One report described a possible flare-up of pre-existing POTS, however, the latency information is unknown. Important information was missing for all the case reports.
- For elasomeran/davesomeran (3 cases)
  - There have been 3 reports, which were all considered unassessable as a case according to the case definition as well as causality assessment. Important information was missing for these case reports.

There have been no new significant safety findings related to POTS from the ongoing clinical development program for elasomeran, elasomeran /imelasomeran and elasomeran/davesomeran.

Discussion

Evaluation of cases of reported POTS is presented, cumulative as of 17 Jun 2023, given that the observed number of cases were higher than the expected number of cases. In the observed to expected analyses, the lower bound of the 95% CI of the rate ratio was > 1 for the 40-49 years and the 50-64 years subgroups. Cumulatively, there were 157 cases reports for individuals that had been vaccinated with one or more doses of elasomeran (151 cases; 96%), elasomeran/imelasomeran (3 cases; 2%) and elasomeran/davesomeran (3 cases; 2%).

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

A large number of POTS-related events identified in the GSDB included some of these conditions as part of their concurrent medical history, including EBV, RSV infections, hypermobile Ehlers-Danlos syndrome, CFS, mast cell activation syndrome, as well as recent history of COVID-19 infection as well as diagnosis of Long-COVID.

Based on the total number of doses administered estimated (as of 17 Jun 2023), the reporting rates for cases reported as POTS in the GSDB per million doses administered of elasomeran is 0.2 cases; for elasomeran/imelasomeran is 0.04 cases and elasomeran/davesomeran is 0.02 cases. There have been no reports with a fatal outcome.

Furthermore, while some cases had a plausible temporal relationship from time of vaccine administration to development of reported POTS event, no consistent or independent risk factors were identified in any of the cases that could support a causal association with administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical

literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

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

16. SIGNAL AND RISK EVALUATION

16.1. Summaries of Safety Concerns

Table 16.1 provides the Summary of Safety Concerns as per RMP v6.3 approved on 15 Dec 2022 in place at the beginning of the reporting period.

Table 16.1 Summary of Safety Concerns valid at the beginning of the reporting period (as per RMP v6.3 approved 15 Dec 2022)

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

During the reporting period, the Spikevax RMP v6.3 was updated to v6.4 (not approved) to include the proposed indication for the US vaccine elasomeran for individuals 12 years of age and older and updated studies mRNA-1273-P903, mRNA-1273-P904, mRNA-1273-P911 and mRNA-1273-P910 as per Part III with no changes to the list of safety concerns.

Further v6.3 was updated to v6.5 (approved on 26 May 2023) to include the proposed indication and posology for Spikevax bivalent BA.4-5 for individuals 6 years of age and older. Risk

Management Plan v6.5 was updated to v6.7 (endorsed on 20 Jul 2023) with no additional changes to the list of safety concerns. Additionally, v6.3 was updated to v7.0 (endorsed by PRAC after the DLP of this PBRER, on 06 July 2023) to update the list of safety concerns by removing VAED including Vaccine-Associated Enhanced Respiratory Disease (VAERD) as an important potential risk, and use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns, as missing information. Also, v7.0 was updated to include mRNA-1273-P910 for pericarditis and study details for mRNA-1273-P901, mRNA-1273-P910 and mRNA-1273-P919 in Part II.C.2 as per Part III update. Of note, a consolidated Spikevax EU RMP v7.1 including all versions endorsed/approved by PRAC/CHMP (v6.5, 6.7 and 7.0) received positive opinion by CHMP on 21 Jul 2023 and the opinion was adopted within procedure EMEA/H/C/005791/II/0104/G by European Commission on 11 Aug 2023 after the DLP of this PBRER.

Table 16.2 Summary of Safety Concerns valid at the end of the reporting period (as per RMP v6.5 approved 26 May 2023)

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

16.2. Signal Evaluation

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

Four signals were closed by the MAH during the reporting period. Based on scientific evaluation of the available information, all the four closed signals were refuted [Amenorrhea (re-evaluation), Diarrhea (re-evaluation), Pemphigus and pemphigoid and IIM/ Myositis] by ModernaTx, Inc.

16.2.1 Amenorrhea (re-evaluation)

The topic of "Amenorrhea" was evaluated by the MAH as two signals. The first signal ("Amenorrhea") was triggered by Pharmacovigilance Risk Assessment Committee (PRAC) Signal EPITT 19781 and closed on 30 Mar 2022. The second signal ("Amenorrhea [Re-evaluation]") was triggered by the PRAC's request to provide an updated analysis of Amenorrhea in PBRER#4, which the MAH considered a validated signal. This signal was closed by the MAH on 25 Jan 2023, during the reporting period of this PBRER, hence included here again for completeness. Please find below a tabular summary to clarify when these two signals were presented in PBRERs.

Table 16.3 Amenorrhea (re-evaluation)

Signal	Date Detected	Date Closed By MAH	PRAC Signal Details	Presented in PBRER#
Amenorrhea	14 Feb 2022	30 Mar 2022	EPITT 19781 Trigger for MAH signal (PRAC Meeting 07-10 Feb 2022) EPITT 19781 signal was closed by PRAC in Jun 2022 (PRAC Meeting 07-10 Jun 2022)	**PBRER#3** (signal closed by MAH, presented in Section 16 of PBRER#3, signal evaluation report appended to PBRER#3).
Amenorrhea (Re-evaluation)	13 Jun 2022	25 Jan 2023	Not a signal for PRAC. As an outcome of closed EPITT 19781, PRAC requested MAH to provide an updated analysis in PBRER#4. This was the trigger for MAH to open a "re-evaluation" signal.	**PBRER#4** (signal ongoing by MAH, signal not presented in Section 16.2 of PBRER#4, signal evaluation report not appended to PBRER#4. The updated analysis requested by PRAC was submitted to PRAC separately) **PBRER#5** (signal closed by MAH, presented in Section 16.2.1, signal evaluation report appended to PBRER#5 [same content as the updated analysis submitted separately to PRAC]).

16.2.2 Pemphigus and pemphigoid

Table 16.4 Pemphigus and pemphigoid

Signal evaluation criteria	Summary
Source	On 01 Dec 2022, the MAH received a request from the PRAC for a signal assessment

Signal evaluation criteria	Summary
	(EPITT No. 19860) including a cumulative review of all evidence concerning the association between pemphigus and pemphigoid and vaccination with Spikevax (Moderna Biotech Spain S.L.): • *Review from information from post-marketing cases reporting pemphigus or pemphigoid, CTs and relevant scientific literature.* • *Perform a causality assessment of all cases of pemphigus and pemphigoid using the WHO-UMC causality assessment criteria, including a clear breakdown of all cases identified. Justification of causality category should be given for each case. A discussion of cases assessed as WHO Possible, Probable or Certain should be presented.* • *MAH responses to a list of questions (e.g., WHO-UMC causality assessment; potential reporting patterns (gender, age, TTO), risk factors, seriousness, treatment of ADR and outcome; tabular presentation of cases; literature review regarding plausibility and Mechanism of action overview of PT Dermatitis bullous and other related terms within HLT Bullous conditions for identification of pemphigus/pemphigoid cases; O/E analyses with a risk window of 28 days).* • *In addition, to account for all possible cases of blistering conditions, the MAH should provide an overview of the HLT Bullous conditions including cases of various blisters especially outside of administration site and the Important medical event PT dermatitis bullous. Case reports likely describing pemphigus/pemphigoid should be presented with the same level of details as mentioned above.* • *Including the need for potential amendment to the product information and/or risk management plan should be provided by 09 Feb 2023.*
Background	Pemphigus/ pemphigoid represents a group of autoimmune blistering/bullous disease of skin and/or mucous membranes; antibodies (mainly IgG) are formed against adhesion molecules (desmoglien) on the cell surface of keratinocytes; Clinically presents as erosions on mucosal surfaces (blisters), generalized; acantholysis (loss of intercellular connections/integrity); Treatment for the condition usually includes Rituximab, corticosteroids, adjuvant corticosteroid-sparing immunosuppressants (azathioprine, cyclosporine, mycophenolate mofetil, etc.). **Main types:** Pemphigus Foliaceus (PF)–Mostly limited to skin; Pemphigus vulgaris (PV) – Mucosal erosions, appearing as flaccid blisters on the skin; other types e.g., Bullous Pemphigoids, which represent a more chronic presentation of cutaneous signs/symptoms); Prognosis/Outcomes: PF more favorable than PV (Infectious complications septicemia, pneumonia, etc.). **COVID-19 and Pemphigus:** Clinical evidence of COVID-19 infestation itself can trigger Pemphigus (or related events) is still evolving; the data are very limited and sometimes conflicting at present. There is emerging published data / case reports suggestive of PV/ Bullous Pemphigoids reported in patients with a COVID-19 infection [53] [54].
Methodology	The assessment of Pemphigus and Pemphigoid in association with the use of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analysed data sources is described below: • Clinical Trial Data: The topic of Pemphigus and Pemphigoid was cumulatively reviewed in the CT datasets, within the following studies: mRNA-1273-P301 study

Signal evaluation criteria	Summary
	(ages ≥18 years; DLP: 04 May 2021), mRNA-1273-P203 study (ages 12-17 Years; DLP: 27 Jan 2022) and mRNA-1273-P204 study (ages 6 Months to 11 Years; DLP: 21 Feb 2022). The following PT were used according to MedDRA dictionary (version was 23.0 and 24.0). Blister; Dermatitis bullous; Pemphigoid; Pemphigus; Blister rupture; Generalized bullous fixed drug eruption; Linear IgA disease; Mucous membrane pemphigoid; Oedema blister; Acquired epidermolysis bullosa; Autoimmune blistering disease; Autoimmune dermatitis; Autoimmune disorder; Immune-mediated adverse reaction; Immune-mediated dermatitis; Benign familial pemphigus; Paraneoplastic pemphigus; Ocular pemphigoid; Pemphigus disease area index. • External Databases: VAERS and EVDAS were reviewed for the PT of Pemphigus and Pemphigoid and neither of these databases showed disproportionality of EB05 or ROR. • Review of the Phannacovigilance Database: Given that this request from the PRAC included two different evaluations of reports associated with pemphigus or bullous pemphigoid, and cases associated with "blister", the MAH conducted two separate searches by querying the GSDB, cumulatively to 17 Dec 2022 for valid case reports received from HCP, HA, consumers, and literature worldwide reported for elasomeran (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). The first search was conducted using the PTs of "Pemphigus" and "Bullous pemphigoid". This search retrieved 124 cases. The second search conducted for the purpose of identifying "blisters" cases that may potentially be cases of pemphigus/bullous pemphigoid, was conducted using a customized MedDRA SMQ created using: the MedDRA SMQs Narrow (Severe cutaneous ARs, Drug reaction with eosinophilia and systemic symptoms syndrome and Immune-mediated/autoimmune disorders), the MedDRA HLT (Bullous conditions) as well as the list of PTs included in the PRAC's report. Given the broad search criteria, a large volume of cases were retrieved (1870 cases; 1938 events). The 124 cases (that were retrieved as part of the first search) were removed to avoid duplication of cases. The remaining 1746 cases were reviewed further by the MAH using the specific 'key terms' in each of these cases that could be associated with the identification of a "case" according to the established case definition, these included: '*Immunofluorescence; Autoantibodies; IgG; Immunoglobulin G; ELISA; Acantholysis; Desmoglein; Complement deposits; Keratinocytes cell surface; Transmembrane glycoproteins; Nikolsky; C3; Complement factor*'. • Literature search review: A focused literature search and review was performed using PubMed cumulative till 17 Dec 2022. Multiple search strategies were used to identify articles related to Pemphigus and Moderna COVID-19 vaccines.
Results	Clinical Trial Data: *mRNA-1273- P301 Study:* In mRNA-1273-P301 the following PTs were reported (n=30,000): • Blister: mRNA-1273 (3) vs Placebo (3) • Dermatitis bullous: mRNA-1273 (0) vs Placebo (2) No imbalance was noted in mRNA-1273-P301. *mRNA-1273-P203 Study:*

Signal evaluation criteria	Summary
	There were no reports observed with the MedDRA search terms mentioned above. *mRNA-1273-P204 Study:* There were 3 reports received under the above mentioned MedDRA customized query for "Pemphigus" for participants of P204 in the mRNA vaccination arm. Overall, very few cases were reported in all three mRNA studies with no imbalance noted between the vaccine-treated subjects compared to the subjects in the placebo arms. There was no imbalance noted in any of the Moderna sponsored CTs, and all the reported events in the mRNA-1273 arm were reported as not related by the investigators. External Databases: • VAERS: No Disproportionate Reporting of Events Using EB05 > 2 (mRNA-1273 versus All vaccines) in VAERS as of 31 Dec 2022; Pemphigus (EB05: 0.88; N=89) and Pemphigoid (EB05: 0.82; N=34). • EVDAS: The PT of Pemphigus and Pemphigoid did not show Disproportionality as the ROR was <1. The observed ROR for Pemphigus (N=30; ROR=0.13) and Pemphigoid (N=90; ROR=0.35). Review of the Pharmacovigilance Database: A total of 152 case reports of pemphigus/ bullous pemphigoid or related events were retrieved from the 2 searches, including: • 124 cases (Bullous Pemphigoid [93 cases]; Pemphigus [31 cases]), retrieved as part of the first search conducted using the PTs of "Pemphigus" and "Bullous pemphigoid". • 28 case reports from the second search, after applying "key terms" (PTs: Blister 6 cases, dermatitis bullous 2 cases, linear IgA disease 1 case; Autoimmune disorders 19 cases) (*see also Responses to Spikevax-Signal Pemphigus and pemphigoid/EPITT ref.no.19860-preliminary PRAC AR 15 Mar 2023*). **First Search Results- Summary of Bullous pemphigoid (93 cases); Pemphigus (31 cases) [total 124 cases]** Cumulatively, a total 124 cases (124 events) with 116 serious cases (115 serious events) with PTs of Pemphigus and/or bullous pemphigoid PTs were identified for elasomeran. There were 3 cases reporting a fatal outcome (see below). There were 91 cases medically confirmed. There have not been reports of pemphigus and/or bullous pemphigoid terms after vaccination with any of the two bivalent vaccines. There were no important differences between reports involving females (65; 52.4%) compared to males (59; 47.6 %). The largest proportion of the reports were in individuals ≥50 years of age (92; 74.2%) The median age of reported cases was 70.0 years (min 24/ max 96 years) with a mean age of 66.5 years. When dose number and TTO information was provided, most of the events were reported after Dose 1 (21; 16.9%) and Dose 2 (25; 20.2%), and within 7 days after vaccination (33; 26.6%) regardless of dose number. Most

Signal evaluation criteria	Summary
	of the events (56; 45.2%) did no provide dose or TTO information. Overall, review of the 124 cases reporting pemphigus or bullous pemphigoid identified 22 cases as confirmed cases, 1 as probable case, 53 as possible cases, 3 as not a case, and there were 45 cases that were unassessable due to the lack of information including clinical presentation as well as supportive diagnostic laboratory data for confirmation of the cases. Further, using the WHO causality assessment, out of the 76 cases (which were classified as either confirmed, probable or possible), 38 cases were assessed as possible, 1 case as probable, 32 cases as unassessable, and 5 were considered unlikely related to the vaccine due to very prolonged TTO of more than 128 days to 397 days, as well as associated comorbidities that may provide a more plausible explanation for the occurrence of the reported events. **Second search results- Summary of cases under the customized MedDRA SMQ (28 cases):** A total of 28 relevant case reports were identified. These included cases/PTs of: Blister (6 cases), dermatitis bullous (2 cases), linear IgA disease (1 case); Autoimmune disorders (19 cases). Off these, 20 cases (72%) were reported in females; 8 in males, where the age is known, 11 (40%) of these cases were reported in patients aged >60 years. According to the established case definition for pemphigus or pemphigoid, there was 1 confirmed case (after Dose 1; onset day 11), 1 possible case (after Dose 3; day 13), 22 unassessable cases, and 4 cases classified as 'not a case'. The two cases that met the case definition criteria (1 confirmed; 1 possible) were further assessed for causality using the WHO-UMC criteria as: probable in one case and possible in the other. Out of those 1,746 cases (1,790 events), there were 621 serious cases (544 serious events) with 8 cases with a fatal outcome reported. There were 979 (52.4%) cases medically confirmed. There were more reports involving females (1,260; 72.2%) compared to males (448; 25.7 %), and 38 (2.2 %) cases did not specify gender. The largest proportion of the reports were in individuals ≥50 years of age (1,068; 61.2%) The median age of reported cases was 56.0 years (min 0.1/ max 121.0 years) with a mean age of 54.4 years. Overall, following the evaluation of the total 152 cases retrieved, 78 reports were identified that fulfill the established case definition criteria for pemphigus or bullous pemphigoid: 23 cases classified as confirmed cases, 1 as probable case, and 54 as possible cases. Of the remaining 74 cases: 67 were deemed 'unassessable' as contained insufficient clinical and/or diagnostic information for assessment in the context of pemphigus/pemphigoid and 7 cases were assessed as 'not a case' (alternative/ unconfirmed diagnosis, negative specific laboratory findings for pemphigus/pemphigoid). Further, using the WHO-UMC causality assessment, the evaluation of 78 cases which fulfilled the established case definition criteria, 2 cases were assessed as probable,

Signal evaluation criteria	Summary
	39 assessed as possible, 32 cases as unassessable, and 5 were considered unlikely related to the vaccine due to very prolonged TTO of more than 128 days to 397 days, as well as associated comorbidities that may provide a more plausible explanation for the occurrence of the reported events. Overall, following the evaluation of the total 152 cases retrieved, 78 reports were identified that fulfill the established case definition criteria for pemphigus or bullous pemphigoid: 23 cases classified as confirmed cases, 1 as probable case, and 54 as possible cases. Of the remaining 74 cases: 67 were deemed 'unassessable' as contained insufficient clinical and/or diagnostic information for assessment in the context of pemphigus/pemphigoid and 7 cases were assessed as 'not a case' (alternative/ unconfirmed diagnosis, negative specific laboratory findings for pemphigus/pemphigoid). Further, using the WHO-UMC causality assessment, out of the 78 cases which fulfilled the established case definition criteria, 2 cases were assessed as probable, 39 assessed as possible, 32 cases as unassessable, and 5 were considered unlikely related to the vaccine due to very prolonged TTO of more than 128 days to 397 days, as well as associated comorbidities that may provide a more plausible explanation for the occurrence of the reported events. **Review of Fatal Cases**: Off the total 152 cases, there were 8 cases with a reported fatal outcome, of which 7 cases were from regulatory authority and 1 was spontaneous case. All the patients reporting a fatal event were ≥66 years of age and majority of they were female (6) compared to males (2). Review of these 8 fatal cases with case definition, identifies most of them as Unassessable (6 cases), followed by Unlikely (1 case) and Possible (1 case). **Cases that Qualified for Pemphigus and Pemphigoid Review After Receiving Booster Dose with elasomeran/imelasomeran (Cumulatively through 17 Dec 2022):** Cumulatively, there were no reports that qualified for Pemphigus and Pemphigoid review in patients vaccinated in elasomeran/imelasomeran. **Cases that Qualified for Pemphigus and Pemphigoid After Receiving Booster Dose with elasomeran/davesomeran (Cumulatively till 17 Dec 2022):** Cumulatively, there was one report that qualified for Pemphigus and Pemphigoid review in patients vaccinated with elasomeran/davesomeran. Literature search review: There are few articles that describe Pemphigus in COVID-19 and in association with COVID-19 vaccination. But none of these articles were indicative or suggestive of a potential for a causal association or a potential MoA. • The following article by Martora F et al [55] with limited evidence and sample size, describes 32 patients with PV at the Dermatology Center of the University of Naples Federico II. All subjects received three COVID-19 vaccine doses (mRNA-BNT162b2 and mRNA-1273 were the vaccines administered). The

Signal evaluation criteria	Summary
	authors reported that 21.9% (n = 7) of patients with history of PV, experienced disease worsening after new lesions development, usually within 5–11 days after vaccination. These relapses were usually easily managed by increasing oral corticosteroid dosage, and all patients completed the vaccination cycle. According to the authors most PV patients (80%) showed no changes on the disease and the remaining were managed increasing corticosteroid dosage without significant complications. • Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. Immunol Res. 2018;66(2):255-270. doi:10.1007/s12026-018-8986-7. This review provides a brief overview about the different subtypes of pemphigus: pemphigus vulgaris, PF, paraneoplastic pemphigus, pemphigus herpetiformis, and IgA pemphigus. In addition, it summarizes the most recent understanding of the epidemiology, mortality data, and comorbidities of this group of organ-specific autoimmune diseases [24]. • According to a systematic review by Avallone, et al, 2022 [56] the introduction of large-scale vaccination programs, patients should be monitored for cutaneous manifestations following vaccine administration, and dermatological evaluation should be offered, when needed. However, if compared to the high number of vaccine doses already administered worldwide, cutaneous ARs seem to be rather infrequent and not life-threatening/severe, albeit heterogeneous and worth being studied. Being largely based on case reports and case series to date, our knowledge of SARS-CoV-2 vaccine-related dermatological manifestations should be further developed, and the underlying mechanisms should be clarified. Conclusion: Literature search results did not provide evidence of a potential mechanism of action or for a causal association between mRNA vaccines and Pemphigus/Pemphigoid (or related events).
Discussion	In the MAH's sponsored CTs, no imbalance was noted with 6 reports of Blisters identified on mRNA-1273 arm compared to 5 reports on the placebo arm (n=~20,000) group. No cases in the vaccination arms were considered related by the investigator. Cumulatively, in the MAHs GSDB, utilizing two different searches requested by the PRAC, a total of 152 cases were identified for pemphigus and/or bullous pemphigoid or related events. These included: 124 cases (PTs of BP [93 cases]; Pemphigus [31 cases]), retrieved as part of the first search and another 28 case reports from the second search containing various other relevant terms (Blister 6 cases, dermatitis bullous 2 cases, linear IgA disease 1 case; autoimmune disorders 19 cases). These cases were received via a Regulatory Authority (94 cases; 62%), spontaneous reporting (32 cases; 21%) and in published literature (26 cases; 17%). A review of the cases that fulfilled the established case definition (total 78 cases) showed

Signal evaluation criteria	Summary
	no specific reporting pattern by gender (40 female (51%); 38 male (49%)); 45 cases (58%) occurred in patients aged above 65 years (old age is a risk factor). Where the relevant information was available and the WHO-UMC causality was assessed as at least 'possible' by the MAH, a total of 32 cases (31 possible; 1 probable – see case below) were assessed as new onset (41%); and 9 cases (all assessed as 'possible') reported a flare-up (12%). Most cases were reported after Dose 1 and 2 (41%; 32 cases) while the Dose number was unknown in 40 cases (51%). The TTO following Dose 1 was ≤ 1 week in 5 out of 15 cases (33%) and 7 out of 17 cases (41%) following Dose 2. The event outcomes were recovered/ recovering/resolving/resolved/ resolved with sequelae in 29 out of 78 cases (37%), not recovered/ not resolved at the time of reporting in 24 cases (31%), unknown in 23 cases (29%) and fatal in 2 cases (3%). Overall, the WHO-UMC causality was assessed by the MAH as probable in 2 cases, both involved the event of pemphigoid: a possible re-challenge was reported in one case; the second case described an atypical bullous pemphigoid in terms of clinical manifestations and development in a patient with known eczema and it was postulated that the vaccination may have unmasked subclinical disease, defined by the presence of antibodies before clinical symptoms through the immunostimulatory process of the vaccine. In the other 39 cases for which the WHO-UMC causality was assessed as possible by the MAH, a number of potential contributory/pre-disposing risk factors were noted, for example, relevant medical history/comorbidities or concomitant medications having close associations with pemphigus/pemphigoid (e.g. autoimmune disorder(s), SLE, myasthenia gravis, multisystem inflammatory syndrome, psoriasis, dementia, nasopharyngeal cancer, dermatitis, eczema, depression, anxiety, hypothyroidism, skin cancer, pemphigus/pemphigoid and diabetes, etc.), and use of medications e.g. anti-hypertensives (such as lisinopril, ramipril, etc.), NSAIDs, aspirin, etc. Confirmatory diagnostic laboratory data for pemphigus or pemphigoid were not reported in some of these cases. Where the information was available, the events appeared to be generally manageable in clinic with appropriate treatment given. No specific patterns were identified from a review of cases with a reported fatal outcome, all these cases were reported in elderly patients >65 years of age. With a total of 152 cases reported in the GSDB containing the reported PTs of pemphigus/pemphigoid (or related events) following elasomeran vaccination among an estimated 772,908,958 million doses administered, this represents a reporting rate of 0.19 cases of pemphigus/pemphigoid per million doses of elasomeran administered. A review of the published literature did not provide evidence suggestive of a potential for a causal association between mRNA vaccines or mRNA-1273 and Pemphigus/Pemphigoid. A small study by Tomayako M M et al [57], have opined that the association of whether the mRNA-based vaccines may have a role in BP activation may simply be coincidental given the variable incidence of BP worldwide and the mass

Signal evaluation criteria	Summary
	vaccinations that have been carried out. It is possible that the individuals harbored subclinical forms of BP that were unmasked following the vaccination. Additional investigations/studies will need to be undertaken to study any off-target side effects of these medications. Similarly, a major review by Avallone et al [56], noted that the similar cutaneous manifestations were generally manageable in clinical practice with appropriate treatment. The overall reporting rates are still infrequent (in relation to the large-scale vaccinations globally) and opined that further studies need to be undertaken to allow better understanding of the cutaneous manifestations following the COVID-19 vaccination including that of the underlying mechanisms of action.
Conclusion	Cumulative analysis of the data as of 17 Dec 2022, for elasomeran, presented in this report showed that no specific patterns or concerns were identified. The reports of pemphigus/bullous pemphigoid are rare, and reports associated with the term "blister" did not identify any different pattern of reports than those that include the pemphigus and bullous pemphigoid terms. The CCDS (version 15.0) is considered to adequately reflect the safety profile of elasomeran. ModernaTx, Inc. concludes that no further action is warranted at this time and will continue to monitor events of pemphigus and bullous pemphigoid using routine surveillance. The benefit-risk evaluation remains positive. The PRAC final assessment report received on 14 Apr 2023, provided the following adopted PRAC recommendations: Having considered the available evidence from EudraVigilance, literature, the data submitted by the MAH and the analysis by EMA of real-world data, the PRAC has concluded that the current evidence is insufficient to establish a causal relationship between Spikevax and pemphigus or pemphigoid. The MAH for COVID-19 mRNA vaccine Spikevax (Moderna Biotech Spain, S.L.) should continue to monitor these topics in PBRERs. In the next PBRER (DLP 17 Jun 2023), the MAH should perform a review all new emerging data (which were not assessed in the current signal procedure) on pemphigus and pemphigoid (separately) after exposure to Spikevax, including data from CTs, post-marketing exposure and new scientific literature. The MAH should perform the assessment of causality, an O/E analysis and provide all case narratives within this review. The MAH is requested to clearly state if cases identified using the MedDRA HLT "bullous conditions" fulfil the definitions of bullous pemphigoid or pemphigus, and group them accordingly.

16.2.3 Diarrhea (re-evaluation)

Table 16.5 Diarrhea (re-evaluation)

Signal evaluation criteria	Summary
Source	a) Diarrhea was evaluated as a signal and refuted by Moderna in Apr 2021; however, it was listed as a labeled event in the EEA; UK and Swiss local labels (Section 4.8 Undesirable effects, ARs Table) as per health authority request. b) As post-marketing data continued to accrue, the SMT reviewed the topic of diarrhea on 10 Feb 2023 and validated the signal to perform a re-evaluation of the topic.
Background	Although diarrhea is typically self-limiting, it can be severe and can lead to profound dehydration, which can lead to abnormally hypovolemic shock with end organ damage. Acute diarrhoea remains a major cause of infant mortality around the world. Over 2 million deaths are attributed to acute diarrhea each year world-wide, most of them in the developing world. Children and the elderly are particularly prone to dehydration secondary to diarrhea. Diarrhea has been reported as an AEs following immunization for various vaccines administered to adolescents and adults, including: • Herpes zoster vaccine (reporting rate of 1.8 cases per 100,000 doses distributed [58]. • Influenza vaccine (0.15 cases per person per week • Polio vaccine (9.9% of vaccine recipients in Kinshasa, DRC with median age of 16.8 [59]. • Comirnaty (The frequency is listed as >1/10; "Very common" in Section 4.8 Undesirable effects; Table 1; Gastrointestinal disorders of the SmPC).
Methodology	The MAH's clinical database and the GSDB were queried for valid case reports of Diarrhea received from HCP, HA, consumer, and literature sources, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) as of 17 Mar 2023, using the MedDRA PTs "Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Diarrhoea neonatal, Post procedural diarrhoea". Due to inherent differences in CTs and pharmacovigilance operations, MedDRA version 23.0 was utilized to query the CTs database, and MedDRA version 25.1 was used for querying the GSDB. There was no impact to the search due to the differences in the dictionary versions utilized. • Clinical Trial Data: Data from three Moderna sponsored clinical studies (mRNA-1273-P203, mRNA-1273-P204 and mRNA-1273-P301) were queried as part of this signal evaluation. • External Databases: VAERS and EVDAS were reviewed for reported PTs "Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Diarrhoea neonatal, Post procedural diarrhoea. • Review of the Pharmacovigilance Database: The MAH GSDB was queried for valid case reports of Diarrhoea received from HCP, HA, consumers, and literature sources, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) as of 17 Mar 2023, using the MedDRA v25.1 PTs "Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Diarrhoea neonatal, Post procedural diarrhoea". • Literature search review: A focused literature search and review was performed using

Signal evaluation criteria	Summary
	PubMed since the IBD of elasomeran through 17 Mar 2023. Multiple search strategies were used to identify articles related to Diarrhea and Moderna COVID-19 vaccines.
Results	Clinical Trial Data: *mRNA-1273-P203 Study (Cutoff date: 27 Jan 2022):* There were a total of 21 (0.6%) participants (16 [0.6%] on mRNA-1273 and 5 [0.4%] on Placebo) were identified who reported the treatment-emergent AEs of Diarrhea via unsolicited reporting. *mRNA-1273-P204 Study (Cutoff date: 21 Feb 2022):* There were 172 reports of diarrhea with mRNA-1273 and 52 reports of Diarrhea with Placebo. *mRNA-1273-P301 Study (Cutoff date: 04 May 2021):* There were 317 (1.3%) participants (157 [1.3%] on mRNA-1273 and 160 [1.3%] on Placebo) who reported the treatment-emergent AEs of diarrhea via unsolicited reporting. Overall, the review of relevant CT data did not show any meaningful imbalance in events of diarrhea reported between patients vaccinated with mRNA-1273 and placebo. External Databases: • Overall, there was no disproportion observed in VAERS. • There was a minor disproportion observed in EVDAS with North America which did not reveal any significance in overall Diarrhea-related EB05 scores. Review of the Pharmacovigilance Database: Cumulatively, through 17 Mar 2023, there were 18,259 (18,956 events) reported cases of diarrhea with elasomeran, of which 4,136 cases (3,016 serious events) were considered serious. Of the 18,259 cases reported after elasomeran, 8,205 (44.9%) cases were medically confirmed and 86 had a fatal outcome. The outcome in the majority of the reports was reported as recovered or recovering 9,481 (50.0%) followed by not recovered 4,981 (26.3%) and unknown 4,408 (23.3%). Of the 18,259 reports, 73.2% (13,358) involved males and 24.5% (4,465) involved females; gender information was missing for 2.4% (436) cases. The mean age was 51.2 years (SD: 17.7), and the median age was 51.0 years (range 0 to 120). Age distribution is shown below with no unusual pattern identified. Cumulatively, 14,157 (77.5%) reports were from regulatory authorities, 4,076 (22.3%) were spontaneously reported to the MAH, and 22 (0.1%) were literature reports. Most of the cases were received from the United States (8,016; 43.9%) and the EEA (7,229; 39.6%). Of the 18,956 reported events, 4,981 events (26.3%) had an outcome of "Not Recovered/Not Resolved", with 9,481 events (50.0%) having an outcome of "Recovered or Recovering" and 4,408 (23.3%) having unknown outcome. There were 86 (0.5%) cases with a fatal outcome, of which 2 cases have reports of "Diarrhoea" as the only event. The remaining 84 cases included diarrhea along with other co-occurring event(s). When dose number and TTO could be determined, most of the events were reported following Dose 1 and Dose 2, however most events (35.6%) were missing dosage information. Most events had an onset of less than 7 days from the time of vaccination (2,438; 65.6%), inclusive of 1,680 (8.9%) events following a third/booster dose, with a significant proportion occurring within 3 days of vaccination which reflects expected vaccine reactogenicity, consistent with the safety profile. Most cases lacked important information for proper assessment including details of

Signal evaluation criteria	Summary
	medical history, concomitant medications, clinical course and workup. Furthennore, a significant proportion of reports were received from health authorities and in such cases, follow-up is not possible due to privacy restrictions. **Diarrhoea Reports with Booster elasomeran/imelasomeran and elasomeran/davesomeran**: Cumulatively, through 17 Mar 2023, there were 462 (464 events) cases, of which 243 cases (231 serious events) were serious with diarrhea-related events for patients receiving a dose of bivalent vaccines elasomeran/imelasomeran and elasomeran/davesomeran. Of the 462 cases reported after administration of Bivalent vaccines, 63 (13.6%) cases were medically confirmed and 1 had a fatal outcome. The outcome in the majority of cases was reported as recovered or recovering 296 (63.8%) followed by not recovered 144 (31.0%) and unknown 23 (5.0%). Of the 462 reports, 66.7% (308) involved males and 28.6% (132) were females; gender information was missing for 4.8% (22) cases. The mean patient age was 61.0 years (SD: 15.4), and the median age was 64.0 years (range 6 to 92). No unusual pattern was identified based on age and gender. Following review of reports pattern of occurrence of diarrhea-related events. no meaningful differences were noted in the reported cases of diarrhea after administration of bivalent vaccines. Literature search review: The search retrieved 141 articles and upon review, 121 were excluded since they pertained to topics not germane to this review such as COVID-19 disease or its impact on diarrhea, effect of the pandemic on diarrhea, therapeutic approaches for treatment of diarrhea, case reports/series, review articles and studies that did not include elasomeran. A critical analysis of the remaining 20 articles was performed, identifying 16 articles elasomeran and diarrhea and 4 articles describing non-Moderna COVID-19 vaccination. There were articles describing diarrhoea as predominantly non-life-threatening and transient events following administration of mRNA vaccine against COVID-19. While these articles described diarrhea following vaccine administration (predominantly following Dose 1 and Dose 2, as expected due to the prevalence the doses), no compelling causal association between diarrhea and elasomeran vaccine administration could be established.
Discussion	Evaluation of CTs data does not show any difference in the pattern of diarrhea-related event compared when with the prior previous signal evaluation with no imbalance observed in evaluable subjects > 6 months age. Review of the post-marketing data similarly do not reveal evidence of a change in the observed pattern of diarrhea when compared to the prior evaluation with no identifiable causal association between elasomeran and events diarrhea. Most cases lacked important information for proper assessment including details of medical history, concomitant medications, clinical course, and workup. Furthermore, a significant proportion of reports were received from health authorities and in such cases, follow-up is not possible due to privacy restrictions. Nonclinical studies demonstrated that mRNA-1273 vaccines are safe and well-tolerated. Overall, there is no conclusive plausible mechanism of action for elasomeran to cause diarrhea. The observed to expected analyses within 7-day risk window, using background incidence from Sweden and the UK showed that the reporting rates for diarrhea were substantially below expectation. Based on the analysis of all the safety data available as of 17 Mar 2023, the MAH considers that the nearly two more years of data accumulated since last evaluation in Apr 2021 do not reveal new infonnation that would impact the benefit/risk balance of elasomeran. The

Signal evaluation criteria	Summary
	MAH considers that the currently core labeling adequately reflects the known safety profile of elasomeran and will continue to monitor diarrhea-related events through its routine post-marketing safety surveillance.
Conclusion	Overall, based on the analysis of all available safety data as of 17 Mar 2023, the MAH considers that there is insufficient information at this time to establish a causal relationship between the administration of elasomeran or elasomeran/imelasomeran and elasomeran/davesomeran and the development of Diarrhea. The MAH considers that this validated signal is refuted and no change to the reference safety information is required. The benefit-risk profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran continues to be positive.

16.2.4 Idiopathic inflammatory myopathy/Myositis

Table 16.6 Idiopathic inflammatory myopathy/Myositis

Signal evaluation criteria	Summary
Source	On 12 Jan 2023, Moderna received a Health Authority request to perform for Spikevax (Moderna Biotech Spain S.L.): • *A cumulative review of all cases of IIM/myositis from all sources including, but not limited to, available data from CTs, scientific literature and post-marketing exposure.* • *Search strategy should include, but not be limited to the following PTs: Anti-melanoma differentiation associated protein 5 antibody positive, Anti-signal recognition particle (SRP) antibody positive, Anti-synthetase syndrome (ASS), Autoimmune myositis, Dermatomyositis, Focal myositis, Idiopathic inflammatory myopathy, Immune mediated myositis, Inclusion body myositis, Juvenile polymyositis, Lupus myositis, Myositis, Necrotizing myositis, Orbital myositis, Overlap syndrome, Polymyositis. The discussion should include considerations on whether the identified cases of IIM/myositis are considered "new onset" or "flare". The MAH should use a DLP as recent as possible.*
Background	Idiopathic inflammatory myopathies, also referred to as (autoimmune) myositis or autoimmune myopathies, are a group of autoimmune disorders with a heterogenous and specific spectrum of muscular and extra-muscular involvement. Idiopathic inflammatory myopathies classifications vary but the main subtypes include dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy and inclusion body myositis (IBM). Forms of IIM that share features with other connective tissue diseases are referred to as overlap myositis. These include Anti-synthetase syndrome. Idiopathic inflammatory myopathies are rare conditions (DM/PM annual incidence 0.4-4 cases per 100,000 patients) more common in women and people of Black ethnicity. The usual onset age of PM is between 45-60 years while DM shows a bimodal age distribution (5-15 and 45-60 years). Patients with IIM typically present with progressive symmetric proximal weakness that may manifest as difficulty rising from chairs, climbing stairs, or combing one's hair. Patients with DM also show typical skin lesions (heliotrope rash, shawl sign, Gottron papules, mechanic's hands) while those with ASS experience a variable combination of myositis, arthritis, Raynaud phenomenon, mechanic's hands, and interstitial lung disease.

Signal evaluation criteria	Summary
	Diagnosis of IIMs is based on muscle biopsy (gold standard), clinical signs, serology (autoantibodies), laboratory parameters (e.g., creatine kinase), electromyography (EMG) and/or magnetic resonance imaging (MRI). Therapeutic management is based on immunomodulating and immunosuppressive agents: corticosteroids, methotrexate, mycophenolate, tacrolimus, azathioprine, rituximab, Vig. About 50% of treated patients experience long-term remission. The 5-year survival rate is around 75%, with causes of death linked to generalized weakness, dysphagia/undernutrition, respiratory failure, or infections. IIMs are associated with both genetic factors (certain HLA subtypes) and environmental triggers such as drugs, infections, UV light, vitamin D deficiency, smoking and cancer. SARS-CoV-2 infection has been linked to a viral myositis attributable to direct myocyte invasion or induction of autoimmunity. COVID-19-induced myositis may vary in presentation, from typical dermatomyositis to rhabdomyolysis, and a paraspinal affliction with back pain. The pathophysiology of IIM is complex with various pathways: DM is a complement-mediated microangiopathy leading to destruction of capillaries, distal hypoperfusion and inflammatory cell stress on the perifascicular regions, while PM is characterized by cytotoxic CDS-positive T-cells which clonally expand in situ and invade muscle fibres expressing the major histocompatibility complex (MHC)-1. An autoimmune response to nuclear and cytoplasmic autoantigens is detected in 60-80% of patients with PM/DM. The autoantibodies involved in IIM are divided into myositis-specific autoantibodies (MSA), which are found primarily in patients with IIM, and myositis-associated autoantibodies (MAA), which are shared with other connective tissue diseases. Target antigens of MSA include the nuclear antigens Mi-2a, Mi-213, SAEl, NXP2, MDA5, cN-lA and TIFly and the cytoplasmic antigens Jo-1 PL-7, PL-12, EJ, OJ, SRP, and further tRNA synthetases. Target antigens of MAA are the nuclear antigens Ku, PM-Scl75, PM-ScllO0 and the cytoplasmic antigen Ro-52. These antibodies are important markers of diagnosis and prognosis and guide therapeutic management of IIM. For instance, anti-MDA5 antibodies are associated with a fonn of DM with a poor prognosis, while anti-Jal antibodies are found in ASS.
Methodology	The MAH's clinical database and the GSDB were queried for valid case reports of IIM/myositis received from HCP, HA, consumers, and literature, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran and elasomeran/davesomeran) using the following below criteria: • Clinical Trial Data: Three Moderna sponsored clinical studies (mRNA-1273-P203, mRNA-1273-P204 and mRNA-1273-P301) were queried as part of the response to the agency's request for information. For study mRNA-1273-P203, the data cutoff was 27 Jan 2022; for mRNA-1273-P204, the data cutoff date was 21 Feb 2022, and for mRNA-1273-P301, the data cutoff date was 04 May 2021. • External Databases: VAERS and EVDAS were reviewed for the list of PTs: Anti-melanoma differentiation associated protein 5 antibody positive, Anti-SRP antibody positive, Anti-synthetase syndrome, Autoimmune myositis, Dermatomyositis, Focal myositis, Idiopathic inflammatory myopathy, Immune-mediated myositis, IBM, Juvenile polymyositis, Lupus myositis, Myositis, Necrotizing myositis, Orbital myositis, Overlap syndrome and Polymyositis. • Review of the Pharmacovigilance Database: The MAH GSDB was queried for valid case reports of IIM/myositis received from HCP, HA, consumers, and literature, worldwide, for elasomeran, and for both bivalent vaccines (elasomeran/imelasomeran

Signal evaluation criteria	Summary
	and elasomeran/davesomeran) as of 17 Dec 2022, using the following PTs: "Anti-melanoma differentiation associated protein 5 antibody positive, Anti-SRP antibody positive, ASS, Autoimmune myositis, Dermatomyositis, Focal myositis, Idiopathic inflammatory myopathy, Immune mediated myositis, IBM, Juvenile polymyositis, Lupus myositis, Myositis, Necrotizing myositis, Orbital myositis, Overlap syndrome, Polymyositis". • Literature search review: A focused literature search and review was performed using PubMed cumulative till 17 Dec 2022. Multiple search strategies were used to identify articles related to Pemphigus and Moderna COVID-19 vaccines.
Results	Clinical Trial Data: *mRNA-1273-P203 Study (Cutoff date: 27 Jan 2022):* No participants were identified who reported the treatment-emergent AEs of Myositis related terms via unsolicited reporting. *mRNA-1273-P204 Study (Cutoff date: 21 Feb 2022):* No participants were identified who reported the treatment-emergent AEs of IIM/Myositis-specific terms. *mRNA-1273-P301 Study (Cutoff date: 04 May 2021):* Only one participant ([redacted]) who received placebo was identified who reported the treatment-emergent adverse event of IIM/Myositis-specific terms via unsolicited reporting. She is a 55-year-old female who received placebo and reported the event of "Myositis" (right shoulder muscle inflammation) 27 days after the first placebo dose and 1 day prior to second placebo dose. It was a mild non-serious event that lasted for 76 days, it was deemed not related and the participant recovered. External Databases: • VAERS: Overall, there is no disproportion observed in VAERS. There was minor disproportion observed in EVDAS with Focal myositis (1.15) and Autoimmune myositis (1.03) which did not trigger any significance in overall Myositis related EB05 scores. Review of the Pharmacovigilance Database: Cumulatively, through 17 Feb 2023, there were 295 (306 events) reported cases, of which 164 cases (149 serious events) were considered serious with IIM/Myositis related events after receipt of elasomeran. There were two cases with two non-serious events reported after elasomeran/imelasomeran and no cases reported after the elasomeran/davesomeran. Of the 295 cases reported after elasomeran, 151 (51.2%) cases were medically confirmed and three had a fatal outcome (one case [redacted] was identified as a fatal case during medical review. The reported outcome for the event of "dermatomyositis" was "unknown" and the reported cause of death was "gastrointestinal hemorrhage and anti-MDA-5 antibody positive interstitial pneumonia" 9 months after vaccination). Of the 295 reports, 62.0% (183) were females and 36.6% (108) were males; gender information was missing for 1.4% (4) cases. The mean age was 51.5 years (SD: 17.0), and the median age was 51.0 years (range 17.0 to 91.0). The reporting of these events is consistent with the known natural history of IIM/ Myositis events with more cases reported in women and in the older age groups with 51.5% of cases in individuals >50 years of age. According to epidemiological studies conducted on these rare and diverse events, there is a female preponderance for IMM/Myositis (specifically for dermatomyositis and

Signal evaluation criteria	Summary
	polymyositis) and a higher prevalence among older age group. There was only one (0.3%) case report among adolescents 12-17 years of age. No unusual pattern was identified based on age and gender. **Confounders for IIM/Myositis:** Cumulatively, of the 291 cases, 35.4% (103) had at least one confounder, 57.0% (166) had extremely limited information and so the lack or presence of a confounder could not be determined, and 7.6% (22) cases did not report a medical condition or concomitant medication that were confounders. Most of the non-literature cases were missing critical information such as diagnostic evaluation, treatment, and clinical course needed to make an informed case classification and WHO causality assessment. Given that IIM has many causes, the list of confounders was extensive and included: 1) age 2) infections including EBV, hepatitis, SARS-CoV-2; 3) autoimmune disease such as giant cell arteritis, Sjogren, mixed connective tissue disease, sclerodenna, myosclerosis, Crohn's, ulcerative colitis, multiple sclerosis (MS), polymyalgia, fibromyalgia, (and specifically for just cutaneous findings, lupus erythematosus, 17 psoriasis); 4) rhabdomyolysis; 5) medications such as lipid-lowering drugs (statins, ezetimibe), alcohol (long standing use), immune checkpoint inhibitors, glucocorticoids, anti-malarial drug (hydroxychloroquine), antiretroviral drugs, chemotherapy; 6) endocrine: hypothyroid and diabetes and 7) others: malignancy, neuropathy. **EULAR/ACR classification criteria and WHO-UMC Causality**: Overall, there were 8 fatal cases of which 7 cases were from regulatory authority and 1 was spontaneous case. All the patients reported a fatal event were ≥66 years of age and majority of them were female (6) compared to males (2). Review of these 8 fatal cases with case definition, identifies most of them as Unassessable (6), followed by Unlikely (1) and Possible (1). Evaluation of the 291 cases with at least one IIM/myositis-specific event after elasomeran cumulatively through 17 Feb 2023 was conducted using the EULAR/ACR classification criteria. Evaluation of the spontaneous reports, particularly, the non-literature cases, was challenging because most of them had limited available data; information regarding the characteristics of the events e.g., "myositis", clinical examination to assess muscle weakness and skin manifestation, results (including the value) of laboratory measurements (e.g., muscle, liver enzymes and myositis antibody panel), whether a biopsy was performed and results if done were not available. Additionally, the reports also lacked medical history, concomitant medications, detailed evaluation including tests to exclude other etiologies (e.g., infections, malignancy workup), treatment and clinical course. Review of the 295 cases, also revealed that PT of "Myositis" was applied to a heterogenous group of symptoms that were unrelated to IIM, such as expected reactogenicity, as well as vaccination-related events like injection site pain and swelling, possibly extensive limb swelling, COVID-19 arm etc. The EULAR/ACR classification was not applied to the nine case reports that noted a flare after elasomeran of their prior diagnosis of IIM, as they were already considered cases of IIM/Myositis. There were also 4 reports that were excluded from the case evaluation as the TTO of the events were reported before administration elasomeran. Of the remaining 282 cases, four case report were classified as "definite" IIM, five cases as "probable", 34 cases as "Not a case", and 239 cases as "Unassessable". As mentioned above, the vast majority of the reports lacked critical information needed to evaluated cases according to the established IIM case classification, as well as to establish causality according to the WHO causality assessment. Information regarding the clinical course of the event of "myositis", clinical examination to assess muscle weakness and skin manifestation, results

Signal evaluation criteria	Summary
	(including the value) of laboratory measurements including muscle, liver enzymes and myositis antibody panel, and whether a biopsy was performed, and results were not provided. Of the nine cases that noted experiencing a flare of IIM/myositis after elasomeran, causality was assessed as "Possible" for three cases because there was limited data regarding their baseline status of IIM, whether they were on treatment and whether they stopped treatment before vaccination as well as the lack of clinical evaluation including labs to establish the diagnosis of a flare. Three cases were assessed as "Unassessable" due to very limited available data including dose number and TTO, important to establish a temporal association to elasomeran vaccination. The reports are also missing information to accurately assess causality such as baseline status of condition, concomitant medications, diagnostic evaluation, treatment, and clinical course. One case was assessed as "Unlikely" because he also reported COVID-19 pneumonia around the time of reported IIM/myositis events and there are reports that infections including SARS-CoV-2 can cause IIM/myositis and two cases were deemed as "Not a case" of IIM/myositis flare. **Cases Who Received a Booster with elasomeran/imelasomeran**: Cumulatively, through 17 Feb 2023, two non-serious cases were reported after receipt of a booster with elasomeran/imelasomeran with only two non-serious IIM/myositis events. Only one case had enough data reported to assess the dose and TTO, the event was reported five days after Dose 5. Both cases had very limited available data and lacked the critical information needed to perform an informed IIM case classification and causality assessment. Information regarding the quality of the reported "myositis", clinical examination to assess muscle weakness and skin manifestation, results (including the value) of laboratory measurements including muscle, liver enzymes and myositis antibody panel, whether a biopsy was performed and results if done as well as detailed evaluation including tests to exclude other etiologies (e.g., infections, malignancy workup), medical history, and concomitant medications are not provided. Both cases were deemed "Unassessable" by the modified EULAR/ACR classification criteria and causality was also "Unassessable" by WHO-UMC causality criteria. Literature search review: Five hundred and twenty articles were identified. The title and abstracts were reviewed and after exclusion of articles that discussed COVID-19 disease or its impact on IIM/myositis, effect of the pandemic on IIM/myositis, therapeutic approaches for treatment of IIM/myositis, case reports/series, review articles and studies that did not include elasomeran, 34 articles underwent an in-depth full length text review. A critical analysis of the 34 articles was performed, identifying only 16 articles regarding elasomeran and IIM/myositis and 5 articles describing COVID-19 vaccination (other than Moderna vaccine). The other 13 articles were general articles describing COVID-19 associated myopathy. The 16 articles with elasomeran and IIM/Myositis were case reports/series describing 19 cases with IIM/myositis-specific events. These case reports have important limitations including lack of a comparison group, lack of ability to generalize, no possibility to establish cause-effect relationship, possibility of over-interpretation, selection bias, and recall bias. Evaluation of those published literature reports do not support a causal relationship between IIM and elasomeran. **Conclusion**: Overall, the published data currently does not support an association between Myositis and elasomeran or elasomeran/imelasomeran and elasomeran/davesomeran.
Discussion	To date, there is no definitive evidence to demonstrate association between receipt of elasomeran and IIM as there is no clear biological plausibility. Idiopathic inflammatory myopathies like all autoimmune diseases, is a complex disorder and, most likely, multiple

Signal evaluation criteria	Summary
	factors including genetic, immunological, and environmental ones in combination all play a role in its development. Although much is known about the pathologic processes present in this group of disease and that the clinical and histopathologic distinctions between these conditions suggest that different processes underline each of the inflammatory myopathies, the pathogenesis is poorly understood, and the precise cause of IIMs remains unknown. Additionally, although there have been case reports of IIM occurring after other vaccines including those against viruses (hepatitis B, influenza, smallpox, mumps, rubella, and poliomyelitis) or bacteria (Mycobacterium tuberculosis, Clostridium tetani, Corynebacterium diphtheria and Bordetella pertussis), mostly, any connection between the immunization and autoimmune reaction was temporal and the exact pathogenesis still unknown [60] [61] [62] [63]. Overall, the observed to expected rate ratios for IIM using post-marketing data and expected incidence from Sweden, reported no increase in the rate ratios. However, the age and gender stratified analyses, using 7-day risk window reported an increased rate ratio in females 25-49 years. As the background incidence was based on cases identified as IIM compared to the observed cases identified using PTs not restricted to IIM, there is possible overestimation of the rate ratio. Hence, the results of the observed to expected analyses should be interpreted with caution. In the P203, P204 and P301 CTs, no participants who received mRNA-1273 reported an IIM/myositis-specific event. Post-marketing data showed a geographic disproportion in the origin of reports of IIM/myositis-specific events with majority of reports originating from EEA (55.9%). The distribution of reports by age and gender is consistent with limited available data on the epidemiology of IIM; there were no unusual patterns identified based on age, gender, doses administered and medical history. The most frequently reported co-reported PTs by cases with IIM/myositis-specific PTs were consistent with reactogenicity events. Medical review of the cases revealed that PT of "Myositis" was applied to a heterogenous group of symptoms that were unrelated to IIM, such as expected reactogenicity, as well as vaccination-related events like injection site pain and swelling, possibly extensive limb swelling, COVID-19 arm etc. A focused literature review identified literature articles that only described case reports/case series of IIM/myositis after COVID-19 vaccination. Case reports and case series are limited for many reasons including lack of a comparison group, lack of ability to generalize, no possibility to establish cause-effect relationship, danger of over-interpretation, publication bias, recall bias and retrospective design. These studies cannot establish a causal relationship and support the need for well-designed prospective and longitudinal studies to study. Additionally, the pathogenesis of IIM is complicated and not well-defined and the exact pathogenesis of reports of IIM occurring after vaccines is still unknown. The total number of reports of IIM/myositis related events included in the MAH GSDB can be considered very low in relation to the number of people who have received COVID-19 vaccines to date (as of 17 Feb 2023, 1,347,109,306 elasomeran doses have been distributed with 791,426,717 doses elasomeran administered). The reporting rate of IIM/Myositis related events elasomeran is 0.4 events per 1 million doses administered. Based on the analysis of all available safety data as of 17 Feb 2023, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran and the development of IIM/ myositis. No new or emerging safety concern was identified.
Conclusion	Overall, based on the analysis of all available safety data as of 17 Feb 2023, the MAH

Signal evaluation criteria	Summary
	considers that there is insufficient information at this time to establish a causal relationship between the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran and the development of IIM/Myositis. The observed to expected analyses within 7-day risk window, using background incidence from Sweden and the UK showed an increased rate ratio in females 25-49 years old. However, there was no increase in rate ratio using the background incidence from Spain. As mentioned, myositis cases as reported in the GSDB lack medical history, concomitant medications and other clinically relevant information to assess the validity of the case, thus limiting the interpretation of the observed to expected analyses. The MAH considers that this health authority validated signal is refuted and no change to the reference safety information, labeling or risk management plan is required. The benefit-risk profile of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran continues to be positive. Given the increased report of IIM/myositis-specific events among females aged 25-49 years of age, the MAH will monitor IIM/myositis related events closely through enhanced signal detection activities. Idiopathic inflammatory myopathies /Myositis will be included as a topic of interest in the MAH' Signal Management Process. Additionally, given the conflicting results and limitations of the observed to expected analyses, the MAH will assess myositis in an ongoing PASS study using US claims data (mRNA-1273-P903). The evaluation in the PASS study, will enable the MAH to mitigate the concerns of case definition by using the same case definition for observed and expected cases, also it will minimize the confounding factors using self-controlled risk analysis. The results of systematic evaluation of myositis in the ongoing PASS study will be submitted with the final study report in Jun 2023. Please refer to Section 8 for results from the PASS study. The PRAC final assessment report received on 12 May 2023, provided the following adopted recommendations: Having considered the available evidence, including from the cumulative review performed by the MAH, the PRAC has agreed that a causal association between COVID-19 mRNA vaccine (nucleoside-modified) elasomeran and myositis cannot be concluded at present. No update to the product information and/or the risk management plan is warranted. The PRAC has agreed that the MAH of COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should continue to monitor IIM/myositis and their flares through routine pharmacovigilance in the upcoming PBRERs. Any relevant new cases (including those reporting rechallenge information) and scientific literature on possible pathogenic mechanisms should be presented. The MAH should include and follow-up on IIM/myositis in the final study report of EU PASS study mRNA-1273-P904 to be submitted in Dec 2023.

16.2.5 Sensorineural hearing loss

Table 16.7 Sensorineural hearing loss

Signal evaluation criteria	Summary
Source	There have been multiple evaluations conducted on the medical topic of sensorineural hearing loss (SNHL) due to requests from health authorities, as well as internal evaluation through the signal detection process for hearing loss since Jun 2021.

Signal evaluation criteria	Summary
	• **01 Jun 2021**: The signal "Deafness" was evaluated and subsequently refuted. • **06 Jul 2021**: PRAC agreed with this decision in the Assessment Report of MSSR5 mentioning the following: *"Overall, PRAC Rapporteur agrees on the MAH's conclusion that available evidence is currently insufficient to establish a causal association between the risk of hearing loss and COVID-19 vaccine Moderna. The closure of the signal is accepted, and the MAH should continue to monitor cases reporting hearing loss as part of their routine pharmacovigilance practices."* • **28 Mar 2022**: Sudden hearing loss was reviewed internally as a safety topic triggered by EVDAS results of DLP 28 Feb 2022. • **27 Apr 2022:** Closed with the following conclusion: *"Based on review of available data, there is insufficient evidence to consider Hearing Loss as a potential signal. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities".* • **31 May 2022:** Triggered by a RTQ from Health Canada, the topics "Tinnitus, vertigo, and hearing losses" were addressed in the RTQ response to the agency. • **14 Sep 2022**: Hearing loss and Tinnitus were internally re-assessed as a safety topic review triggered by publication of the French Healthcare Authority (ANSM) on its website. • **19 Sep 2022**: Closed with following conclusion: "*Based on the analysis of the cumulative data, the MAH considers that there remains insufficient evidence for an increased risk for tinnitus, vertigo and hearing loss after vaccination with SPIKEVAX. The MAH will continue to evaluate these events using routine surveillance."* • **On 22 Dec 2022:** PRAC requested the MAH to address the topic "Hearing loss" in the next PBRER4. This topic was addressed with following conclusions: *"Based on the cumulative review of available data as of 17 Dec 2022, the MAH considers there is insufficient evidence to consider Hearing Loss as a safety concern. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities. No changes to the product information are required at this time."* • **11 May 2023**: PRAC confirmed that there is not sufficient evidence to establish a causal association between elasomeran and sudden hearing loss mentioning the following: *"Overall, the evidence presented by the MAH is not sufficient to establish a causal association between elasomeran and sudden hearing loss. However, given that the MAH did not provide any information on the causality of the cumulative cases and did not state whether any of the 2,116 reports could be classified as 'index cases', the assessor cannot form an opinion about the strength of the evidence available in the cumulative case reports. Thus, further information is needed. Within the current PSUSA, the MAH is requested to present in detail (including case narratives and MAH's causality assessment) all reports that fulfil level 1-3 BC case definition of sudden hearing loss AND that can be considered as 'index cases'*."* • **22 Jun 2023**: PRAC mentioned the following:

Signal evaluation criteria	Summary
	"Following review of additional data submitted by the MAH in response to RSI, the PRAC Rapporteur considers that a causal association between hearing loss and Spikevax cannot currently be established. No further actions beyond routine PV pharmacovigilance are required. " • **TGA RTQ Request for Review of Signal SNHL**: TGA's Medicines and Vaccines Investigation and Surveillance Section reviewed signal of **SNHL** with elasomeran. Signal detected in Nov-Dec 2022 Disproportionality Analysis Report. Thirty-four **reports** of hearing loss associated with elasomeran (including one report associated with Spikevax Bivalent Original/Omicron) in the TGA's Adverse Event Management System). Requests sponsor to provide ***"updated signal analysis on hearing loss cases including age stratified and age specific observed versus expected analyses in the next PSUR to enable further evaluation of this signal. Please confirm your agreement with this request by 23 Jun 2023.*** **On 09 Aug 2023, the validated signal of** SNHL was evaluated at the SRMT Meeting. Results from this meeting and SER will be submitted with PBRER #5 (PSUR). The SRMT decision was to refute the signal of SNHL. There were no changes to the product information or RMP. Additionally, the following actions were recommended: • Routine PV monitoring Sensorineural hearing loss will be included as an ad-hoc adverse event to study mRNA-1273-P920 (Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States).
Background	Hearing loss is defined as a person who is not able to hear as well as someone with normal hearing–hearing thresholds of 20 dB or better in both ears–is said to have hearing loss. Sensorineural hearing loss is estimated to be the most common type of hearing loss and affects between 5-27 per 100,000 people each year, with approximately 66,000 new annual cases in the US. Incidence estimates of sudden sensorineural hearing loss after COVID-19 vaccination ranged from 0.3 to 4.1 per 100 000 per year. New onset is investigated by a full audiometric evaluation by a multidisciplinary team (e.g., otolaryngologist, audiologist, radiologist, and speech/language therapist). There are two types of hearing loss: conductive and SNHL. Sensorineural hearing loss results from pathology of the cochlea, auditory nerve, cranial nerve VIII or central nervous system. Conductive hearing loss is secondary to lesions affecting the external auditory canal or middle ear. Two types of hearing loss: conductive and SNHL 1. SNHL: results from pathology of the cochlea, auditory nerve, cranial nerve VIII or central nervous system. 2. Conductive: secondary to lesions affecting the external auditory canal or middle ear. Sensorineural hearing loss is more common in women than men and can be diagnosed in all ages; however, diagnosis is most common in older adults aged 50-64 years old and elderly with bilateral HL in patients aged >70+ years at time of diagnosis. In sudden onset

Signal evaluation criteria	Summary
	SSNHL, the exact pathophysiology is still unknown; however, it is most likely caused by a viral infection. Confounders for SNHL include the following: • **Infections:** Viral cochleitis associated with herpesviruses, parainfluenza virus, influenza, mumps, measles, rubella or HIV; bacterial meningitis; Mycoplasma pneumoniae infection; Lyme Disease; tuberculosis, syphilis or fungal infection • **Ototoxic Drugs:** Aminoglycosides, vancomycin, erythromycin, loop diuretics, antimalarials, cisplatin, sildenafil, cocaine • **Endocrine:** Diabetic vasculopathy, hypothyroidism • **Neoplasms:** Acoustic neurinoma meningeal carcinomatosis; lymphoma, leukemia, or plasma cell dyscrasia. • **Trauma:** Head injury, barotraumas; exposure to loud noise or music • **Autoimmune Disease**: Autoimmune inner ear disease, Cogan's syndrome, Susac syndrome, systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, Sjogren's syndrome, Kawasaki disease, Wegener's granulomatosis, temporal arteritis of primary central nervous system vasculitis. • **Vascular Disorders**: Vertebrocerebellar cerebral vascular accident or transient ischemic accident, cerebellar infarction, inner ear hemorrhage. • **Other Causes:** Meniere's disease, osteosclerosis, Paget's disease, multiple sclerosis, age, idiopathic. Treatment includes steroids to improve the prognosis. Also, decrease exposure to loud music or sounds in cases due to noise-induced hearing loss observed in young adults is recommended. Autoimmune related causes are rare clinical entity in which progressive fluctuating bilateral asymmetric SNHL that develop over several weeks to months. Vestibular symptoms, tinnitus and aural fullness are present in up to 50% of patients.
Methodology	The assessment of SNHL in association with the use of mRNA-1273 in all patients exposed was performed using several data sources. The methods of evaluation used in each of the analyzed data sources is described below • Clinical Trial Data: The company clinical database was queried cumulative from 18 Dec 2020 to 17 Jun 2023. Safety data from six clinical trials in different age groups (adults, adolescents, and children) and in one clinical trial in immunosuppressed adults was reviewed to identify unsolicited events (serious and non-serious) reported using the MedDRA (version 23.0) PTs 'Deafness neurosensory', 'Hypoacusis' and 'Tinnitus'. The topic of SNHL was cumulatively reviewed in the clinical trial datasets, within the following studies: o mRNA-1273-P301, data as of 04 May 2021 o mRNA-1273-P203 Part 1A and Part 1B, data as of 31 Jan 2022 o mRNA-1273-P204 Part 1 and Part 2, data as of 21 Feb 2022 o mRNA-1273-P306 Part 1 and Part 2, data as of 05 Dec 2022 o mRNA-1273-P205:

Signal evaluation criteria	Summary
	➢ Day 91 Interim Clinical Study Report, Part G (mRNA-1273.214), data as of 08 Sep 2022 ➢ Day 29 Interim Clinical Study Report, Part H (mRNA-1273.222), data as of 31 Oct 2022 o Immunocompromised Adults: mRNA-1273-P304, data as of 01 Sep 2022 • Epidemiological studies: A total of 1,664,690,323 doses of elasomeran have been distributed as of 17 Jun 2023. Elasomeran was distributed in 91 countries, elasomeran/imelasomeran in 42 countries, and elasomeran/davesomeran in 41 countries. The estimated administered doses were used to calculate the denominator for the observed to expected analyses. Person-years were estimated by assigning 21 days after each dose including all products elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). The assumed age and gender distribution was based on CDC data as of 11 May 2023. • External Databases: Disproportionality was performed for external safety databases. • Review of the Pharmacovigilance Database: A cumulative search in the GSDB, through 17 Jun 2023 for reports under the MedDRA HLT of "Hearing losses" was performed. An additional search string of the narrative and PTs using an algorithm was applied to avoid any missing cases. Cumulative analysis of HLT of hearing loss cases focused on PTs of hypoacusis, and any combination of sensorineural hearing loss/deafness including: MedDRA Version 26.0 PTs: 'Deafness neurosensory', Neurosensori hypoacusis', 'Hypoacusis', 'Neurosensory Deafness'. All case reports identified from the above search (whether or not the PT SNHL was coded) were medically reviewed for evidence of SNHL based on Brighton Collaboration (BC) case definition which included evidence of physical examination (e.g., ENT) to rule out conductive hearing loss, and for specific diagnostics to determine index cases of SNHL (e.g., audiometry, MRI, tuning fork exams), medical diagnosis of SNHL or reported diagnosis of hypoacusis. • Literature search review: A targeted literature search was performed from 18 Dec 2022 to 17 Jun 2023 using PubMed.
Results	Clinical Trial Data: No imbalance was observed between the placebo arm and mRNA-1273 vaccination arm for PTs "Deafness neurosensory", "Hypoacusis" or "Tinnitus" in any of the studies were reports for the evaluated PTs were reported (P301 and P204). No cases associated with the PTs "Deafness neurosensory", "Hypoacusis" or "Tinnitus" were reported in: • mRNA-1273-P205 • mRNA-1273-P304 • mRNA-1273-P203 • mRNA-1273-P306 There was no imbalance or change to the benefit risk safety profile. Epidemiological studies: In data from a US, administrative claims-based study of sudden sensorineural hearing loss identified an incidence of 27 cases per 100,000 person-years [64]. Increases by age were consistent for men and women. The literature-based estimates varied widely: • Taiwan: 10.2/100,000 person-years [65]

Signal evaluation criteria	Summary
	• Japan: 27.5/100,000 person-years [66] • Germany: 160/100,000 person-years [67] External Databases: • VAERS: No Disproportionate Reporting of Events using EB05 > 2 (mRNA-1273 versus All vaccines in adults) in VAERS as of 10 May 2023. • EVDAS: Disproportionality was observed in EVDAS (27 May 2023, to 09 Jun 2023). PTs for HLT of hearing loss including SNHL, deafness neurosensory, and hypoacusis showed Disproportionality as the ROR was >1. There was higher disproportionality in North America compared to other regions. Deafness neurosensory (ROR=7.38) was disproportionate in general population and in geriatric population and increased overall (All ROR: 2.03; N=170, ROR>1). While disproportionality is not uncommon in EVDAS, results should be taken with caution given the limitations in EVDAS and based on low case counts. For bivalents, regional disproportionality was seen in elasomeran/imelasomeran (deafness in EU and hypoacusis in Asia). For elasomeran/davesomeran, disproportionality was reported in North America only; deafness neurosensory was reported in general population Review of the Pharmacovigilance Database: Two analyses were performed. A cumulative review was submitted as part of a health authority request (EMA/PRAC) for PBRER4 (cumulatively from 18 Dec 2020 through 17 Dec 2022) and an updated analysis of cases reported during the reporting period for PBRER#5 (17 Dec 2022 to 17 Jun 2023) based on a request received from another health authority (TGA). **Summary of Cumulative HLT Hearing Loss Cases (18 Dec 2022 to 17 Dec 2022):** Of the 2,327 cases (2,589 events) identified, 25.2% (586) of cases were reported as non-serious and 74.8% (1,741) were reported as serious, of which 3 were fatal cases. There were 1,254 (53.9%) medically confirmed cases. Gender distribution was highest among women (57.5%) with 40.4 % in men and 2.1% of unknown gender. The mean age was 52.0 years (SD: 17.0) and the median age was 52.0 years (range: 0.3 to 101.0 years, noting that the cases in very young children were found to have age coding discrepancies which are being corrected). The highest proportion of cases occurred in the 50–64-year-old age group (28.5%) followed by the elderly 65 years and older (24.4%), and the 25-39-year-old age group (18.3%). There were 16 cases (0.6%) in the pediatric age group. The majority of these cases originated from the United States (51.6%), followed by EEA countries (35.5%) and the United Kingdom (5.8%). The highest events were for the PTs of hypoacusis (33.3%) followed by deafness (25.9%). When time to onset (TTO) was reported, most events occurred after Dose 1 (30.1%), with Dose 2 (28.9%), and Dose 3 (7.6%) with TTO not reported in 32.9% of the events. The time to onset of all doses was on average 13.7 days (SD: 33.9) with a median of 3.0 days (range of -217 to 379 days). Almost 60% of the 2,589 events (59.6%; 1,544) were not resolved, 14.4% (372 events) resolved, and 8.6% (224) were either resolving or resolved with sequelae. Note: Not resolved outcomes must be interpreted with caution as most reports do not have follow-up. Serious events represented 65.3% (1,220) of the "not resolved" outcomes; 44.9% (324) of the "not resolved" events were non-serious. Most cases were confounded by extensive medical history and/or concomitant medication use. The MAH conducted a detailed evaluation of the cases of SNHL by searching both the narratives and filtering for the MedDRA PTs which contained verbatim combinations of

Signal evaluation criteria	Summary
	SNHL or hypoacusis. Using the results from the MAH SAS algorithm of the 2,327 cases, there were 994 cases of SNHL/hypoacusis and 1,333 cases of 'Other hearing loss (HL)' identified. Of the 994 cases, gender distribution was highest among women (599; 60.3%) with 380 (38.2%) in men and 15 (1.5%) of unknown gender. There were 689 cases (69.3%) in the adult age group, 254 cases (25.6%) in the elderly 65 years and older population, and 51 cases (5.1%) in the pediatric age group with a mean age of 49.6 years and median age of 50 years. Of the 994 cases, over 76% of the cases reported treatment with steroids, antibiotics or other medications; the remaining cases had (237) missing/unknown treatment information. There were 242 cases, which had confounders of either medical history, concurrent illnesses, or concomitant medications. However, 432 cases had missing or unknown medical history. A total of 785 cases did not report diagnostic studies (e.g., audiogram/acoustic test, magnetic resonance image [MRI], computerized tomography) information. The remaining 209 cases were identified with diagnostic studies and underwent medical review and assessment (BC case definitions for acute neurosensory hearing loss and WHO causality). Of these 209 diagnostics cases, 64% met the Level 3 criteria. Overall, there were no index cases for SNHL identified; there were 6 cases classified as Level2 and 129 cases as Level 3. Among the 6 Level2 cases, all cases were in adult age range 38 to 67 years. No cases had relevant medical history of hearing disorders. However, 2 cases had a history of high cholesterol, 4 had histories of other vaccines (Shingles), severe hypersensitivity reactions and allergies/respiratory problems. All cases had documented abnormal audiograms of >30 db-71db. Of the 4 cases that reported treatment, 2 cases did not resolve, and 2 cases were resolving/resolved after receiving therapy for the event. All cases were assessed as possible except for one case assessed as probable, which did not resolve with treatment. All Level 3 cases (129) had diagnostics studies (e.g., audiogram, MRI, etc.). In the 129 cases, the ages ranged from 27 to 90 years in 39 females and 24 males. Overall, although the majority of cases presented with a plausible temporal association; however, there were 63 cases that had confounders (medical history and/or concomitant medications). The outcomes reported in these cases were "not resolved" (111 cases), "resolved" (10), and "resolving" (8). In 49 cases, the patients received steroid treatment (either oral steroids and/or intra-tympanic steroid injections) in which 42 were not recovered/resolved and 7 resolved or resolving after treatment. **Summary of HLT Hearing Loss Cases during the PBRER 5 reporting period (18 Dec 2022 to 17 Jun 2023)** During the reporting period of this PBRER (18 Dec 2022 to 17 Jun 2023), a total of 152 cases were identified using the same search strategy as before, with the HLT of "Hearing losses". After application of the same SAS algorithm, a total of 82 cases of SNHL were identified (70 for elasomeran; 8 for elasomeran/ imelasomeran, and 4 for elasomeran/ davesomeran), of which, 18 cases provided information in order to evaluated cases for SNHL. Given that the number of reported cases during this RP was small, all cases in the RP were medically reviewed and evaluated using the Brighton Collaboration and WHO causality assessment. **Overview of Reporting Interval Hearing Loss Cases**: As part of this analysis, a comparison of SNHL cases reported for PBRER 4 (2,327 cases) vs those reported for PBRER 5 (152 cases) was performed and is presented below. No differences were observed between the two reports regarding gender, age and time to onset (TTO). There

Signal evaluation criteria	Summary
	were 3 cases reporting a fatal outcome during the PBRER 4; no fatal outcomes were reported during this RP. The demographic presentation was similar across both PBRERs with more cases reported for females compared to men, and higher proportion of reports in the 50-60 years old age group with a mean age of 56.87 years; time to onset was similar for both analysis (<3 days). Young adults (18-49 years old) had similar proportion of cases compared to elderly. There was significant number of missing data during the RP, which impacted the assessment. No cases were reported in children during this reporting period. When dose number was known, events occurred more often after dose 1 and dose 2, and time to onset was similar for both analysis (<3 days), regardless of dose number. Among the 152 new cases (168 events) of the SHNL HLT, the most commonly reported PT was hypoacusis (48; 12.5%), followed by deafness neurosensory (35; 9.1%). Overall, most of the cases did not report relevant medical history or concomitant medications and for those that provided that information most cases were confounded including use of ototoxic medications (loop diuretics) or relevant medical history (other vaccines, cardiovascular history or viral infections). Out of the 152 cases included in PBRER#5 RP, 82 Cases (383 events) were identified as SNHL using the described algorithm, of which 18 cases met diagnostic criteria. There were 55 serious cases and none with fatal outcomes. Most cases were medically confirmed (50; 61.0%). Most of the cases were reported after vaccination with elasomeran (70 cases); there were 12 cases after vaccination with the bivalent vaccines (8 for elasomeran/imelasomeran and 4 for elasomeran/davesomeran). Literature search review: From the search result 104 unique articles captured, 5 articles were related to SNHL and mRNA vaccination. Of the 5 relevant articles, 2 discussed the Moderna vaccine and SNHL and 3 discussed the Pfizer vaccine and SNHL. 99 articles were not relevant and consisted of 2 articles discussing SNHL/HL in COVID-19 infection, 3 editorials on SNHL studies in COVID-19 vaccine, and 43 about the Moderna vaccine with no SNHL. One article discussed a hypothetical mechanism of action and etiology of SNHL and mRNA vaccines [68]. Of note, hearing loss is associated with other medications and vaccines in the literature (Rabies, tetanus-diphtheria and meningococcal, MMR, Influenza, HBV, and oral poliomyelitis). Thai-Van H, Valnet-Rabier MB, Anciaux M, et al [69]: This is a nationwide retrospective study aimed to assess the relationship between SSNHL and exposure to mRNA COVID-19 vaccines and to estimate the reporting rate of SSNHL after mRNA vaccination per 1 million doses (primary outcome) in France between Jan 2021 and Feb 2022. This is a review of all suspected cases of SSNHL after mRNA COVID-19 vaccination spontaneously reported based on a comprehensive medical evaluation, including the evaluation of patient medical history, side and range of hearing loss, and hearing recovery outcomes after a minimum period of 3 months. Demographics included a median age of 51 years (range: 13-83 years old) and 59.2% female and 40.8% male. The two comparator groups were tozinameran and elasomeran. The median time to onset (TTO) for SNHL in <21 days in the tozinameran arm (n=108, 76.1%) was 4 (2-9) days, the TTO for SNHL in >21 days in the tozinameran arm (n=34, 23.9%) was 41 days (25-67). In the elasomeran arm, the median TTO for SNHL in <21 days (n=26, 86.7%) was 8 (1-21) days, and the median TTO for SNHL in >21 days (n=3, 10.3%) was 50 (26-144) days. Autoimmune, cardiovascular, or audio vestibular risk factors were present in approximately 29.8% (51/171) of the cases. Eligible SSNHL cases were selected using the MedDRA hierarchy, with preferred term selected from the narrow Standardized Medical

Signal evaluation criteria	Summary
	Queries "Hearing impairment." All data analyzed according to the American Academy of Otolaryngology-Head and Neck Surgery Foundation guidelines; patients were categorized according to a grading system modified from the Siegel criteria. No mechanism of action was listed in the article. Steroids were administered orally in 47.2% of cases. There were 8 positive rechallenges. Limitations include a large population-based pharmacovigilance studies or a case-control study appropriate for rare events is needed to further define the role of mRNA COVID-19 vaccination in the occurrence of SSNHL. Nationwide post-marketing surveillance did not include any control group, thus preventing the consideration of potentially important variables such as age or SSNHL time to onset. In conclusion, SSNHL after COVID-19 mRNA vaccines are very rare adverse events that do not call into question the benefits of mRNA vaccines but deserves to be known given the potentially disabling impact of sudden deafness. Therefore, it is essential to properly characterize post injection SSNHL, especially in the case of a positive rechallenge, to provide appropriate individualized recommendations. The lack of available data for the general population precluded comparisons with historical incidence or incidence in the unvaccinated population. Further studies are needed to establish the correlation between SSNHL and mRNA vaccination. Leong S, Teh BM, Kim AH. [70]: This was a cross-sectional study of patients seen in the otology clinic at an academic center. Patients completed a questionnaire on the development of new otologic symptoms within 4 weeks of COVID-19 vaccination. Demographics included a median age of 56.6 years (range: 16-101 years), and 59.4% female and 40.2% male. All mRNA vaccines were studied. No TTO or risk factors were provided. Diagnostic and audiometric data were obtained via retrospective chart review and may not have been reflective of the full workup that patients received. No mechanism of action provided. Cochlear implant and steroids (intratympanic dexamethasone or oral prednisone) were used as corrective treatment. No mention of rechallenge or dechallenge. Limitations included no specified diagnostic criteria were used for the collected data. Retrospective chart review may be reflective of the full workup the patients received. Otologic symptoms following COVID-19 vaccine are likely over-represented and thus cannot be generalized. Patients self-reported otologic symptoms. Patients were screened from otologic clinics only. Small sample size of 500 otology patients. In conclusion, patients reporting otologic symptoms following COVID-19 vaccination received various diagnoses of uncertain etiology. The incidence of SSNHL in these patients is comparable to the general otology patient population. Additional studies are required to determine the incidence of specific diagnoses following vaccination. Otologic symptoms following COVID-19 vaccination do not appear to have mechanistic associations with these specific vaccines. This study further affirmed that the benefits of COVID-19 vaccination significantly outweigh the risk. Cohen Michael O, Tamir SO, O'Rourke N, Marom T [71]: This was a retrospective study that compared SSNHL incidence rates over the COVID-19 outbreak and the COVID-19 vaccination campaign periods to pre-COVID-19 periods. Patients >12 years with auditory-confirmed SSNHL were enrolled. COVID-19 status and BNT162 inoculation records ≤28 days before SSNHL diagnosis were retrieved. Patients were categorized according to their date of presentation over four equal periods. Demographics included in the pre-pandemic Period 1 (07/2018–04/2019) (N = 22), the median age was 52 years (23–81), 6 (27.3%) females, and 16 (72.7%) males. In the pre-pandemic Period 2 (05/2019–02/2020) (N = 21), the median age was 47.5 years (20–75), 10 (47.6%) females, and 11 (52.4%) males. In the post-pandemic Period 3 (03/2020–12/2020) (N = 23), the median age was 51 years (20–82), 11 (47.8%) females, and 12

Signal evaluation criteria	Summary
	(52.2%) males. In the post-pandemic Period 4 (01/2021–10/2021) (N = 34), the median age was 49.5 years (17–82), 15 (44.1%) females, and 19 (55.9%) males. The BNT162b2 vaccine was studied. Eight out of 127,543 patients presented with SNHL on the median 13th day after vaccination. No risk factors were included. Patients with clinical history and audiometry supported an SNHL with other ICD-9 codes were determined to have SNHL. No mechanism of action discussed. Oral steroids, intratympanic steroids, and hyperbaric oxygen treatment were used as corrective treatment. Limitations included due to the pandemic, hearing tests were not routinely conducted, and confirmed COVID-19 patients were even less likely to be sent to undergo audiometric studies. At-home and mobile SSNHL tests have been developed and seem to be reliable but could not eventually replace an objective audiometry. Small sample size, no comparator. No mention of Moderna vaccine. No specified diagnostic criteria were used for the collected data. Large-scale audiometrically confirmed research is required. In conclusion, despite the increase in SSNHL cases during the period when vaccination with BNT162b2 had taken place, there was no increase in audiometrically confirmed SSNHL cases among these vaccine recipients. The association between COVID-19 disease and its vaccination warrants further large-scale, audiometrically confirmed research conducted over many years post-pandemic. Fisher R, Tarnovsky Y, Hirshoren N, Kaufman M, Stern Shavit S [72]: This was a retrospective chart review of all patients diagnosed with idiopathic sudden sensorineural hearing loss (ISSNHL) during 2021 was conducted and compared to patients who presented in 2018-2020. Patients collected in 2018 (n = 41) had a mean age of 51 (± 17.5) years, and 15 (37%) females. In 2019 (n = 38), the mean age was 49 (± 17.07) years, and 17 (45%) females. In 2020 (n = 31), the mean age was 49 (± 20.3) years, and 19 (63%) females. In 2021 (n = 51), the mean age was 48 (± 18.4) years, and 25 (50%) females. In 2021 of the nonvaccinated population (n = 38), the mean age was 47 (±20) years, and 16 (43%) females. In 2021 of the vaccinated population (n = 13), the mean age was 52 (± 18.55) years, and 9 (70%) females. The 2018–2019 group was used as a control group before the SARS-CoV-2 pandemic and vaccination era. The 2020 group was used for the period in the presence of the pandemic and before the vaccination era. Comparisons were made between patients diagnosed in 2021 with previous years and between the vaccinated and nonvaccinated. The time to onset was 14.9 ± 9.87 days. No risk factors were included. All medical records of patients diagnosed and treated with ISSNHL at a tertiary medical center between Jan 2018 and Dec 2021. Patients were excluded if (1) their diagnosis did not meet ISSNHL criteria, (2) they had Meniere's disease, (3) were later diagnosed with vestibular Schwannoma per MRI, (4) had a progressive or bilateral loss, or (5) lacked information regarding their diagnosis, treatment, or vaccination status. The vaccinated group consisted only of vaccinated patients who received a vaccine dose in the 30 days preceding the ISSNHL presentation. No mechanism of action was discussed. Systemic prednisone for 7 days and intratympanic dexamethasone injection were used for corrective treatment. No rechallenge or dechallenge discussed. Limitations included this was a retrospective, relatively small cohort from a single center. As such, it was exposed to selection bias and may not accurately represent other medical centers, even though we found a similar incline as the Israeli large-scale population-based study. No statistically significant difference was found between different years or between the vaccinated and nonvaccinated groups. This study evaluated a population vaccinated with the Pfizer COVID-19 vaccine almost exclusively. No risk factors documented. In conclusion, a marked incline in ISSNHL incidence was seen in 2021, of which 25% of patients reported experiencing symptoms within a month post-anti-COVID-19 vaccination. While other

Signal evaluation criteria	Summary
	causative factors could be sought, an association with the vaccine cannot be ruled out, and further large-scale research is needed. Nevertheless, the benefits of the anti-COVID-19 vaccine immensely outweigh any potential otologic adverse effects. Ekobena P, Rothuizen LE, Bedussi F, et al [68]: This was four case studies with only 1 case of SNHL in a 61-year-old female vaccinated with Pfizer-BioNTech. Time to onset was 10 days. No risk factors were discussed. Patient received a pure tone audiogram, bilateral otoscopy, and video head impulse test as diagnostic tests. Prednisone 5 days after and vestibular physiotherapy was initiated as corrective treatment. The patient declined the second vaccine. Limitations included this was an isolated case report with Pfizer-BioNTech vaccine. In conclusion, the occurrence of audio-vestibular manifestations following mRNA-based vaccines needs ENT monitoring to support their causality in such rare vaccine-related adverse events. Audio-vestibular disorders appeared of transitory nature, including hearing loss, and should not deter further efforts in large-scale vaccination campaigns against SARS-CoV-2. The benefits of the COVID-19 vaccination appear to outweigh the risks of audio-vestibular disorders, since reported cases are mostly transient with favorable outcome. Conclusion: In conclusion, the literature is consistent with findings from the GSDB. Overall, the literature search results did not provide evidence of causal association between mRNA vaccines or mRNA-1273 and SNHL.
Discussion	The MAH conducted an extensive evaluation of a validated signal of SNHL due to a request from a health authority (TGA) received on 22 Jun 2023. The signal evaluation included a cumulative review (18 Dec 2020 to 17 Jun 2023) of clinical trial data as well as post-marketing information from the GSDB and the literature for reports included in the HLT of "Hearing Losses". SNHL is the most common type of hearing loss estimated at 5-27/100,000 per year with higher reported rates in men and elderly populations. In sudden onset sensorineural hearing loss (SSNHL), the exact pathophysiology is still unknown; however, it is most likely caused by a viral infection. According to the National Institute on Deafness and other Communication Disorders, men are twice as likely to experience hearing loss, but are less likely than women to seek help. There is evidence in the literature that sex and gender may influence the development of SNHL. The prevalence of hearing impairment is higher among older men than older women. However, the GSDB cases showed the highest cases were seen in the 50–64-year-old age group and higher proportion seen in women compared to men. Potential triggers include infections and ototoxic medications, as well as other immune activation events resulting in inflammation to the ear as postulated in the literature. The exact etiology and pathophysiology of SNHL remain unknown. New-onset hearing loss should be investigated and undergo full audiometric evaluation by a multidisciplinary team (e.g., otolaryngologist, audiologist, radiologist, and speech/language therapist). There was no imbalance reported from clinical trials for events within the terms included in the MedDRA HLT "Hearing Losses", as well as for the specific PT of Hypoacusis, Tinnitus, and information from the GSDB as well as the literature supports the recommendations received from the PRAC from the review of PBRER#4 (Procedure EMEA/H/C/PSUSA/00010897/202212), that stated: "The data presented above does not change the PRAC Rapporteur's opinion that the available evidence is insufficient to establish causal association between 'hearing loss' and Spikevax. No further actions beyond routine PV are thus considered warranted at this stage."

Signal evaluation criteria	Summary
	A review of cases identified during the reporting period did not show any prominent clinical pattern of occurrence of SNHL outside of what would be expected in a large, vaccinated population. Many of the reports were heavily confounded by historical conditions, concurrent illnesses, and concomitant medications. The observed reporting rates of SNHL are well below background incidence rates. Overall, 18 SNHL reports in 978,005,565 doses administered, shows an approximate reporting rate of 0.02 per 1 million doses administered.
Conclusion	A cumulative review, including an updated review conducted during the reporting period of PBRER 5, of the GSDB for reports under the HLT of "Hearing losses" received after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran was conducted, as per request received from a HA. Cumulative, as of 17 Jun 2023, the MAH identified 2,479 cases (2,757 events), including reports from the PBRER#5 RP, for individuals between the ages of 5 to 101 years old. The review of cases identified showed that most of the cases were heavily confounded by known risk factors associated with acute sensorineural hearing loss. There were five cases associated with herpes zoster reactivation. In general, it is difficult to adequately analyze post-authorization data due to inherent limitations in spontaneous reporting. Evaluation of the data did not provide any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Based on the literature review of the mechanisms of action postulated including direct viral invasion of the middle ear and vascular injury to the terminal vessels of the middle ear and the three epidemiological studies that aimed to assess the relationship between COVID 19 vaccination and hearing loss do not provide convincing evidence to show an association with vaccination; moreover, a pathophysiologic process to explain such an association has not been shown. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Based on the cumulative review of available data as of 17 Jun 2023, the MAH considers there is insufficient evidence to consider Hearing Loss as a safety concern as this signal is considered refuted. Hearing loss will continue to be monitored as part of routine pharmacovigilance activities, and the topic of SNHL will be added as an ad-hoc adverse event to study mRNA-1273-P920 (Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States). No changes to the product information or inclusion in to the RMP are required at this time.

16.3. Evaluation of Risks and New Information

16.3.1 New Information on Important Identified Risks

16.3.1.1 Anaphylaxis (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the known identified risk of Anaphylaxis, has not identified any additional clinically relevant new safety

information for this topic. The characterization of this important risk as described in Section 16.4, below, remains valid.

16.3.1.2 Myocarditis and Pericarditis

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

Table 16.8 Myocarditis and Pericarditis

Source of New Information	o Modema GSDB o Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 240 o New and Significant Safety Information: None (0).
Background	An association between myocarditis and pericarditis and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events, particularly among adolescent and young-adult males within 7 days after Dose 2.
Methods	Cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [73] [74], and the CDC working case definition [75] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	*Myocarditis and Pericarditis Cases Involving Elasomeran* During the review period, the MAH received 263 cases (271 events) of myocarditis and pericarditis with all cases considered serious cases. There were 13 cases reporting a fatal outcome (See Appendix 12.17). There were 147 medically confirmed cases involving elasomeran. A total of 162 (61.6%) cases involved males and 94 cases (35.7%) involved females; 7 cases (2.7%) were missing gender information. The mean age of the patients was 42.1 (SD: 17.5), with a median 40.0 years (range 3.0 to 90.0 years); 44 cases were missing age data. Most events were reported after Dose 2 (89; 33.8%), followed by Dose 3 (74; 28.1%). There were 51 (19.4%) reports with an unknown dose number. Of the 212 cases with a known dose number, 65 cases (30.7%) were within 7 days of vaccination. During the reporting period, 101 events (38.4%) were reported as "Recovered/ Resolved/ 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

	in patients ≥ 18 years of age, 28 cases met Level 1; 19 cases met Level 2; 9 cases met Level 3; 185 cases met Level 4, and 12 cases met Level 5. Also, there was one report where the event of myocarditis was reported after Dose 2 with Comimaty, hence case classification and causality assessment were not conducted. (See Appendix 12.17). According to the CDC working definition [75], 22 cases were classified as "Confirmed"; 34 cases were classified as "Probable"; 184 cases were classified as "Unassessable"; one case was classified as "Acute Pericarditis", and 13 cases were considered "Not a case" of myocarditis or pericarditis. (See Appendix 12.17). According to the WHO causality assessment, there were 3 cases considered "Probable"; 40 cases considered "Possible"; 166 cases considered "Unassessable", and 32 cases considered "Unlikely" related to the vaccine. Thirteen case reports were not assessed given that they were not considered cases of myocarditis or pericarditis, including the case that reported the events after dose 2 with another mRNA COVID-19 vaccine. (See Appendix 12.17). For the 13 cases reporting a fatal outcome, six were the same literature report from Korea, and they were all considered "Unassessable" according to the WHO causality assessment given that important information is missing from these reports including concomitant and treatment medications, medical histories, additional test conducted, among others. This study has several limitations that are included in Section 11. For the other seven fatal reports four were considered unassessable due to the lack of information, and 3 were considered unlikely related to the vaccine based on associated comorbidities that provide a more plausible explanation for the occurrence of the reported events. (See Appendix 12.17). *Subpopulation Analyses for cases involving elasomeran* • **Children (2 years to 5 years):** During this reporting period, 2 cases (2 events) were reported. Both reports were from [redacted] Both were classified as Level 3 according to the Brighton Collaboration case definition, as Probable according to the CDC case definition, and as Possible according to the WHO causality assessment evaluation. One case ([redacted] reported the events two days after Dose 1; and the second case ([redacted] was two days after Dose 2 (See Appendix 12.17). • **Children (6 years to 11 years):** During this reporting period, there were no cases reported in this age group. • **Adolescents (12 years to 17 years):** During this reporting period, 7 cases (7 events) were reported. One case ([redacted]) was reported three days after Dose 1. Five reports were after Dose 2 with one case reporting a fatal outcome ([redacted]. The reported cause of death was liver transplant, sepsis and endocarditis. There was one case reported after Dose 3 ([redacted]. See Appendix 12.17 for more information.

	Myocarditis and Pericarditis Cases Involving elasomeran/imelasomeran During the review period, the MAH received 49 cases (49 events) of myocarditis and pericarditis involving elasomeran/imelasomeran. All cases were considered serious, and 18 cases were medically confirmed. There were 2 cases with a fatal outcome. There were no gender differences in the number of cases reported involving males (24; 49.0%) compared to cases involving females (24; 49.0%); 1 case (2.0 %) was missing gender information. The mean age of the patients was 59.4 (SD: 18.9), with a median 64.5 years (range 24.0 to 95.0 years); 9 cases were missing age data. During this reporting period, most events were reported after an unknown dose number (24; 49.0%). Of the 24 events with a known dose number, 14 events (56.0%) were within 7 days of dosing. There were 27 cases (55.1%) reporting an outcome of "Recovered/Resolved/ Recovering." During the reporting period, there were no reports of myocarditis or pericarditis received for individuals <18 years of age. According to the Brighton Collaboration case definition for myocarditis and pericarditis, 1 case met Level 1; 6 cases met Level 2; 2 cases met Level 3; 38 cases met Level 4, and 2 cases met Level 5. According to the CDC working definition (Gargano 2021), 1 case was "Confirmed"; 7 were considered "Probable"; 39 were "Unassessable" cases, and 2 were considered "Not a case". According to the WHO causality assessment, there were 4 cases considered "Possible"; 38 cases considered "Unassessable"; 5 cases considered "Unlikely", and 2 cases were not assessed as they were not considered a case of myocarditis or pericarditis. For the 2 cases reporting a fatal outcome, according to the WHO causality assessment, one case was considered "Possible", and the other was "Unassessable" due to lack of information. [redacted] (WWID: [redacted]) is a regulatory authority case concerning a 77-year-old male patient, with relevant medical history of transcatheter aortic valve implantation, who experienced pyrexia, dyspnoea, chest pain, chills, and tremor on the same day after receiving a dose of elasomeran/imelasomeran. CRP was elevated and there was pericardial effusion. Patient was tolerating symptoms well to start with and was treated with anti-inflammatories at full dose and colchicine. Patient developed sudden shortness of breath, tamponade and was admitted to the hospital where a pericardial drain was inserted, but patient continued to deteriorate and died. On an unknown date patient had an electrocardiogram which showed normal sinus rhythm, echocardiogram showed good LV function. Cardiac MRI, CT pulmonary angiogram, Jugular venous pressure, CT scan, and a Transcatheter aortic valve implantation (TAVI) were done with no results reported. This case was considered a Level 2 according to the Brighton Collaboration case definition; Probable according to the CDC case definition and was considered Possible according to WHO causality assessment. [redacted] (WWID: [redacted]) is a regulatory authority case concerning a 95-year-old female patient, with relevant medical

	history of chronic kidney disease, atrial fibrillation, angina pectoris, hypertension, left ventricular hypertrophy, and thrombosis, who experienced myocarditis. The event occurred on the same day after a booster dose of elasomeran/imelasomeran. The report mentioned the patient became unwell approximately 12 after vaccination. Her respiratory rate was high (60), with "wet" cough and low O2 Saturations (60%). Paramedics attended and suspected a heart attack, then suspect COVID, but all tests were negative. Hospitalization was refused and the patient received "end of life pathway treatment" for symptom control. She died one week after vaccination. Reported cause of death was myocarditis. It is unknown if an autopsy was performed. No further information regarding the event and cause of death have been provided. Patient's age and mentioned medical history remains as confounders for the fatal outcome. According to the WHO causality assessment this report is unassessable due to the complete lack of information. *Myocarditis and Pericarditis in Pregnancy involving Elasomeran/imelasomeran* There was one report of pericarditis reported following exposure to elasomeran/imelasomeran during pregnancy ([redacted] - [redacted] This regulatory report involved a 33-year-old female patient, with medical history of pre-eclampsia and current condition of factor V Leiden mutation, who 5 weeks after a dose of elasomeran/imelasomeran vaccination which was first dose of COVID-19 vaccination schedule, experienced tachycardia, dyspnea, palpitations, fatigue, and dyspnea and was diagnosed with pericarditis and pulmonary embolism. In addition, maternal exposure during pregnancy was reported in the case since the patient was vaccinated with elasomeran/imelasomeran during pregnancy of approximately 7 weeks gestation period at exposure. Last menstrual period (LMP) was 26 Jul 2022 and expected delivery date was 02 May 2023. An echocardiogram confirmed pericarditis. Cardiac troponin level was normal, and a chest x-ray did not detect any abnormality; however, the ventilation/perfusion scan reported a diagnosis of pulmonary embolism. Treatment for the event included enoxaparin and aspirin and the patient was hospitalized for 1 week. The outcome of pregnancy is pending and unknown at the time of the report. Outcome for pericarditis was resolved and for pulmonary embolism was resolving. *Company assessment*: The prolonged TTO made this report unlikely related to vaccination and the concurrent medical history of myotonic dystrophy (type 2 myotonic dystrophy) and Factor V Leiden mutation, as well as diagnosis of COVID-19 at an unknown time are important confounders in this report. There is also a report of pre-eclampsia at an unknown time and with no additional information provided. This case was considered Level 2 according to the Brighton Collaboration case definition, a probable case according to the CDC case definition, and unlikely related to vaccination according to WHO causality assessment. *Myocarditis and Pericarditis Cases Involving Elasomeran/davesomeran* During the review period, the MAH received 26 cases (26 events) of myocarditis and pericarditis involving elasomeran/imelasomeran, all of which were considered serious cases, and 23 cases were medically confirmed. There were no cases with a fatal outcome. A total of 18 (69.2%) cases involved males and 8 cases (30.8%) involved females. The mean age of the patients was 32.8 (SD: 21.3), with a median 30.0 years (range 11.0 to

	78.0 years); 4 cases were missing age data. During this reporting period, most cases were received after an unknown dose number (12; 46.2%). Of the 14 cases with a known dose number, 9 cases (64.3%) were within 7 days of vaccination. There were 14 cases (53.8%) reporting outcome as "Recovered/ Resolved/Recovering". According to the Brighton Collaboration case definition for myocarditis and pericarditis, 1 case met Level 1; 9 cases met Level 2; 1 case met Level 3; 14 cases met Level 4, and 1 case met Level 5. According to the CDC working definition [75], 1 case was "Confirmed"; 10 cases were "Probable"; 14 cases were "Unassessable", and 1 case was considered "Not a case". According to the WHO causality assessment, there were 11 cases considered "Possible"; 12 cases considered "Unassessable"; 2 cases considered "Unlikely", and 1 case was not assessed as it was not considered a case of myocarditis or pericarditis. *Subpopulation Analyses for cases involving elasomeran/davesomeran* • **Children (2 years to 5 years):** During this reporting period, there were no cases reported in this age group. • **Children (6 years to 11 years):** During this reporting period, there was one case reported in this age group. [redacted] is a report received from Taiwan involving an 11-year-old male child, who received elasomeran/davesomeran as a 3rd dose and two days later experienced chest tightness, nausea, decreased appetite, and non-radiating chest pain located in midsternal area. He was then taken to ED and his vital signs were reported to be stable without tachycardia or dyspnea. His physical examination revealed no remarkable finding and the ECG showed normal sinus rhythm. Two-dimensional echocardiography and PET scan were normal. However, lab data showed elevated hs-Troponin-I (2.55) and hs-CRP (2.2). Treatment for the events included fluid supplement and management of accompanied symptoms. The outcome of the event was recovered. • **Adolescents (12 years to 17 years):** During this reporting period, there were eight cases reported in this age group. All cases, except one that had an unknown outcome, reported a "Recovered/ Resolved/Recovering" outcome. There were no fatal reports. There were seven cases after a 3rd or a 4th dose with elasomeran/davesomeran, and 1 case with an unknown dose number. All reports were within 8 days after vaccination. All 8 reports were considered Level 2 according to the Brighton Collaboration case definition: "Probable" according to the CDC case definition, and "Possible" according to the WHO causality assessment. See Appendix 12.17 for additional information.
Discussion	A review of the data received during the reporting period of this PBRER, showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. There were seventy-five reports of myocarditis or pericarditis following exposure to any of the bivalent vaccines (elasomeran/imelasomeran or elasomeran/davesomeran) in this

	reporting period. To date, the clinical presentation of myocarditis after any of the bivalent vaccines (elasomeran/imelasomeran or elasomeran/davesomeran) does not differ from those with elasomeran, with cases presenting as mild cases, and recovering within a short time following standard treatment and rest. Analysis of safety data housed in the MAH's GSDB, as well as review of the literature, showed that most of the individuals who experienced an event of myocarditis/ pericarditis after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran 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 [76]. Please refer to Section 8 for results from the PASS study on the evaluation of myocarditis and pericarditis. Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers cases of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for these vaccines far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.
Conclusion	Evaluation of the data during this reporting period did not provide any new safety information that would differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Review of the data also show no difference in the observed safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran for children (6 months to 12 years of age), the adolescent population (12 years to 17 years of age), or in those individuals receiving a 3rd dose of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran when compared to >18 years old. Reporting rates are lower for children than for adolescents and young adults. Based on the analysis of all the safety data received during the reporting period of this PBRER, ModernaTx, Inc. considers that cases of myocarditis and pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Periodic data analysed during the reporting period of this PBRER, supported an update of the product information, indicating that most cases recover, and that some cases required intensive care support and fatal cases have been observed. Data presented in a study conducted by Le Vu et al., and included in PBRER 4, indicated that in a period of 28 days after the second dose, there were 1.88 (95% CI: 0.956, 2.804) extra cases of myocarditis in 16- to 24-year-old males per 10,000 compared to unexposed persons. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including PASS to further characterize them. Based on the cumulative review of safety data, including literature and case reports, the SmPC and the PIL have been updated in section 4.4 Special

	warnings and precautions indicating that most cases recover, some required intensive case support and fatal cases have been observed. The benefit-risk evaluation remains positive.

16.3.2 New Information on Important Potential Risks

16.3.2.1 Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)

Based on the final assessment report for PBRER #4 (Procedure no.: EMEA/H/C/ Periodic Safety Update Single Assessment (PSUSA)/00010897/202212, received after the DLP of this PBRER) the final recommendation regarding removal of VAED including VAERD as an Important Potential Risk from the EU RMP, was endorsed, and that "based on the cumulative evidence, this risk is refuted and no longer considered important in the context of the RMP and the PBRER. It should be removed from the PBRER list of safety concerns and an evaluation of new information on this topic in future PBRERs is not expected".

16.3.2.2 IgA Nephropathy (Safety concern in PBRER only)

Evaluation of information received during the PBRER reporting interval relating to the known important potential risks of IgA Nephropathy for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran has not identified any additional clinically relevant new safety information for this topic. The characterization of this important risk as described in Section 16.4 below, remains valid. IgA Nephropathy is monitored in accordance with a request from a Health Authority.

Table 16.9 IgA Nephropathy

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 140 ○ New and Significant Safety Information: None (0).
Background	Following review of PBRER#4, a Health Authority requested the following information on IgAN: • *The rapporteur concludes that reporting of IgAN is rare and that the evidence is currently inconclusive regarding a possible causal role of vaccination with elasomeran or bivalent. Thus, the MAH should maintain IgAN as an important potential risk in the future PBRERs. In the next PBRER, it is therefore expected that the MAH will present new information on IgA nephropathy and risk characterization in PBRER section 16.3 and 16.4, respectively.*

	• *The vaccine type is now specified (in the Ota paper) the MAH is requested to confirm the origin of these 3 cases ([redacted], [redacted] and [redacted]) and to reclassify their causality status accordingly. This request should be addressed in the next PBRER.*
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 utilizing the WHO-UMC standard causality categories and criteria.
Results	Refer to Appendix 12.18 for information about the medical topic. During the review period, the MAH received 29 reports (36 events) that had PTs within the HLT of Glomerulonephritis and Nephrotic Syndrome. There were 25 medically confirmed reports involving elasomeran or bivalent. The 29 reports (whether or not the PT IgA Nephropathy was coded) were medically reviewed Appendix 12.18. Out of the 29 reports, there were 8 cases, all serious, that involved IgA nephropathy; there were no cases reporting a fatal outcome. Of the 8 cases, 7 involved elasomeran, and one (1) case involved elasomeran/davesomeran. Out of the 8 cases involving IgA Nephropathy, five (5) cases were new onset (de novo) IgA nephropathy, and two (2) cases were considered IgA nephropathy flares because they were reported to have exacerbation of IgA nephropathy that had been diagnosed prior to elasomeran or bivalent vaccination. One (1) case report did not provide information allowing determination of de novo vs flare. The majority of cases involved females (6 cases; 75.0%) compared to males (2 cases, 25.0 %). The mean age was 49.4 years (SD: 21.3) and median age was 38.5 years (range: 29.0 to 80.0 years). Time to onset ranged from day 0 to 248, with no common pattern observed regarding TTO. **Health Authority Requests** A Health Authority requested that the origin of three previously reported cases with unknown vaccine type be reviewed because an article reporting those cases was subsequently published that identified the vaccines involved [77]. The Moderna COVID-19 vaccine was reported for the case [redacted] (Appendix 12.18). The other two cases reported in the article involved Pfizer vaccine ([redacted] and [redacted]) and are now classified as invalid in the MAH's GSDB.
Discussion	During the reporting period in the MAH's GSDB, there were 8 cases of IgA nephropathy that were identified through medical review: 7 cases involved elasomeran, no cases involved elasomeran/imelasomeran and one case involved elasomeran/davesomeran. Of the 8 cases of IgA nephropathy, five cases were de novo and two cases were flares, one case had no information on de novo vs flare. No new patterns were observed with regard to IgAN-related data for the three vaccines noted above. Renal patients are at increased risk of serious illness and death due to COVID-19 disease; thus, vaccination is of great benefit to them.

	Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers cases of IgA nephropathy to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for elasomeran or bivalents far outweigh any possible vaccine-associated risks, including the risks of IgA nephropathy.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Mention of a literature article by Ma and Xu [78] was requested by a Health Authority. This article began with a summary of cases of new onset IgAN published in the medical literature before 10 Jul 2022; analyses based on these cases may be susceptible to publication bias. The authors also made general reference to the "multi-hit hypothesis of IgA nephropathy" and to the mucosal origin of hypogalactosylated IgA1 in IgA nephropathy. Also, the authors proposed three hypotheses for the possible 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. The authors acknowledged that they were unable to infer a causal relationship between vaccine and IgAN and that the mechanisms that they proposed for the vaccine-IgAN association are not proven. Based on the analysis of all the safety data received during the reporting period, and taking the above mentioned publication into consideration and risk characterization, the MAH considers that cases included under the medical topic of IgA Nephropathy, reported in temporal association with the administration of elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern and the information provided does not support evidence of causal association between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure and IgA nephropathy. The MAH will continue to monitor events for IgA Nephropathy using routine surveillance. The benefit-risk evaluation remains positive.

16.3.3 New Information on Other Potential Risks Not Categorized as Important (if applicable)

Not applicable.

16.3.4 New Information on Other Identified Risks Not Categorized 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 elasomeran-containing vaccines before and during pregnancy has not identified any additional clinically relevant new safety information for this topic. The characterization of these important risks as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, below, remains valid.

Table 16.10 Use in pregnancy

Source of New Information	○ Modema GSDB ○ Literature Sources ○ Search Criteria Applied: Appendix 13.4 ○ Retrieved: 519 ○ New and Significant Safety Information: None (0).
Background	Use of elasomeran-containing vaccines before and during pregnancy is an area of missing information in the RMP; no CTs were conducted among pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Since elasomeran-containing vaccines 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 elasomeran-containing vaccines 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 12.19 for Methods of Evaluation
Results	Refer to Appendix 12.19 for additional information. **Overview of Pregnancy Cases Who Received Elasomeran** During the review period, the MAH received 206 pregnancy cases (802 events) with 64 serious cases (210 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. Five (5) cases reported a fatal outcome, and 69 cases were medically confirmed. A slightly lower proportion (31.1%) of cases during the review period were reported as "serious" compared to the cumulative period (35.4%). Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" in addition to known reactogenicity events and are reported as "serious" cases; See below in "Serious and Fatal Cases and Serious Pregnancy-related Events Elasomeran." Serious cases should be interpreted with caution as many do not meet the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness

	classification in some countries, and in part due to some regulatory authorities' coding all events as serious in a given serious case. The majority (73.0%) of pregnancy-specific cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been seen in previous review periods. The most frequently reported PTs during the reporting period were reactogenicity events, consistent with the product safety profile and is similar between the reporting period and the cumulative period. During the review period, there were no pregnancy cases reporting events of myocarditis and/or pericarditis after receipt of elasomeran. *Pregnancy-specific Events – Elasomeran)* During the review period, of the 206 pregnancy cases received by the MAH, only 137 pregnancy cases reported a pregnancy-specific adverse event/outcome in individuals who received or had a medical history of maternal exposure to elasomeran. (Please note: Not all pregnancy cases report a pregnancy-specific event as identified by the MI-Preg SMQ). These 137 cases reported 154 pregnancy-specific events with 49 serious cases (46 serious events). One case reported a fatal outcome, and 33 cases were medically confirmed. After the exclusion of PTs that do not indicate an adverse pregnancy-specific event/outcome, "Abortion spontaneous" remains the most frequently reported adverse pregnancy event/outcome for both the reporting and cumulative periods. (Refer to Spontaneous abortions, Stillbirths, and Foetal Deaths evaluations added below). A summary table of all pregnancy outcomes, stratified by timing of exposure as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/313666/2005)" is presented in Appendix 12.19. *Serious Pregnancy-specific Events and Fatal Cases– Elasomeran* During the review period, of the 64 reported serious pregnancy cases, when restricted to pregnancy cases reporting only pregnancy-specific events, only 32 serious cases were identified as including serious pregnancy-specific events (34 events). One case reported a fatal outcome, and 15 cases were medically confirmed. Review of the serious pregnancy-specific events during this reporting period did not identify any new safety concerns. These cases reflect obstetric events observed in temporal association with elasomeran administration. Many of these cases had limited information about past medical and obstetric history, gestational age at time of vaccination, or onset of AE, diagnostics, treatment, and outcome. Where data were available, confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy [including advanced maternal age, concomitant medications, comorbidities (such as hypothyroidism, diabetes) and previous relevant obstetric history including fetal loss] were present.

Fatal Pregnancy Cases– Elasomeran

During the review period, 5 pregnancy cases were coded as fatal in individuals who received or had a medical history of maternal exposure to elasomeran. Case [redacted] concerns a neonatal death which was previously reported during the PBRER #3 review interval but had updates regarding PTs added during this reporting interval. These updates did not affect original causality assessment. Case [redacted] appears to be misclassified as a pregnancy case given the patient's age (48 years) and that there was no indication that this individual was either pregnant or lactating. The remaining 3 cases describe 2 maternal deaths ([redacted] and [redacted]) and 1 neonatal death ([redacted]).

The 2 cases of maternal death are summarized below:

[redacted]: This regulatory authority case concerns a 33-year-old female who about 5 months after receipt of an unspecified dose of elasomeran experienced nasal sinus cancer ("a fast-growing SNUC tumour stage 4 was detected"). A past medical history of "pregnancy (6 premature month)" was reported; outcome of the pregnancy was unknown. Patient died about 9 months after the diagnosis of cancer and the reported cause of death was listed as sinonasal undifferentiated carcinoma. It is unknown if an autopsy was performed. Causality is "Unassessable" given the limited data available regarding LMP, obstetrical history, concomitant medications, COVID-19 vaccination history, clinical course, investigations and treatment.

[redacted] This regulatory authority case was reported by another health care professional concerning a 30-year-old female with history of complete right bundle branch block, ventricular extrasystoles, and mitral valve billowing with regurgitation, who 404 days (approximately 13 months) after a dose of elasomeran, reported as third dose of her COVID-19 immunization schedule, experienced sudden death. The patient previously received two doses of Tozinameran COVID-19 vaccine. The report stated that the patient was pregnant at the time of death (gestation week was not reported). Reportedly, she was asymptomatic the morning of the event. Approximately 6 months after vaccination with elasomeran, she had a cardiological control performed with normal and stable results compared to the previous check-up (one year prior). The report revealed normal sized cardiac cavities, left ventricular ejection fraction of 61%, global longitudinal strain of -21%, normal diastology, slight billowing of the mitral valve with minimal insufficiency. The resting ECG showed a well-known block of complete right branch; the long-term ECG reported monomorphic isolated ventricular extrasystoles with a 6.1% load. The cause of death was not reported. An autopsy was performed, although the report was not provided. No further information has been disclosed. Causality is "Unlikely" given long latency (13 months) and her underlying cardiac disease provides an alternate plausible explanation to the event.

The case reported as neonatal death with prenatal exposure to elasomeran is summarized below:

[redacted] This regulatory authority case reported by a consumer concerns an 18-day-old female neonate who 18 days after birth

	experienced brain neoplasm and congenital hydrocephalus and died 3 days later. The cause of death was reported as neonatal respiratory failure and hydrocephaly obstructive; no autopsy was performed. It is reported that the diagnosis of brain tumour and congenital hydrocephalus was made 235 days after her mother received a third COVID-19 vaccination with first dose of elasomeran. It is unclear if the mother received elasomeran during pregnancy given no LMP, estimated due date, or gestational age at delivery was provided. Based on the timing of vaccination, it is possible that the mother received the vaccination prior to conception if the neonate had a preterm birth. Causality is "Unassessable" given extremely limited data available to determine if elasomeran was given during pregnancy and temporal association, fetal/infant diagnostic evaluation, and treatment. No safety concerns were identified from the review of serious and fatal cases received during the reporting period for the pregnancy subpopulation. *Fetal Deaths– Elasomeran* The MAH performed medical reviews of all reports coded as "fetal death" and "stillbirth". Fetal 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 United States [79]. *Spontaneous and Missed Abortions – Elasomeran* During the review period, 10 serious pregnancy cases with a medical history of maternal exposure to elasomeran reported spontaneous abortion with 11 serious events. Of the 10 cases, 3 cases were medically confirmed, and no cases were coded as fatal. The mean age of the cases was 35.6 years (SD: 4.5) and median age of 35.5 years (range 26-41 years). Of the cases with available data on the dose number prior to the event, there were more events reported after Dose 2 (27.3%) than Dose 1 (18.2%), and Dose 3 (9.1%). This must be interpreted with caution as one does not know how many pregnant women have received one versus two versus three or more doses; and, of note, 45.5% of events are missing dose information. Although the data are limited, when TTO and dose number were known, events most frequently (50.0%) occurred 30 or more days after vaccination. The median TTO was 82.0 days (range 1-435); there was no unusual clustering by dose or TTO. *Stillbirth – Elasomeran)* Stillbirth has varying global definitions based on GA and fetal weight. For the purposes of this PBRER, and as described above, the MAH applied a definition of stillbirth as fetal death after 20 weeks gestational age [79]. Congenital anomalies, placental dysfunction associated with fetal growth restriction, and maternal medical diseases and obstetric complications (such as pre-eclampsia, chorioamnionitis, and infections such as group B Streptococcus and cytomegalovirus) are common causes of stillbirth. Advanced maternal age (over 40 years) has been associated with an increased risk of stillbirth as well. Evaluation of spontaneous reports are limited due to a lack of complete information, such as medical and obstetric history

	as well as diagnostic evaluation and results performed to determine the cause of the stillbirth. During the reporting period, 4 pregnancy cases that reported stillbirth were identified through medical review of cases that were coded as "fetal death" and/or "stillbirth." These cases are summarized below: [redacted]: This spontaneous retrospective pregnancy case reported by a consumer described a female patient of an unknown age, who received an unspecified dose of elasomeran at an unknown timing and relation to pregnancy. It was reported that the outcome of the pregnancy was a stillbirth, and the cause of stillbirth was not provided. Causality is "Unassessable" given the limited data available regarding LMP, estimated due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinical course. [redacted]: This regulatory authority case reported by another health care professional concerns a 16-year-old female who received a third dose of elasomeran at an unknown time and relation to pregnancy. It was reported that a stillbirth occurred 3 months and 14 days following vaccination. The cause of stillbirth and whether an autopsy was performed was not provided. Causality is "Unassessable" given the limited data available regarding LMP, estimated due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinical course. [redacted]: This regulatory authority case reported by a consumer concerns a 36-year-old female, who received an unspecified dose of elasomeran at an unknown time and relation to pregnancy. It was reported that pregnancy ended in a stillbirth at 20 weeks gestational age (seven months after vaccination). The cause of stillbirth and whether an autopsy was performed was not provided. Causality is "Unassessable" given the limited data available regarding LMP, estimated due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinical course. [redacted]: This regulatory authority case reported by a consumer concerns a 36-year-old female, with previous vaccination history with Comirnaty (two doses), and who experienced a stillbirth at an unknown GA, 32 days after receipt of the first dose of Pfizer-BioNTech vaccine. She received a second dose of Pfizer-BioNTech vaccine 20 days after stillbirth and a first dose of elasomeran as the third dose of her COVID-19 immunization schedules, 192 days after the stillbirth. The cause of the stillbirth and whether an autopsy was performed was not provided. Causality is 'Unlikely" given that there is no temporal association with receipt of elasomeran as the stillbirth occurred prior to vaccination. Based on medical review of the "stillbirth" reported cases many reports had limited data and lacked crucial information to make a robust case and causality assessment. In addition, it is well known that, typically, up to 60% of stillbirths cannot be attributed to an identifiable fetal, placental, maternal, or obstetric etiology due to lack of sufficient information or because the cause cannot be determined at the current level of diagnostic

ability [79].

It was noted that for many of the pregnancy reports coded as "prospective," there was no evidence in the report to support this classification; thus, this classification must be interpreted with caution as there is a high likelihood of coding errors.

Overall, cases of stillbirth and spontaneous abortion received during the reporting period were similar to the cumulative period and no safety concerns were identified.

A summary table of all pregnancy outcomes classified as retrospective and prospective and stratified by timing of exposure, as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorization Data (EMEA/CHMP/ 313666/2005)", is presented.

Congenital Anomaly– Elasomeran

During the reporting period, 15 pregnancy cases that reported a PT from the Congenital, familial and genetic disorder SOC were identified. After medical review, no reporting patterns and no safety concerns were identified. Of the 15 pregnancy cases, 5 cases occurred among foetuses and neonates from pregnancies exposed to elasomeran and 10 cases were determined to be "non-pregnancy cases" as they either represented medical history miscoded as an AE, or a pre-existing congenital anomaly detected in a non-pregnant person. All 5 pregnancy cases reported live birth at delivery. One case ([redacted] reported a fatal outcome (neonate died 3 days after birth) (See Fatal Pregnancy Cases-elasomeran section), 2 cases ([redacted] and [redacted] reported outcome as "not recovered/not resolved", and 2 cases [redacted] and [redacted]) reported outcome as "recovered/resolved.

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

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 (14 total events; 10 serious events) among children under 6 years of age with a medical history of maternal exposure to elasomeran during pregnancy. Two cases reported fatal outcomes and 2 cases were medically confirmed. Both fatal cases ([redacted] and [redacted]) were discussed in the *Fatal Pregnancy Cases– elasomeran* section above.

The 4 remaining serious cases are summarized below:

[redacted]: This regulatory authority case reported by a consumer concerning a [redacted] old infant with unknown gender, who experienced talipes (club foot). Reportedly, the mother received elasomeran reported as third dose of her COVID-19 immunization schedule, around the time of pregnancy conception. The foetus was diagnosed with bilateral club foot at 18 weeks of

	gestation. The outcome of the event of talipes was reported as "recovered with sequelae". Causality is "Unassessable" given the extremely limited available data regarding maternal medical, family and obstetric history, complete results of the fetal ultrasound at 18 weeks, diagnostic evaluation including genetic testing of the fetus, and clinical course. [redacted]: This regulatory authority case, reported by a consumer, concerns a full-term newborn ("0-year-old") male patient who experienced "heart disease congenital." His mother (age not provided) was vaccinated with an unspecified dose of elasomeran at approximately 3 weeks gestation (around the time of conception) and he was diagnosed with persistence of the left superior vena cava with coronary sinus dilation, accentuated trabeculature in the septum and wall of the left ventricle at an unknown time after birth at approximately 41 weeks gestation. At the time of the report, the outcome was reported as "not resolved". His mother had received two doses of Vaxzevria vaccine prior to pregnancy with no reported AEs, and last dose was eight months prior to the unspecified dose of elasomeran. Causality is "Unassessable" given the limited information regarding maternal obstetric and medical history, concomitant medications, infant diagnostic evaluation and results, as well as clinical course. [redacted]: This regulatory case reported by a physician concerns an [redacted]-month-old female infant with no medical history reported, who experienced "epilepsy" 314 days after maternal exposure to the third dose of elasomeran. She was exposed to the second dose of elasomeran vaccine during first trimester of pregnancy and to third dose during second trimester. The delivery occurred on an unknown date and reported as abnormal pregnancy outcome ("Term birth w Cong Anomaly"). On unknown dates, electroencephalogram, magnetic resonance imaging-head, and urine analysis with urine metabolic screening all showed normal results. Causality is "Unassessable" given the limited information regarding maternal obstetric and medical history, concomitant medications, infant diagnostic evaluation and results, as well as clinical course. [redacted]: This regulatory authority case reported by a physician concerns a [redacted]-old female neonate who experienced "cardiac aneurysm" and "atrial septal defect" following an unspecified dose of elasomeran at approximately 3 weeks gestational age. During the first trimester, the neonate was also exposed to progesterone, which was reported as a co-suspect drug. The birth was via vaginal delivery with a ventouse extraction due to a pathological continuous cardiotocography at 35+2 weeks gestational age. Delivery date was unknown, and outcome was reported as pre-term birth with congenital anomaly. Six weeks after birth, an echocardiogram showed an atrial septal aneurysm with two small ostium secundum defects (4-5 mm and 2 mm). The heart defects were still present after 1 year and 8 weeks of life. No further relevant information was disclosed. Causality is "Unassessable" given the limited information regarding obstetric history and diagnostic evaluation including genetic testing of the foetus. In addition, progesterone was considered a co-suspect drug. No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period.

	Pregnancy Cases Among Adolescents (12-17 Years of Age – Elasomeran) During the review period, the MAH received 2 serious medically confirmed pregnancy cases (2 serious events) among adolescents (12-17 years of age) who received elasomeran. Neither case reported a fatal outcome. These cases are summarized below: [redacted]: This regulatory authority case reported by another health care professional concerns a 16-year-old female who received a third dose of elasomeran at an unknown time and relation to pregnancy. It was reported that a stillbirth occurred 3 months and 14 days following vaccination. The cause of stillbirth and whether an autopsy was performed was not provided. Causality is "Unassessable" given the limited data available regarding LMP, estimated due date, obstetric and medical history, concomitant medications, diagnostic evaluation for stillbirth and clinical course. [redacted]): This is a regulatory case concerning a 17-year-old female who experienced "amniotic cavity infection" 153 days after receiving the Dose 2 of elasomeran. Causality is "Unassessable" as no additional information regarding maternal obstetric and medical history, concomitant medications, infant diagnostic evaluation and results, as well as clinical course was provided. No unusual patterns or pregnancy-specific safety concerns were identified during reporting and cumulative period. *Pregnancy Cases Who Received Three or More Doses of Elasomeran)* During the review period, the MAH received 40 cases (104 events) with 18 serious cases (31 serious events) among individuals who received or were maternally exposed to a third or more doses of elasomeran. Two cases reported a fatal outcome, and 18 cases were medically confirmed. During the review period, after excluding PTs that do not indicate an adverse pregnancy-specific event/outcome, similar to the events reported by pregnancy cases for all doses, the majority of the most frequently reported PTs represent expected reactogenicity for elasomeran. The most frequently reported PT indicating an adverse pregnancy-specific event/outcome was "Premature baby" (3 events). The types and distribution of the most frequently reported events during this reporting period is similar to the cumulative period. The 2 fatal cases ([redacted] and [redacted]) were summarized in the *Fatal Pregnancy Cases-elasomeran* section above. Overall, based on current available information, regardless of the type of COVID-19 vaccines used for the primary series, no unusual patterns or pregnancy-specific safety concerns were identified. **Pregnancy Cases After Receiving a Booster Dose with Elasomeran/imelasomeran** During the review period, the MAH received 25 pregnancy cases (89 events) with 17 serious cases (53 serious events) among individuals who received or were maternally exposed to a booster dose of elasomeran/imelasomeran. One case reported a fatal

	outcome, and 3 cases were medically confirmed. The most frequently reported clinical events/PTs represent expected reactogenicity for elasomeran. Of the 89 events reported, 29 were pregnancy-specific events. The only PT's indicating a pregnancy-specific adverse event/outcome were "Abortion spontaneous" (4 events), "Pancreas divisum" (1 event), "Poor feeding infant" (1 event), "Premature separation of placenta" (1 event), and "Stillbirth" (1 event). Events of "Spontaneous abortion," "Premature separation of placenta," and "Stillbirth," while previously reported with elasomeran exposure, mark the first reports of fetal death or stillbirth associated with elasomeran/imelasomeran exposure. During the review period, the MAH received 1 pregnancy case ([redacted]) reporting events of pericarditis after receipt of elasomeran/imelasomeran vaccine. This was the first pregnancy case reporting events of myocarditis and/or pericarditis following a booster dose with an elasomeran bivalent vaccine. This case is further discussed in the Section 16.3.1.2. *Serious Pregnancy-specific Events and Fatal Cases– Elasomeran/Imelasomeran* During the review period, 17 serious pregnancy cases were received. Of those 17 serious cases, only 7 cases reported pregnancy-specific events. One case reported a fatal outcome, and no cases were medically confirmed. The fatal case describes events of stillbirth and is summarized in the *Fatal Pregnancy Cases-Elasomeran/Imelasomeran* section below. Review of the serious pregnancy-specific events during this reporting period did not identify any new safety concerns. These cases reflect similar obstetric events observed in temporal association with elasomeran vaccination. Many of these cases had limited information about past medical and obstetric history, GA at time of vaccination, or onset of AE, diagnostics, treatment, and outcome. *Fatal Pregnancy Cases– Elasomeran/Imelasomeran* During the review period, the MAH received 1 case reporting a fatal outcome following maternal exposure to a booster dose of elasomeran/imelasomeran. This was the first fatal case reported following vaccination with a booster dose of an elasomeran bivalent vaccine. This case concerns a stillbirth and was described in 2 cases as a mother/neonate dyad. This case is summarized below: [redacted]: This is a regulatory case concerning a 34-year-old female, who experienced premature separation of placenta (placenta abruption) and delivery of a female infant at 28 weeks, a day after receipt of the fourth COVID-19 vaccine with elasomeran/imelasomeran. The infant died 4 days later, and the reported cause of death was "abruptio placentae." It is unknown if an autopsy was performed. Maternal obstetrical/medical history reported included history of early miscarriage and laboratory confirmed SARS-COV-2 infection at unknown date. This case is part of a mother/neonate dyad and linked to Case [redacted] (which was reported earlier in the review period). Causality with regard to elasomeran/imelasomeran for placenta abruption and infant death is "Unassessable" given missing information on

	maternal concomitant medication, social history, events that occurred around vaccination that could cause or be risk factors for abruption, maternal and infant diagnostic evaluation, treatment and clinical course. *Fetal Deaths – Elasomeran/Imelasomeran* *Spontaneous and Missed Abortions – Elasomeran/imelasomeran* During the review period, 4 serious pregnancy cases reported spontaneous abortion. None of the 4 cases were medically confirmed or coded with a maternal fatal outcome. All 4 events reportedly occurred following vaccination during the first trimester. The mean age of the cases is 34.0 years (SD: 2.9), median age 34.5 years (range: 30-37 years). Although the data are limited, when TTO was known, events most frequently (75.0%) occurred within 2 days of vaccination. The median TTO was 1.5 days (range: 1-4). These were the first cases received by the MAH that reported events of spontaneous abortion in relationship with elasomeran/imelasomeran. *Stillbirth – Elasomeran/imelasomeran)* During the review period, the MAH received 1 case reporting stillbirth following maternal exposure to elasomeran/imelasomeran. This case ([redacted]) is described above in the *Fatal Pregnancy Cases-elasomeran/imelasomeran* section. *Congenital Anomaly– Elasomeran/Imelasomeran* During the reporting period, the MAH received 2 pregnancy cases that either reported a PT from the Congenital, familial and genetic disorder SOC or were identified after medical review, no patterns and no safety concerns were identified. Case [redacted] This is a regulatory case concerning a 43-year-old female who experienced "Pancreas divisum" 1 day after receiving a booster dose of elasomeran/imelasomeran. This case appears to be misclassified as a pregnancy case due to the woman's age (43 years) and that there was no indication in the report that she was either pregnant or lactating. [redacted] (This case was found during medical review) This regulatory authority case reported by a consumer concerns a [redacted] year-old, female patient, who experienced atrioventricular block (with a ratio of 2:1 heart block), COVID-19, and fetal exposure during pregnancy. It was also reported that the infant had a mild infection which was treated at home and experienced episodic severe pain, rash, cough, congestion, fever, diarrhea, and vomiting. Temporal relation of the events to elasomeran/imelasomeran administration is unclear as vaccination date as well as the date of diagnosis of atrioventricular block were not provided. Reportedly, the infant and her mother both were exposed to the medicine in the third trimester (29-40 weeks). It was also reported that the mother had received Comirnaty at an unknown timing and relation to the pregnancy. Details of previous pregnancies were reported as Low PAPP-A and details of scans or investigations were reported as normal antenatal screening. It is reported that the infant "had developmental milestones". The events were reported to be "not resolved". Causality is "Unassessable" because of the limited available data regarding the date of receipt elasomeran/imelasomeran, the date of atrioventricular block, estimated due date or

	gestational age of delivery, obstetric history, maternal and infant medical history, diagnostic evaluation of the atrioventricular block and clinical course. Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified. **Pregnancy Cases After Receiving a Booster Dose with Elasomeran/Davesomeran** During the review period, the MAH received 14 pregnancy cases (36 events) with 1 serious case among individuals who received a booster dose of elasomeran/davesomeran. Ten (10) cases were medically confirmed. Cumulatively and during the review period, there have been no pregnancy cases reporting a fatal outcome, stillbirth, or foetus/infant with congenital anomalies following exposure to a dose of elasomeran/davesomeran. The most frequently reported events/PTs represent expected reactogenicity for elasomeran. The only pregnancy-specific PT reported has been "Maternal exposure during pregnancy." During the review period, the reported serious case ([redacted]) was for a previously reported case, reviewed during the PBRER#4 review period. Updates were added to the case narrative during this review period and did not affect the previous assessment of this case. Based on current available information, no unusual patterns or pregnancy-specific safety concerns have been identified.
Discussion	During the reporting period, the pattern of the reports remained generally consistent when compared with the cumulative data. Review of serious pregnancy-specific events and non-pregnancy-specific events during the review period did not identify any new safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran with no other causal association to vaccination. Reported cases reflect obstetric events observed after administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of AE, diagnostics, treatment and/or outcome. Where data were available, noted confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy included advanced maternal age, concomitant medications, comorbidities (such as hypothyroidism), previous relevant obstetric history, and congenital anomalies which predated the vaccination. Spontaneous abortion was the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster was identified. During the review period there were 5 cases reporting stillbirth (4 cases following vaccination with elasomeran and 1 case following a booster dose of elasomeran/imelasomeran). Considering that some cases had clear alternate etiologies, there is an absence of a clear TTO cluster, and published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth after COVID vaccination. There is

	insufficient evidence to support a causal relationship between elasomeran-containing vaccines and stillbirth. The MAH will continue to review and evaluate cases of spontaneous abortion, fetal death and stillbirth, using routine surveillance as well as PASS. Review of the 17 cases reporting congenital anomalies (15 cases following vaccination with elasomeran and 2 cases following a booster dose of elasomeran/imelasomeran) during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with elasomeran-containing vaccines. Review of 6 serious cases received during the reporting period concerning children under 6 years of age who were exposed during gestation did not identify any unusual patterns or safety concerns. There were 2 pregnancy-related cases among adolescents received during the reporting period. Also, there continues to be a decreasing number of pregnancy-related cases following receipt of three or more doses of elasomeran (40 pregnancy cases reporting receipt of three or more doses of elasomeran). Overall, based on current available information there are no unusual patterns or pregnancy-related safety concerns identified among these subpopulations. During the reporting period, the MAH received 39 pregnancy cases reporting events after an exposure to a booster dose of elasomeran bivalent vaccines [25 cases reported an event after elasomeran/imelasomeran, and 14 cases reported an event after elasomeran/davesomeran]. Most events reflect expected reactogenicity. The most frequently reported pregnancy-specific event was "Maternal exposure during pregnancy." However, during this review period, the MAH received the first reports indicating pregnancy-specific adverse events/outcomes for elasomeran/imelasomeran. These events mark the first cases of fetal death or stillbirth and congenital anomaly associated with maternal exposure to a mother vaccinated with a booster dose of elasomeran/imelasomeran. No unusual patterns or pregnancy-specific safety concerns have been identified; MAH will continue to review cases that received the bivalent vaccines using routine surveillance. In-depth literature reviews performed have not identified any new safety concerns for the use of elasomeran during pregnancy. Thus far, published literature has not identified any evidence of an increased risk of fetal or neonatal complications related to maternal immunization with elasomeran-containing vaccines. Furthermore, published literature have reported that there is transfer of maternal antibodies, reduction in COVID-19 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. This is acknowledged that COVID-19 infection may be more serious and cause complications for both the mother and the fetus and published literature supports the favorable benefit/risk profile of maternal immunization with elasomeran-containing vaccines. Data continues to provide supporting evidence for the use of

	elasomeran-containing vaccines 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 elasomeran-containing vaccines 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern. The MAH will continue to monitor events for pregnancy using routine surveillance and ongoing post-authorization studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation remains positive.

16.3.5.2 Use in Breastfeeding

Evaluation of information received during the PBRER reporting interval relating to the known important missing information risks of elasomeran-containing vaccines during breastfeeding has not identified any additional clinically relevant new safety information for this topic. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, remains valid.

Table 16.11 Use in breastfeeding

Source of New Information	• Moderna GSDB • Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 519 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	The topic of Breastfeeding is summarized because the use of elasomeran-containing vaccines among breastfeeding women is an area of missing information in the currently approved RMP. Real world evidence and literature demonstrate that elasomeran-containing vaccines are well tolerated by lactating women and their children, and side-effects experienced are similar to side-effects in the general population. No specific safety concerns for breastfeeding have been identified.
Methods	**Identification of Case Reports in ModernaTx, Inc. GSDB:** Lactation cases were identified as any case containing at least one lactation-specific event or PT term identified in the SMQ: "Lactation-specific topics (including neonatal exposure through breast milk)" described in the SSP 2.0. Identified lactation cases were pulled by case identification numbers to obtain all PTs reported; the PTs that are captured in the Lactation-specific topics (including neonatal exposure through breast milk) SMQ are referred to as lactation-specific events, and those that are not, are referred to as non-lactation-specific events.

	The MAH reviewed and performed descriptive analyzes of all events reported for the reporting period by type of vaccine (elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran). These analyses were also performed for lactation cases who received third or subsequent doses of elasomeran, lactation cases among 12-17 years old (adolescents) and 6-11 years old, as well as lactation cases among children younger than 6 years of age (breastfed children). For the calculation of TTO and the attribution of Dose Number to individual events an algorithm was applied that compared the date of vaccination for each dose to the date of event onset. Attribution of the event to a dose was determined by the vaccination date that was closest to and that also preceded the event date. When either no dose number was reported or the date comparison was inconclusive, an event was attributed to an "Unknown" dose number. All fatal cases were medically reviewed and summarized; deaths among lactating women within 1 year of pregnancy completion is considered a pregnancy-specific death and will be discussed in Section 16.3.5.1. Deaths among lactating women occurring more than one year after pregnancy completion or breastfed infants only with a possible exposure to a ModernaTx, Inc. COVID-19 vaccine through breastmilk will be discussed here. However, the MAH receives reports in which fetal deaths among breastfeeding mothers are coded as fatal cases, originating from regulatory reports or due to coding discrepancies. Finally, serious lactation-specific cases among children younger than 6 years were medically reviewed and summarized.
Results	Refer to Appendix 12.20 for additional information. **<u>Overview of Lactation Cases Who Received Elasomeran</u>** During the review period, the MAH received 53 lactation cases (208 events) with 10 serious cases (33 serious events) among individuals who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran. No lactation cases reported a fatal outcome, and 21 lactation cases were medically confirmed. A higher percentage (81.1%) of the cases reported during this reporting period were non-serious compared to the prior review period (74.1%). During the reporting period, no meaningful changes have been observed in the age distribution of the cases of lactating women and their breastfeeding children and are consistent with the expected age of lactating women and their breastfeeding children. Note there are some cases that describe mastitis in non-breastfeeding individuals, particularly older women. Additionally, cases coded as males likely represent children who were exposed to breastmilk from mothers who had been vaccinated with Moderna COVID-19 vaccines or data entry and/or coding error. During the review period, the most frequently reported PTs were consistent with reactogenicity events and common breastfeeding issues such as mastitis and lactation insufficiency. When restricted to lactation-specific adverse events/outcomes, the only PTs reported in decreasing order were "Mastitis" (11 events), "Lactation insufficiency" (10 events), "Lactation disorder" (1 event), "Lactation puerperal increased" (1 event), and "Breast milk discoloration" (1 event). There has not been a significant change in the pattern of PTs reported during the reporting period when compared to cumulative data. Most of the

	lactation-related events were transient and occurred within 2 days of vaccination. Medical review of the HLT "Lactation Disorders" was performed and the data for the review period are similar to the previous cumulative experience; no concerning patterns or notable trends were identified. Of the 10 serious lactation cases reported during the review period, only 4 cases reported a lactation-specific adverse clinical event/outcome. Following medical review, it was determined that 2 cases ([redacted] and [redacted]) describing events of mastitis were not lactation cases due to the age of the individuals (55 years and 52 years, respectively) and that there was no information indicating that either individual was breastfeeding or lactating. The remaining 2 serious cases (Case [redacted] and [redacted]) described events of mastitis and lactation insufficiency, both common challenges in breastfeeding women. **Subpopulation Analyzes** *Lactation Cases Under 6 Years of Age–Elasomeran)* During the review period, the MAH received 4 cases (15 events) with 1 serious case (7 serious events) among children under 6 years of age with exposure to breastmilk from mothers who had been vaccinated with elasomeran (referred to as lactation cases among children under 6 years of age). No cases reported a fatal outcome or were medically confirmed. Similar to the previous review period, the most frequently reported clinical events reported among children under the age of 6 years of age were pyrexia, diarrhea, and vomiting, which are consistent with reactogenicity events expected for elasomeran. When restricted to only lactation-specific PTs, the most frequently reported lactation-specific PT continued to be "Exposure via breast milk." During the reporting period, the mean age of lactation cases among children under 6 years was 0.4 years (SD: 0.2) and median age was 0.4 years (range: 0.1 to 0.7 years). The sample size was small so there was no meaningful difference in the number of reports involving males (3; 75.0%) and females (1; 25.0%). When TTO was known, most of the lactation-related events were transient and all events occurred within two days after vaccination. During, the review period, no cases of seizure were reported. During the review period, 1 serious lactation case ([redacted]) with 7 serious events was reported in a [redacted]-old male who experienced the serious (medically significant) events of flatulence, vomiting, emotional distress, diarrhea, gastroesophageal reflux disease, and abdominal discomfort after maternal exposure to breastmilk from a mother vaccinated with elasomeran. The only lactation-specific event was "Exposure via breast milk." All events resolved within 3 days. Cumulatively, all serious cases with lactation-specific events have been medically reviewed and are summarized. Many cases lack information on clinical course, outcome, pediatric medical history, or alternate etiologies/concurrent clinical events. Thus, based on the temporal relationship, causality cannot be excluded. To date, no concerning patterns or

	notable trends have been identified. *Lactation Cases Among Adolescents (12-17 Years of Age)* There were no lactation cases reported among adolescents during this review period. *Lactation Cases with Third or Subsequent Doses of Elasomeran* During the review period, the MAH received 5 lactation cases (20 events) with 1 serious case (1 serious event) in individuals who received or were exposed to breastmilk from mothers who had been vaccinated with a third, fourth, or fifth dose of elasomeran. No cases reported a fatal outcome or were medically confirmed. Of the 5 lactation cases reported during the review period, only 3 cases (60.0%) reported a lactation-specific event. This is a higher proportion when compared to cumulative data (25.6%); however, due to the small sample size received during the review period, these data should be interpreted with caution. Regardless of the vaccine regimen originally received, most of events reported were consistent with expected reactogenicity seen with elasomeran. No concerning patterns or notable trends were identified. **Lactation Cases After Receiving Booster Dose with Elasomeran/Imelasomeran** During the review period, the MAH received 25 lactation cases (97 events) with 16 serious cases (67 serious events) in individuals who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran/imelasomeran. No cases reported a fatal outcome, and 5 cases were medically confirmed. During the review period, when restricted to lactation-specific events, the only PTs reported in decreasing order were "Maternal exposure during breast feeding," "Mastitis," and "Exposure via breast milk." During the review period, the only serious case ([redacted]) received with a lactation-specific event reported the serious PT "Mastitis." However, this case appears to be misclassified as a lactation case as the narrative clearly indicates the woman was not lactating or breastfeeding. There have been no fatal lactation cases after receipt of elasomeran/imelasomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/imelasomeran. **Lactation Cases After Receiving Booster Dose with Elasomeran/Davesomeran** During the review period, the MAH received 15 lactation cases (36 events) with 1 serious case in individuals who received or were exposed to breastmilk from mothers who had been vaccinated with elasomeran/davesomeran. No cases reported a fatal outcome, and 14 cases were medically confirmed. During the review period, when restricted to lactation-specific events, the only PT reported was "Maternal exposure during breast-feeding." During the review period, the only serious case reported ([redacted]) was previously received and reviewed during the PBRER #4 review period. Updates to the narrative were made during this review period. These updates did not affect prior

	assessment. The only lactation-specific event reported was "Maternal exposure during breastfeeding." There have been no fatal lactation cases after receipt of elasomeran/davesomeran. No unusual patterns or lactation-specific safety concerns have been identified after receipt of a booster with elasomeran/davesomeran.
Discussion	During the reporting period of PBRER, ModernaTx, Inc. received 53 lactation cases, of which 4 cases were among children under 6 years of age with exposure to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran via breastmilk. There were no reported fatalities. While vaccination can induce cytokines, which can be passed via breast milk, vaccination while 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 [80] [81] [82]. There were no lactation cases reported among the 12-17 age group during this reporting period and there were 5 lactation cases reporting receipt of a third or subsequent doses, with 60.0% reporting a lactation-specific event. Among the serious lactation-specific events, there was no clustering by dose or TTO and no concerning patterns or notable trends of events reported were identified. Reported events were mild and transient. The pattern of reports remained generally consistent during the reporting period when compared with the cumulative data. No new safety concerns were identified. Where duration and outcome are available, many of the events occur within 2 days after vaccination, and most events were mild/moderate, transient events where information is available. Both in the GSDB and in the literature, reports of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhea, and pyrexia are consistent with the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran or what is expected in the general population [81] [83] [84]. Review of the literature to date has not identified any safety concerns related to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran vaccination during lactation. Articles identified through the MAH's focused literature review continue to reveal no significant safety concerns among vaccinated 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 favorable 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 Moderna COVID-19 vaccines during lactation. The MAH is closely monitoring the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran in this population through routine pharmacovigilance [85] [86] [87]. 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 elasomeran remains favorable.
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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety concern. The MAH will continue to monitor events associated with breastfeeding women who receive elasomeran-containing vaccines and their children who are exposed to these vaccines through breast milk using routine surveillance and ongoing post-authorization studies mRNA-1273-P905 and mRNA-1273-P919 as described in the current RMP. The benefit-risk evaluation for this sub-population continues to remain positive.

16.3.5.3 Long-term Safety

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

Table 16.12 Long-term Safety

Source of New Information	As of the DLP of this PBRER, 26 CTs were ongoing 12 of which are sponsored by ModernaTx, Inc. Cumulatively, 53,983 subjects have been are estimated to be exposed to either mRNA-1273, or its variants (mRNA 1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA-1273.222, mRNA 1273.617.2, mRNA-1273.529, mRNA-1273.231 and mRNA-1273.815), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-admin co-administration with mRNA-1010 or coadministration co-administration with mRNA 1345 in the mRNA clinical development program sponsored by ModernaTx, Inc.
Background	Per protocols, the clinical development program has a safety follow-up period of 12 months in the ongoing studies that will assess long-term safety: mRNA1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, and the completed studies mRNA-1273-P101 (DMID 20-0003), and mRNA-1273-P201. Post-authorization safety studies in real world that evaluate long-term safety include ongoing studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P910.
Methods	The long-term safety profile remains to be characterized through continued trial follow-up, active surveillance for safety, PASS, and routine pharmacovigilance. Study mRNA-1273-P904, an EU post-authorization safety study, aims to carry out signal detection followed, if necessary, by safety evaluation of identified possible signals of Moderna vaccines targeting SARS-CoV-2 using routinely collected health data in secondary automated electronic data sources covering all or portions of the populations in Denmark, Italy, Norway, Spain, and the UK. The study population includes all persons with a record of at least one dose of Moderna vaccines targeting SARS-CoV-2 in each database between 06 Jan 2021 and 31 Dec 2022 and members of the database source population selected for each study design, including persons providing historical rates. The final report is planned for 31 Dec 2023.

	Study mRNA-1273-P910 will describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2 in Spain, Denmark, Norway, and the UK. The study will include two distinct designs utilizing secondary data: A case cohort will assess risk factors for development of post-vaccine myocarditis and pericarditis, a case cohort of recipients of Moderna vaccination targeting SARS-CoV-2 will be defined in each participating database. A separate cohort analysis will characterize the clinical course, outcomes, and risk factors for severe disease, a cohort of myocarditis cases (with and without prior exposure to Moderna vaccination targeting SARS-CoV-2) will be studied. Study mRNA-1273-P911 will evaluate patients with myocarditis for up to 5 years after elasomeran exposure to characterize the potential long-term outcomes of vaccine-associated myocarditis compared to myocarditis not secondary to vaccination (non-vaccine myocarditis, NVM). Vaccine exposure and case identification information will be obtained retrospectively from existing real-world data as it accrues in routine clinical practice.
Results	The Phase 3 study mRNA-1273-P301 includes a total of 24 months follow-up; no long-term safety concerns have been identified for the two-dose mRNA-1273 100 mcg primary series on the basis of an interim analysis that includes 16,818.4 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). Participants completing CTs mRNA-1273-P101 (DMID 20-0003), mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, and mRNA-1273-P306 are followed up for a safety for 12 months. In the adolescent Phase 3 Study mRNA-1273-P203, participants from the age of 12 through 17 years had a median follow-up of 342 days after Dose 1 and 312 days after Dose 2. In the pediatric Phase 3 Study mRNA-1273-P204, participants 6 months through 11 years had a median follow-up ranging between 254 and 267 days across age groups. Post-authorization safety studies mRNA-1273-P904, mRNA-1273-P910, and mRNA-1273-P911 are ongoing, and no findings related to long-term safety have yet been identified. As of the DLP of this PBRER, no clinically important safety concerns have been identified upon review of long-term follow-up data in CTs.
Discussion	The long-term safety profile remains to be characterized. In addition to routine pharmacovigilance activities, results from the following studies will be used to evaluate long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. **Ongoing Studies**: • Study mRNA-1273-P904 (final CSR: 31 Dec 2023) • Study mRNA-1273-P910 (final CSR: 30 Jun 2025) • Study mRNA-1273-P911 (final CSR: 31 Oct 2028) • Study mRNA-1273-P203 (final CSR: 31 Jul 2024) • Study mRNA-1273-P204 (final CSR; 31 Mar 2024)

	• Study mRNA-1273-P205 (final CSR: 31 Dec 2023) • Study mRNA-1273-P301 (final CSR: 31 Dec 2023) • **Completed Studies**: • Study mRNA-1273-P201 (final CSR: 30 Sep 2022) • Study mRNA-1273-101/ 20-0003 (final CSR Main Study: 01 Nov 2022)
Conclusion	As of the DLP of this PBRER, there have been no significant safety findings in the above listed ongoing studies nor the 2 completed studies (mRNA-1273-P201 and mRNA-1273-P101) which are being assessed to characterize long-term safety of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

16.3.5.4 Use in immunocompromised subjects

Evaluation of information received during the PBRER reporting interval relating to the known important risks of elasomeran-containing vaccines in relation to immunocompromised individuals, has not identified any additional clinically relevant new safety information for this topic. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, below, remains valid.

Table 16.13 Use in immunocompromised subjects

Source of New Information	o Moderna GSDB o Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 65 o New and Significant Safety Information: There was no new and significant safety information identified for the immunocompromised population.
Background	An association between immunocompromised individuals and COVID-19 mRNA vaccination has been reported since early summer of 2021 as very rare events associated with the administration of COVID-19 mRNA vaccines. The topic of Immunocompromised is summarized because it is an area of missing information in the currently approved RMP. No specific safety concerns for immunocompromised individuals have been identified.

Methods	For the purposes of this PBRER #5, the following operational definitions were applied in the analysis of the immunocompromised/immunosuppressed subpopulation: The "Immunocompromised Subpopulation": Specifically, cases were identified in the MAH GSDB for immunocompromised and immunosuppressed individuals using a past medical history of hematological malignant tumors SMQ, transplantation, primary/innate and acquired immunodeficiency syndromes (including Human Immunodeficiency Virus) and other relevant immunodeficiency PT terms, as well as ATC drug codes for immunosuppressive drugs. The "General Population" (all elasomeran-containing vaccines data) in the ModernaTx, Inc's. GSDB. This refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the ModernaTx, Inc's. GSDB. This data is used to compare the AEs and safety profile in the immunocompromised population vs. the general population.
Results	Refer to Appendix 12.22 for additional information. **<u>Overview of Cases for Immunocompromised Individuals Who Received Elasomeran</u>** During this review period, the MAH received 425 cases (1,059 events) with 123 (28.9%) serious cases (385 serious events) among immunocompromised individuals who received elasomeran. A total of 322 (75.8%) cases were medically confirmed, and 8 cases (1.9%) reported a fatal outcome. Similar to the prior reporting period, there were more cases involving females (130; 30.6%) compared to males (74; 17.4%), with 221 cases (52.0%) that did not report gender information. The median age of patients was 61.0 years (range: 19.0 – 91.0 years). Similar to the previous review period, the most frequently reported MedDRA PTs in the immunocompromised subpopulation included fatigue, pyrexia, headache, nausea, pain, and myalgia. These PTs were comparable to those reported in the general population and reflected expected reactogenicity. Events of COVID-19 infection was the most reported event during this review period (244; 23.0%). 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. This pattern was observed in reports for immunocompromised individuals for both elasomeran and elasomeran/davesomeran. Note that during the review period, 62 cases (including 35 serious and 1 fatal case) overlapped between the subpopulation of those with a medical history of autoimmune/inflammatory diseases (MedHx autoimmune or inflammatory disorders (AI/ID) and immunocompromised/ immunosuppressed subpopulations, as many people with AI/ID are on immunosuppressive therapies. **<u>Subpopulation Analyses:</u>** *<u>Use in Immunocompromised Children (<12 years old) and Adolescents (12-17 years</u>*

	old) – Elasomeran) During the review period, no cases were reported among immunocompromised individuals in these age groups who received elasomeran. *Fatal Cases in Immunocompromised Individuals – Elasomeran* Evaluation of the 8 cases reporting fatal outcome showed that 2 cases were missing age and gender, 5 cases (62.5%) were elderly above 65 years, mostly males, and one case involved a 27-year-old male. All 8 cases had comorbidities including malignancies that were chronic conditions, and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal events. Using the WHO-UMC causality assessment tool, more than half of the cases with fatal outcome (5; 62.5%) were assessed as "Unassessable" (due to insufficient information); 3 cases (37.7%) were assessed as "Unlikely" (due to long TTO outside the risk window and concurrent medical conditions that provided alternate etiologies). 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 344 cases (1,125 events) with 244 (70.9%) serious cases (829 serious events) for immunocompromised individuals who received a booster dose of elasomeran/imelasomeran. Thirty-nine (39) cases (11.3%) were medically confirmed, and 1 case (0.3%) reported a fatal outcome. A higher proportion of cases were reported for females (234; 68.0%) than males (94; 27.3%) with 16 cases (4.7%) which did not report gender information. The median age of patients was 59.0 years (range: 22.0 to 88.0 years). During the review period, the most frequently reported PTs in immunocompromised individuals who received elasomeran/imelasomeran were headache, fatigue, pyrexia, nausea, chills, myalgia, and arthralgia. These events reflect expected reactogenicity and were comparable to events reported in the general population receiving elasomeran/imelasomeran. *Fatal Reports in Immunocompromised Individuals Who Received Elasomeran/Imelasomeran:* Evaluation of the 1 case reporting a fatal outcome in a male showed that it was missing relevant information on age, clinical course of events and treatment provided. The cause of death was not reported. An autopsy was not performed. Concurrent acute myeloid leukemia provides alternate etiology. Using the WHO-UMC causality assessment tool, this case was assessed as unlikely (due to alternate etiology). Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received a booster dose with elasomeran/imelasomeran. **Overview of Cases for Immunocompromised Individuals Who Received**

	Elasomeran/Davesomeran During the review period, the MAH received 24 cases (53 events) with 6 (25.0%) serious cases (10 serious events) for immunocompromised individuals who received elasomeran/davesomeran. A total of 19 (79.2%) cases were medically confirmed, and no case reported a fatal outcome. Similar to the previous review period, there were no meaningful changes in the gender distribution of reports as a slightly higher proportion of cases continued to be reported in females (12; 50.0%) than males (10; 41.7%) and 2 cases (8.3%) did not report gender information. The median patient age was 67.0 years (range: 52.0 to 80.0 years). During the review period, the most frequently reported events were COVID-19 infection and issues related to product storage, expiration, or medication error. Reported "COVID-19" 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. This was observed in data for both elasomeran and elasomeran/davesomeran. Based on current available information, no clustering or trends of safety concerns have been identified regarding immunocompromised individuals who received elasomeran/davesomeran. **Clinical Trial Information** **Interim Clinical Study Report for mRNA-1273-P304 - OPEN-LABEL PART A (PRIMARY SERIES) and PART B (BOOSTER DOSE) - Safety Results (31 Mar 2023)** Study mRNA-1273-P304 is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in solid organ transplant (SOT) recipients and healthy participants. This was a 2-part study. Part A of the study enrolled 214 SOT recipients to receive up to 3 doses of 100 µg mRNA-1273, and 20 healthy participants to receive 2 doses of 100 µg mRNA-1273 (the healthy participant group was intended as a comparator group for SOT in the assessment of the Cell Mediated Immune responses; the vaccine-induced antibody responses in the healthy participants were also described in comparison to the SOT group). In Part A, SOT participants who were unvaccinated and those who were previously vaccinated with 2 doses of mRNA-1273 were enrolled. The primary immunogenicity objective of Part A was to evaluate serum nAb responses obtained 28 days after the second or third dose of the study vaccine. In Part B, a 100 µg booster dose (BD) was administered to participants at least 4 months from the last dose of a completed primary COVID-19 vaccination series. A 100 µg BD was selected for this study due to concern about reduced antibody responses associated with chronic immunosuppression in the SOT population and the potential immune escape associated with variants of concern. The analyses presented in the P304 interim report dated 31 Mar 2023, is based on the results from a database lock date of 22 Nov 2022. Safety follow-up after vaccination includes a median of 292.0 days (range: 37 to 406 days) from Dose 3 in SOT participants

	in Part A and a median of 129.0 days (range: 10 to 181 days) from BD in SOT participants in Part B. **Summary of Safety Results** • Reactogenicity after the 3-dose primary series and BD in immunocompromised participants was similar to that which has been reported for mRNA-1273 in immunocompetent participants. This is also consistent with what has been reported in other CTs and post-authorization use of mRNA-1273 in the general population. • Local and systemic solicited ARs were reported within 7 days after vaccination in 85% and 80% of SOT participants, respectively, after any injection. Systemic solicited ARs, chiefly fatigue, headache, and myalgia, were reported in fewer kidney transplant participants compared to liver transplant participants, particularly after Dose 1, although a trend was evident at all doses; this was attributed to heavier immunosuppressant and anti-metabolite treatment in kidney transplant participants. • Unsolicited treatment-emergent AEs (TEAEs) were reported in 42.1% of SOT participants through 28 days after vaccination after any injection and were considered related to vaccination by the Investigator in 21.5% of SOT participants. The most commonly reported vaccine related events included fatigue (12.6%), headache and myalgia (6.1%, each), and arthralgia (5.6%), which were also frequently reported symptoms of reactogenicity. Other unsolicited TEAEs were largely due to underlying disease or intercurrent illness or injury in SOT participants. • Four cases of biopsy-proven organ rejection were reported during the study, all in SOT liver participants (one involved a kidney transplant in a prior liver transplant recipient). None of the cases were considered related to vaccination and all were due to changes in immunosuppressant medications. • Through the data cutoff date, 4 SAEs in 3 SOT participants were assessed as related to study vaccination by the Investigator. Two SAEs (worsening anemia, angina) occurred in a kidney transplant recipient on Relative Days 10 and 11 after vaccination and were considered vaccine-related by the Investigator; the Sponsor considered the events more likely attributable to underlying disease. One SAE of vomiting was reported as a solicited AR and, per protocol, considered related to vaccine, although the event was not assessed as vaccine-related by the Investigator. One SAE of autoimmune hemolytic anemia occurred 4 months after Dose 2 in a participant with a concurrent COVID-19 infection; autoimmune hemolytic anemia was considered possibly related to vaccine by the Investigator due to the temporal relationship of the decline in hematocrit after vaccination, although the Sponsor considered the event more likely due to pre-existing anemia. • One AESI of non-serious myocarditis was reported on Relative Day 1 after vaccination and was assessed as related to vaccine by the Investigator; the case was adjudicated by the cost-effectiveness acceptability curve as not meeting the CDC definition of myocarditis. One cost-effectiveness acceptability curve -

	adjudicated case of pericarditis occurred on Study Day 122 that was attributed to an underlying inflammatory process and was not considered vaccine related by the Investigator or Sponsor. • Two fatal events (congestive heart failure and death of unknown cause) in participants with underlying comorbidities were reported and were not considered related to vaccination. • Laboratory shifts did not show notable trends after vaccination with mRNA-1273; shifts noted were attributed to underlying disease or intercurrent medical processes. • Shifts in vital signs were explained by underlying disease or intercurrent medical processes. Elevation of systolic or diastolic blood pressure was the most common vital sign change and, in most participants, reflected underlying hypertension. • No mRNA-1273 vaccine-related safety concerns were identified during the study. **Safety conclusion:** The 3-dose primary series and BD of mRNA-1273 were well tolerated with an acceptable safety profile in immunocompromised post-transplant population. **Health Authority Feedback** "*Overall, the regulatory authority considered that there is sufficient evidence to conclude that the gaps in knowledge regarding the safety of elasomeran when used in immunocompromised individuals have been adequately filled and can no longer be considered an area of missing information. Removal of 'use in immunocompromised subjects' from the RMP is endorsed*". *Regardless of the removal of the safety concern in the RMP, continued monitoring through routine pharmacovigilance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904 is warranted, as proposed by the MAH*". Regarding the effectiveness in immunocompromised subjects, the studies P304 and P901 are ongoing and will remain in the pharmacovigilance plan.
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 top five most frequently reported AEs in the immunocompromised population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The pattern of events observed with elasomeran/imelasomeran or elasomeran/davesomeran compared to elasomeran in this population was generally similar. Epidemiological studies have not indicated any

	significantly increased risk of side-effects in immunocompromised 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 review period, there were no cases reported in immunocompromised children or adolescent subpopulations. 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 (1.1%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiology.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in immunocompromised individuals. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Based on the 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern. 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 use in immunocompromised individuals is that there is sufficient evidence to conclude that the gaps in knowledge regarding the safety of elasomeran when used in immunocompromised individuals have been adequately filled and can no longer be considered an area of missing information. Removal of 'use in immunocompromised subjects' from the RMP was endorsed. 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)

Evaluation of information received during the PBRER reporting interval relating to the known important risks of elasomeran/imelasomeran/davesomeran has not identified any additional clinically relevant new safety information in the Frail subpopulation. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, below, remains valid.

Table 16.14 Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders)

Source of New Information	○ Moderna GSDB ○ Literature Sources ○ Retrieved: 169 ○ New and Significant Safety Information: There was no new and significant safety information identified.
Background	Frail patients are considered at higher risk for complications due to coronavirus disease 2019 (COVID-19) infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. Since frail subjects with unstable health conditions and co-morbidities were excluded from the registration CTs, the MAH is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Safety reports for frail subpopulation is summarized because it is an area of missing information in the currently approved RMP. 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 12.23), 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 12.23 for more information. **Overview of Frail Cases Reported for Elasomeran:** During the review period, the MAH received 1,292 cases (5962 events) reported in Frail subpopulation with 634 (49.1%) serious cases (2040 serious events), 531 cases (41.1%) were medically confirmed cases, and 42 (3.3%) cases with fatal outcome involving elasomeran. The majority of cases were reported in females (803, 62.2%) compared to males (476, 36.8%). The median patient age was 55.5 years (range: 0.0 to 98.0 years). A high proportion of reported cases in frail was among the elderly (390, 30.2%). The most frequently reported events are fatigue, headache, pyrexia, myalgia, COVID-19, dizziness, pain in extremity, vaccination site pains, chills, and arthralgia. These events were comparable to that reported in the general population and reflected expected reactogenicity. Further evaluation showed that events of COVID-19 infection (115;1.9%) were reported more frequently in the frail immunocompromised subpopulation. Please note not all frail are immunocompromised, and other comorbidities are associated with frail. This may be due to a lower immune response to vaccination and/or the susceptibility to constantly changing variants. This was observed only in individuals receiving elasomeran. Evaluation of the 42 cases (3.6%) with fatal outcomes showed that majority (29; 69.0%) were elderly above 65 years, and all 42 cases had comorbidities that were confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, most (26; 61.9%) of the cases

	were assessed as unlikely (due to TTO outside the risk window and concurrent medical conditions that provided alternate etiologies); 4 cases were assessed as conditional (more data needed for proper assessment), 2 cases assessed as possible (due to temporal association), and 10 cases assessed as unassessable (due to insufficient information). **Overview of Frail Cases reported for Elasomeran/Imelasomeran:** During the review period, the MAH received 797 cases (2,679 events) reported in Frail subpopulation, with 545 serious cases (1,967 serious events), 189 medically confirmed cases, and 21 cases with fatal outcome. involving elasomeran/imelasomeran. The majority of cases were reported in females (491 cases, 61.6%) compared to males (261 cases, 32.7%). The median patient age was 64.0 years (range: 18.0 to 98.0 years). The most frequently reported MedDRA PTs were fatigue, headache, pyrexia, dyspnea, nausea, chills, dizziness, myalgia, arthralgia, ADRs and palpitations. These events were comparable to that reported in the general population and reflected expected reactogenicity. Evaluation of the 21 cases with fatal outcomes showed that the majority (20; 90.2%) were elderly above 65 years, and all 20 cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, most (12; 57.1%) of the cases were assessed as unlikely (due to TTO outside the risk window and concurrent medical conditions that provided alternate etiologies); and 9 cases were assessed as unassessable (due to due to insufficient information). **Overview of Frail Cases Reported for Elasomeran/Davesomeran:** During the review period, the MAH received 123 cases (367 events) reported in the frail subpopulation, with 36 serious cases (56 serious events), 111 medically confirmed cases, and 7 cases with fatal outcome involving elasomeran/davesomeran. A slightly higher proportion of cases were reported in females (65; 52.8%) compared to males (52; 42.3%). The median patient age was 70.0 years (range: 2.0 to 92.0 years). The most frequently reported MedDRA PTs in frail subpopulation receiving elasomeran/davesomeran were pyrexia, pain in extremity, myalgia, fatigue, dizziness, pain, headache, chills, and insomnia. Most of these events are expected reactogenicity and consistent with reports in the general population. Evaluation of the 7 cases with fatal outcomes showed that majority (5; 71.4%) had missing age reported, and the 2 cases were elderly age >65 years. Most of the deaths were reported in males (6; 85.7%). Four cases were linked as similar. All 7 cases had comorbidities that were chronic conditions and confounders/risk factors that provided alternate etiologies for the occurrence of the fatal event. Using the WHO-UMC causality assessment tool, all 7 cases were assessed as unassessable, due to insufficient information.
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. 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 elasomeran/imelasomeran or elasomeran/davesomeran compared to elasomeran in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals after vaccination with elasomeran. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events or safety concern. Cases with fatal outcome in the frail subpopulation in the reporting period (3.2%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiology.
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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in frail subpopulation. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any new safety concern. 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 use in frail subjects with unstable individuals is that "removal of the missing information 'use in frail subjects with unstable health conditions and co-morbidities' from the EURMP, is endorsed. Nevertheless, the topic shall remain in the PBRER list of safety concerns and an evaluation of new information on this topic is required with future PBRERs." 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)

Evaluation of information received during the present PBRER reporting interval relating to the known important risks of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran 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 these topics. The characterization of this missing information as described in the approved RMP as of the DLP of this PBRER and in Section 16.4, below, remains valid.

Table 16.15 Use in subjects with autoimmune or inflammatory disorders (AI/ID)

Source of New Information	o Moderna GSDB o Literature Sources o Search Criteria Applied: Appendix 13.4 o Retrieved: 141 o New and Significant Safety Information: There was no new and significant safety information identified.
Background	Because there was limited data from CTs on the use of elasomeran in individuals with AI/ID, the MAH has been closely monitoring the safety profile of elasomeran in this population through routine Pharmacovigilance. Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in AI/ID population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in MedHx AI/ID patients to achieve an adequate, more robust immune response to vaccinations. Furthermore, countries are recommending a BD (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in individuals with MedHx of AI/ID, especially now with the bivalent vaccines. The third dose of elasomeran recommended in individuals with known MedHx of AI/ID is 100 mcg dose, whereas the booster (either 4th dose for individuals with AI/ID, or 3rd dose for the general population) is a 50 mcg dose. Thus far, there have been no specific safety concerns for individuals with MedHx of AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran and have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general population receiving elasomeran. 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 a Health Authority.3.1 "*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.*".
Methods	The ModernaTx, Inc GSDB was queried for valid, clinical and spontaneous reports for

	elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran in people with a medical history of autoimmune and/or inflammatory disease, received for review period (18 Dec 2022 to 17 Jun 2023). Reports from individuals with a MedHx AI/ID were identified from MAH GSDB using Immune-mediated/autoimmune disorder SMQ "Immune-mediated/autoimmune disorders SMQ" PTs identified in past medical history. Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment.
Results	Refer to Appendix 12.24 for additional information. **Overview of MedHx AI/ID Cases Reported for Elasomeran** During this reporting period, 685 cases (324 serious, 259 medically confirmed, 7 fatal cases) with 3,325 events (1,146 serious) were reported in individuals with a known MedHx AI/ID after receiving elasomeran. The majority of cases 524 (76.5%) were reported in females compared to males (151 cases, 22.0%), with a small proportion of cases (10, 1.5%) having no gender reported. The mean patient age was 52.1 years (SD: 15.3) and median age was 51.0 years (range: 17.0 to 95.0 years). The most frequently reported serious events during this reporting period often reflected expected reactogenicity events, such as fatigue, headache, and pain in extremity. The types and distribution of events were generally similar to cumulatively reported serious events in individuals with a known MedHx AI/ID. **Subpopulation Analysis:** *Use in Children <18 Years of Age with MedHx AI/ID - Elasomeran* During this reporting period, there was 1 non-serious case reported in 17-year-old female. *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. Refer to Appendix 12.24 for further information. **Overview of MedHx AI/ID Cases Reported for Elasomeran/Imelasomeran:** During the reporting period, 400 cases (276 serious, 54 medically confirmed, 5 fatal) with 1,289 events (952 serious) reported in individuals with a known MedHx AI/ID after receiving elasomeran/imelasomeran. The majority of cases were reported in females 297 (74.3%) compared to males 87 cases (21.8%), with small proportion of cases (16, 4.0%) having no gender reported. The mean patient age was 58.8 years (SD: 14.5) and median age was 60.0 years (range: 20.0 to 98.0 years). The most frequently reported serious events were fatigue, headache, and pyrexia, in individuals with known MedHx AI/ID who received elasomeran/imelasomeran and often represented expected reactogenicity. **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, 5 cases with fatal outcome were reported in individuals with known MedHx AI/ID who received elasomeran/imelasomeran. Please refer to Appendix 12.24 for further information. **Overview of MedHx AI/ID Cases Reported for Elasomeran/Davesomeran:** During the reporting period, 40 cases (15 serious, 31 medically confirmed, 1 fatal) with 145 events (28 serious) reported in individuals with known MedHx of AI/ID after receiving elasomeran/davesomeran. The majority of cases were reported in females (32 cases, 80.0%) compared to males (8 cases, 20.0%). The mean patient age was 58.7 years (SD:19.2) and median age was 65.5 years (range: 8.0 to 81.0 years). During this reporting period, except for diarrhea (2, 7.1%), all other events were reporting once (3.6%) 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, 2 cases (1 serious) were reported in children <18 years of age. The serious case [redacted] - reported Kawasaki's disease in 8-year-old male patient. Please Refer to Section 15.2.4 for further assessment and details. *Fatal Cases in Individuals with MedHx AI/ID -Elasomeran/Davesomeran:* During this reporting period, 1 case with fatal outcome was reported in an individual with MedHx AI/ID who received elasomeran/davesomeran. Please refer to Appendix 12.24 for further information.
Discussion	Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers the cases of MedHx AI/ID to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran, and the benefits for elasomeran far outweigh any possible vaccine-associated risks. Relevant literature findings to support the reporting period discuss the acceptable safety and benefit/risk profile of COVID vaccination among individuals with AI/ID. No new safety concerns were identified in the literature review concerning elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. In AI/ID patients with disease flares, there is a natural waxing and waning course, and there are no reliable referenced data on the background rates of respective flares especially given the number of various AI/ID diseases and how to accurately measure a flare. The identified flare cases did not demonstrate a safety concern for this reporting period. There have been reports of flares after many vaccines, including various COVID vaccines. Both health care providers and patients acknowledge the potential risk of flares after any vaccination, yet flares are not specifically described in any vaccine labels. At present, the global consensus is that the benefit of vaccination outweighs the potential risks of flares but should be discussed between patient and HCP. Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Epidemiological studies have

	indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. For the fatal AI/ID cases, common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, hyperlipidemia, and chronic kidney disease are similar to those reported in the general population fatal reports.
Conclusion	Evaluation of the data during this reporting period did not identify any new safety information that would suggest a possible association between the evaluated events and administration of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. 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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran did not raise any new safety concern. 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 use in subjects with autoimmune and inflammatory disorders is that "*removal of the missing information 'use in subjects with autoimmune and inflammatory disorders' from the EU RMP, is endorsed. Nevertheless, the topic shall remain in the PBRER list of safety concerns and an evaluation of new information on this topic is required with future PBRERs.*" The MAH will continue to monitor events in individuals with known MedHx AI/ID using routine surveillance. The benefit-risk evaluation remains positive.

16.3.5.7 Interactions with other vaccines

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 Interaction with other vaccines as Missing Information from the EU RMP, was endorsed, and that "*based on the cumulative evidence, the knowledge gaps regarding this area of missing information have been filled and interaction with other vaccines has not been shown to constitute an important risk. Therefore, it is no longer considered important in the context of the RMP and the PBRER. It should be removed from the PBRER list of safety concerns and an evaluation of new information on this topic in future PBRERs is not expected.*".

16.4. Characterization of Risks

Table 16.16 Important Identified/Important Potential Risks

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
Potential Mechanism	Immediate type (Type 1), hypersensitivity mediated by immunoglobulin (Ig) E. Naturally existing IgM and IgG can bind to various components commonly present in nanomedicines, (cholesterol, phospholipids and polyethylene glycol).
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and the post-authorization safety.
Characterization of risk	In study mRNA-1273-P301 (Part A), in the anaphylaxis SMQ, 9 events were reported for 5 participants in the mRNA-1273 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 mRNA-1273 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 mRNA-1273 group were all nonserious and described as follows: mild cough and mild eye pruritus for one participant on Day 47 after the second dose (not considered related); mild tachypnea on Day 29 after the first dose (which was reported on the day of the second dose), severe tachypnea on Day 1 after the second dose (which was the same day; event resolved on Day 64), and moderate urticaria beginning 30 minutes after the second dose and resolved in 1 hour with concomitant medication (all events considered related); and moderate dyspnea (considered related; reported as resolving) and severe swelling face (not considered related; resolving with prednisone) beginning on Day 34 after the second dose. In Part B of mRNA-1273-301, amongst the SAEs, a grade 3 anaphylaxis was reported in 2 participants in the placebo-mRNA-1273 group, both of which were considered unrelated to mRNA-1273. These 2 participants had history of asthma. The first participant was a 50s' years old female who experienced anaphylaxis 19 days after the first injection which resolved the same day; the participant did not receive the second dose. The second participant was a 50s' year-old female who experienced anaphylaxis a few months after receiving the second dose of vaccine; however, it was not temporally related to mRNA-1273 and considered associated to a steroid injection per the investigator. In the placebo group, no anaphylaxis was reported. In the mRNA-1273 group, 1 participant experienced anaphylaxis due to antigen challenge allergy testing (CSR mRNA-1273-P301 addendum 1 (Safety from open-label phase [Part B]). Cumulatively as 17 Jun 2023, there is only one case of anaphylaxis reported in a 9-month-old child who the same day after the dose 1 of elasomeran experienced an anaphylaxis reaction. The events were reported to occur after having dinner. It is unclear whether the reported age is correct. The meal reportedly eaten by the child is inconsistent with that expected for a nine-month-old. In addition, the allergic reaction followed dinner which suggests the food rather than the vaccine was the more likely cause of the angioedema and hives. Cumulatively, a total of 26 cases (24 serious, 0 fatal) of anaphylaxis-related events in patients < 18 years were received. Cumulatively, a total of 23 cases (21 serious, 0 fatal) of anaphylaxis-related events in patients of which 12 to 17-years-old have been received, which included 23 events, (21 serious events). Twenty (20) cases were medically confirmed. Of the 23 cases, 10 were male (43.5%) and 13 were female (56.5%) with a mean age of 15.3 [SD: 1.6],

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	and a median: 16.0. Most of the events reported cumulatively had an outcome of recovered/ recovering (16; 69.6%). There have been no fatal cases reported in the adolescents age group. Cumulatively as of 17 Jun 2023, 27 cases (27 Events), of which (26 serious events) have been reported in adults 18 years of age or older after administration of elasomeran/imelasomeran and elasomeran/davesomeran. Of these 27 cases, 21 were medically confirmed, and none of the cases had a fatal outcome. The event outcomes were resolved/resolving in the majority of cases. These cases were reported mostly in females (20; 74.1%), six (22.2%) in males, and one case (3.7%) had missing gender information. The median age was 60.0 years (ranging from 23.0 to 90.0 years). Most of the cases were reported via regulatory authority (17; 63.0%), with Nine (9) cases (33.3%) reported spontaneously and one (1) case (3.7%) from literature. Cases were reported in Japan (12; 44.4%), the UK (11; 40.7%), the United States (3; 11.1%) and Netherlands (1; 3.7%). Review of the data received cumulatively as of 17 Jun 2023, does not suggest any new identifiable pattern or trend in reports of anaphylaxis in children <18 years of age, that may differ from already known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. In most of the cases where the relevant information was available, these cases were not suggestive of a typical anaphylactic reaction, instead an important confounder of medical histories of atopy including different types of allergies (food, animals, medicines, etc.) were noted in most of the patient's reporting anaphylaxis, indicating that the reported events may be an expression of allergic reactions and not true cases of anaphylaxis. Additionally, analyzes of cases of anaphylaxis in adults 18 years and over, including the events reported after elasomeran/imelasomeran or elasomeran/davesomeran appear to be generally consistent in nature and severity to those reported with elasomeran. For the case that involved a fatal outcome, the alternative etiology (emphysema, COPD, and diabetes) provides a plausible explanation for the fatal outcome. Please refer to Section 8 for results from the PASS study regarding the evaluation of anaphylaxis cases.
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	Elasomeran vaccine is 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 elasomeran.
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 Moderna COVID-19 Vaccine. Causal association between elasomeran-containing products and anaphylaxis is considered

Important Identified Risk	Anaphylaxis (Safety concern in PBRER only)
	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 PBRER.
Public health impact	Anaphylaxis associated with vaccines typically occurs at a low incidence, which results in a low public health impact. Although the potential clinical consequences of an anaphylactic reaction are serious, this is a risk known to healthcare professionals.

Important Identified Risk	Myocarditis
Potential Mechanism	Myocarditis is an under-diagnosed cardiac disease resulting from any one of a broad range of infectious, immune, and toxic causes. Most cases of myocarditis are caused by infectious agents, toxic substances, drugs or autoimmune disorders. Hence, it is increasingly recognized that myocarditis is an inflammatory condition of the myocardium triggered by various factors rather than a distinct cardiovascular disease. Infectious causes include viruses, bacteria, 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 [88]. Evaluation of the post-authorization safety studies 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-authorization use outside the United States. These findings suggest that an increased risk for these conditions may be present after receiving Novavax COVID-19 vaccine. These observations strongly suggest that the risk is not specific to the mRNA platform but is related to spike protein antigens. One leading hypothesis for myocarditis after infection and in rare cases after vaccination is that it is mediated by circulating Spike or Spike-S1 protein, and the interaction of that protein with tissues and antigen-experienced immunity. In a prospective pilot study [89] 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

Important Identified Risk	Myocarditis
	site and enables release of S1 from the spike trimer. They hypothesize that release of S1 protein could result from cleavage via mammalian cell proteases or circulating proteases. The authors observed an increase in S1 over an initial period of one to five days, suggesting that mRNA translation begins immediately after vaccine inoculation. Interestingly, spike protein appears in three of thirteen participants on average eight days after S1 is produced.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and post-authorization safety information, including PASS, as well as published literature information.
Characterization of risk	In Study mRNA-1273-P301 (Part A), there were 15,184 participants exposed to the mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were no reported TEAEs of Myocarditis follow-up period after vaccination. No cases have been reported in Part B of the study (CSR mRNA-1273-P301 addendum 1 (Safety from open-label phase [Part B]). Using post-authorization safety data, cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [73] [74] and the CDC working case definition [75] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment. As of DLP of this PBRER, there were 4,663 cases of Myocarditis reported for elasomeran; there were 35 cases for elasomeran/imelasomeran, and there were 21 cases of myocarditis reported for elasomeran/davesomeran. A review of the data received during the reporting period of this PBRER, showed that events of myocarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. To date, the safety profile of those reports of myocarditis after elasomeran/imelasomeran or elasomeran/davesomeran does not differ from the elasomeran safety profile, with cases presenting as mild cases, and recovering within a short time following standard treatment and rest. Analysis of safety data housed in the MAH's GSDB, as well as review of the literature, showed that most of the individuals who experienced an event of myocarditis after vaccination with elasomeran-containing vaccines 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 [76]. Review of the data also show no difference in the observed safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran for children (6 months to 12 years of age), the adolescent population (12 years to 17 years of age), or in those individuals receiving a 3rd dose of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when compared to >18 years old. Reporting rates are lower for children than for adolescents and young adults. Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers cases of myocarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, 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

Important Identified Risk	Myocarditis
	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%) [90]. 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 [91]. 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.
Preventability	Myocarditis presents with a spectrum of symptoms ranging from mild dyspnea or chest pain that spontaneously resolves without treatment to cardiogenic shock and sudden death. The major long-term consequence is dilated cardiomyopathy (DCM) with chronic heart failure. Common viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated [92]. Very rare cases of myocarditis and pericarditis have been observed following vaccination with elasomeran-containing vaccines. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Cumulative and periodic data analyzed during the reporting period of this PBRER, supported an update of the product information, indicating that most cases recover, and that some cases required intensive care support and fatal cases have been observed. Data presented in a study conducted by Le Vu et al., and included in PBRER 4, indicated that in a period of 28 days after the second dose, there were 1.88 (95% CI: 0.956, 2.804) extra cases of myocarditis in 16- to 24-year-old males per 10 000 compared to unexposed persons. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. For patients presenting with myocarditis or pericarditis after the 1st dose CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, it could consider proceeding with 2nd dose [93]. Current SmPC and Package information Leaflet (PIL) were updated to reflect additional new information regarding the risk of myocarditis and pericarditis and to provide up to date information on this risk as well as awareness to the health-care professionals, caregivers and vaccinees. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis

Important Identified Risk	Myocarditis
	using routine and enhanced surveillance activities, including PASS to further characterize them. The benefit-risk evaluation remains positive.
Impact on the benefit-risk balance of the product	Based on the analysis of all the safety data, there have been very rare reports of myocarditis occurring after vaccination with Moderna COVID-19 Vaccine. Causal association between elasomeran and myocarditis is considered of at least a reasonable possibility. The majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, intensive care unit (ICU) admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended [75].
Public health impact	Myocarditis associated with vaccines typically occur at a low incidence, which results in a low public health impact. Although the potential clinical consequences of the occurrence of myocarditis is serious, this is a risk known to healthcare professionals and can be managed with early diagnosis with supportive treatment. Most observed cases have been of mild severity, and spontaneously resolved.

Important Identified Risk	Pericarditis
Potential Mechanism	Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterized by chest pain, pericardial friction rub, changes in the 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 [94]. However, it appears to be the most common form of pericardial disease and a relatively common cause of chest pain. It is diagnosed in approximately 0.1% of patients hospitalized for chest pain and in 5% of patients admitted to the ED for chest pain unrelated to acute myocardial infarction. Although acute pericarditis occurs in all age groups and in men and women, it presents most often in men 20 to 50 years of age. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases. Other common causes include infection, renal failure, MI, post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults. Important to note that cases of pericarditis have been identified in CTs of Novavax COVID-19 Vaccine (a protein subunit vaccine) and have also been reported during post-authorization use outside the United States. These findings suggest that an increased risk for these conditions may be present after receiving Novavax COVID-19 vaccine. These observations strongly suggest that the risk is not specific to the mRNA platform but is related to spike protein antigens. One leading hypothesis for pericarditis after infection and in rare cases after vaccination is that it is mediated by circulating Spike or Spike-S1 protein, and the interaction of that protein with tissues and antigen-experienced immunity. In a prospective pilot study [89] of 13 healthcare workers (HCW), 18 years and older, with no known history of SARS-CoV-2 infection was conducted from Dec 2020 to

Important Identified Risk	Pericarditis
	Mar 2021. Out of the 13 HCW, according to the authors, 11 participants exhibit S1 antigen in plasma after the first injection, while nucleocapsid concentrations are insignificant in all participants, confirming that the detected S1 originates from vaccination and not natural infection. The presence of S1 the authors concluded, was likely due to the nature of the encoded mRNA-1273 spike protein, which contains a cleavable S1-S2 site and enables release of S1 from the spike trimer. They hypothesize that release of S1 protein could result from cleavage via mammalian cell proteases or circulating proteases. The authors observed an increase in S1 over an initial period of one to five days, suggesting that mRNA translation begins immediately after vaccine inoculation. Interestingly, spike protein appears in three of thirteen participants on average eight days after S1 is produced.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from CTs and post-authorization safety information, including PASS, as well as published literature information.
Characterization of risk	In study mRNA-1273-P301 (Part A), in the safety set, there were 15,184 participants exposed to the mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were four TEAE of "Pericarditis" in P301: Two TEAEs in the Placebo arm, and two in the Vaccine arm of the safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the >18 to <65 years of age. The events in the vaccination arm were reported in a male in his 60s' and a female in her 50s'. In Part B, one case of acute pericarditis (verbatim: "acute infective pericarditis") was reported in a male in his 60s' in the placebo group; the event occurred 24 days after a COVID-19 diagnosis. In addition, one case of pericardial effusion was reported as an SAE (resolving) in a 20s' years old male in the placebo– mRNA-1273 group. No participant in the mRNA-1273 group experienced pericarditis (CSR mRNA-1273-P301 addendum 1 (Safety from open-label phase [Part B]). Using post-authorization safety data, cases are classified using both the Brighton Collaboration Myocarditis/ Pericarditis case definition [73] [74], and the CDC working case definition [75] for Acute Myocarditis and Acute Pericarditis. The Company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment. As of DLP of this PBRER, there were 2,663 cases of pericarditis reported for elasomeran; there were 35 cases for elasomeran/imelasomeran, and there were 11 cases of pericarditis reported for elasomeran/davesomeran. A review of the data received during the reporting period of this PBRER, showed that events of pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. To date, the safety profile of those reports of pericarditis after elasomeran/imelasomeran or elasomeran/davesomeran does not differ from the elasomeran safety profile, with cases presenting as mild cases, and recovering within a short time following standard treatment and rest. 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 elasomeran-containing vaccines 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 [76]. Review of the data also show no difference in the observed safety profile of

Important Identified Risk	Pericarditis
	elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran for children (6 months to 12 years of age), the adolescent population (12 years to 17 years of age), or in those individuals receiving a 3rd dose of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran when compared to >18 years old. Reporting rates are lower for children than for adolescents and young adults. Based on the analysis of all the safety data available as of 17 Jun 2023, the MAH considers cases of pericarditis to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran, and the benefits for these vaccines far outweigh any possible vaccine-associated risks, including the risks of myocarditis and pericarditis.
Risk factors and risk groups	Acute pericarditis occurs when the bilayer pericardial sac becomes inflamed. In most cases, the cause of pericarditis is idiopathic or is assumed to be due to a viral infection for which the antecedent virus is not identified. There are several less common infectious and non-infectious causes of pericarditis, but most patients with acute pericarditis present with a history suggestive of recent or concurrent viral illness. Most cases resolve with no long-term sequelae. While pericardial effusions might develop as a result of pericarditis, they are usually minor and rarely result in cardiac tamponade [95]. 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 [94]. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65 [96]. Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.
Preventability	Pericarditis may be caused by many disorders (e.g., infection, MI, trauma, tumors, metabolic disorders) but is often idiopathic. Symptoms include chest pain or tightness, often worsened by deep breathing. Cardiac output may be greatly reduced if cardiac tamponade or constrictive pericarditis develops. Diagnosis is based on symptoms, a friction rub, electrocardiographic changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram [97]. Pericarditis may result in one of two serious complications: cardiac tamponade and chronic constrictive pericarditis. Cardiac tamponade is considered a medical emergency and, if left untreated, can quickly become fatal. Very rare cases of myocarditis and pericarditis have been observed following vaccination with elasomeran-containing vaccines. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Cumulative and periodic data analyzed during the reporting period of this PBRER, supported an update of the product information, indicating that most cases recover, and that some cases required intensive care support and fatal cases have been observed. Data presented in a study conducted by Le Vu et al., and included in PBRER#4, indicated that in a period of 28 days after the second dose, there were 1.88 (95% CI: 0.956, 2.804) extra cases of

Important Identified Risk	Pericarditis
	myocarditis in 16- to 24-year-old males per 10 000 compared to unexposed persons. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, could consider proceeding with 2nd dose [93]. Current SmPC and Package information Leaflet (PIL) were updated to reflect additional new information regarding the risk of myocarditis and pericarditis and to provide up to date information on this risk as well as 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 characterize them. The benefit-risk evaluation remains positive.
Impact on the benefit-risk balance of the product	Based on the analysis of all the safety data, it shows that there have been very rare reports of pericarditis occurring after vaccination with Moderna COVID-19 Vaccine. Although causality cannot be established at this time, the majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of pericarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended.
Public health impact	Pericarditis associated with vaccines typically occur at a low incidence, which results in a low public health impact. Although the potential clinical consequences of the occurrence of pericarditis are serious, this is a risk known to healthcare professionals.

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Based on the final assessment report (Procedure no.: EMEA/H/C/PSUSA/00010897/202212, received after the DLP of this PBRER) the final recommendation regarding removal of VAED including VAERD as an Important Potential Risk from the EU RMP, was endorsed, and that "*based on the cumulative evidence, this risk is refuted and no longer considered important in the context of the RMP and the PBRER. It should be removed from the PBRER list of safety concerns and an evaluation of new information on this topic in future PBRERs is not expected*".	

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)
Potential Mechanism	IgA Nephropathy is included as an important potential risk under Risk Classification for this PBRER as per request from the PRAC Rapporteur. Based on the analysis of all available safety data as of 17 Jun 2022, the MAH refuted this signal and considers that there is insufficient information to establish a causal relationship between the administration of elasomeran and the development of IgA nephropathy; similarly, a signal of IgA Nephropathy Flare-Up based primarily on one literature article [98] was refuted on 22 Jun 2023. There is no known mechanism of action to account for an association of elasomeran vaccination and IgA nephropathy. IgA Nephropathy (also known as Berger's disease) has been observed following infection with any of several viral pathogens,

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)
	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. 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 AEs reports received by the MAH for elasomeran. With regard to IgA nephropathy and subclinical IgA deposits in kidneys, the scientific literature has found that there is a clinically significant cohort of undiagnosed "latent" IgA nephropathy in the general population as seen in native kidney biopsies. It is also noted that the process of mesangial IgA deposition may be separate from the induction of glomerular injury, and IgA deposition does not necessarily result in subsequent nephritis.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from post authorization safety data. Based on the analysis of all available safety data as of 17 Jun 2023, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran, elasomeran/imelasomeran, or elasomeran/davesomeran and the development of IgA nephropathy.
Characterization of risk	The MAH conducted an extensive evaluation of the potential signal of IgA nephropathy as signal trigger based on PRAC PSUR assessment report received on 07 Jul 2022. The signal evaluation included a cumulative review of CTs 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 etiology 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. All case reports identified from the above search (whether or not the PT IgA Nephropathy was coded) were medically reviewed for evidence of IgA nephropathy which could include renal biopsy evidence of IgA nephropathy, medical diagnosis of IgA nephropathy or reported diagnosis of IgA nephropathy. Medical review identified 54 cases of IgA nephropathy. Those cases considered IgA flares or relapses were those in which a diagnosis of IgA nephropathy had been made prior to elasomeran vaccination, where an additional diagnosis was made subsequent to the date of vaccination; 20 such cases were identified, of which 19 were serious. Incident (de novo) cases of IgA nephropathy are those for which the event of IgA Nephropathy occurred after the administration of elasomeran. These reports were identified using renal biopsy, medical diagnosis and reported diagnosis of IgA nephropathy, 34 such cases were identified. Of these 54 cases, most of the cases were reported from United States (18; 33.3%), followed by EEA (17; 31.5%) and Asia (11; 20.4%). There were no reports of fatal cases. There were no important differences between the number of reports for females (29; 53.7%) compared to Males (25; 46.3%), which is different from what is seen in the general population, were IgA Nephropathy have been reported

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)
	approximately at a 2:1 male-to-female predominance in North American and Western European populations in both adults and children. Most of the cases reported onset of IgA nephropathy within two days following vaccination with the greatest number of reports occurring after the second dose of elasomeran. This coincides with the known enhanced immune response seen with boosted vaccinations. This pattern is generally similar to that of all AEs reported following elasomeran immunization and does not evidence any clear unexpected patterns. This pattern could represent reporting bias for events proximal to vaccination or could be related to immune stimulation from vaccination that occurs within the first days after vaccination. At this time, with this limited number of reports, the finding is simply an observation, as there is no clear biological explanation. Most of the cases (29; 53.7%) were considered possible based on temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of important information in the majority of the cases. Review of retrieved literature did not identify any pathognomonic sign that would causally link vaccination against SARS-Covid-19 with any type of glomerulonephritis or nephrotic syndrome and that would distinguish such potential vaccine ARs from background events that occur in the absence of vaccination. In addition, there is heterogeneity in the types of glomerulonephritis reported, rather than one predominant type, which does not support causality with regard to elasomeran. Moreover, multiple and widely varying potential mechanisms have been suggested to explain such a potential link, some of which have already been summarized and reviewed in the initial signal evaluation on this topic, previously submitted. However, to date, there has not been consensus or strong evidence with regard to any of these potential mechanisms. Overall, there have been 76 cumulative IgA nephropathy reports in 894,063,065 doses of elasomeran-containing vaccines (original and bivalents) administered, representing an approximate reporting rate of < 1 case per 10 million doses. Only one of the 76 reports involved bivalent vaccine, a case following vaccination with elasomeran/davesomeran. Of these, 48 cases were de novo, 27 cases were flares/relapses and one (1) unknown. The number of vaccinees with IgA nephropathy is unknown, and therefore a reporting rate of IgA flares cannot be estimated; in addition, there is no established background rate of IgA flares which also precludes an O/E analysis. Persons with IgA nephropathy are already likely to seek medical attention when they have gross hematuria or other signs and symptoms of renal dysfunction.
Risk factors and risk groups	Risk factors and risk groups associated with IgA Nephropathy that have been identified include: • **Sex**: In North America and Western Europe, IgA nephropathy affects at least twice as many men as it does women. • **Ethnicity:** IgA nephropathy is more common in whites and Asians than it is in blacks. • **Age**: IgA nephropathy most often develops between the late teens and late 30s. • **Family history**: In some cases, IgA nephropathy appears to run in families, indicating that genetic factors contribute to the disease. Some studies suggest that genetic factors, immune response to infections in the upper respiratory tract and nutritional imbalance would promote the development of IgAN

Important Potential Risk	IgA Nephropathy (Safety concern in PBRER only)
	[99].
Preventability	No data have indicated the value of active screening or additional education of IgA nephropathy patients' post-vaccination. Time to onset data suggest that patients with flares are mostly diagnosed within 2 days of vaccination. Renal patients are at increased risk of serious illness and death due to Covid-19 disease, thus vaccination is of great benefit to them, as suggested by The European Renal Association and the European Vasculitis Society who stated in Mar 2022: "COVID-19 vaccines are safe, exhibiting a very low risk of de novo or relapsing immune-mediated kidney disease. Population-based studies will determine whether this is causal or coincidental. Such cases respond to standard management, including the use of immunosuppression. We recommend that patients with immune-mediated kidney diseases follow national guidance on vaccination."
Impact on the benefit-risk balance of the product	Overall, based on the analysis of all available safety data as of 17 Jun 2023, the MAH considers that there is insufficient information to establish a causal relationship between the administration of elasomeran-containing vaccines 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 product information regarding IgA nephropathy at present, nor to include IgA Nephropathy to the list of safety concerns in the risk management plan for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.
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) [100]. Half of patients with IgA Nephropathy may progress to ESRD within 25 years of the disease. Overall, 76 IgA nephropathy cumulative reports following vaccination with elasomeran, elasomeran/imelasomeran or elasomeran/davesomeran represent an extremely rare occurrence, with a reporting rate of <1 case per 10 million doses administered.

Missing information	Use in Pregnancy and While Breast-Feeding
Evidence source	Use of Moderna COVID-19 vaccines during pregnancy is an area of missing information in the RMP; no CTs were conducted among pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Since COVID-19 vaccines became available, many countries have adopted recommendations for vaccination during pregnancy to prevent severe COVID-19 disease and related complications in this population. There have been no specific safety concerns identified for COVID maternal immunization. Epidemiological studies have not indicated any increased risk of adverse perinatal outcomes including spontaneous abortion, preterm birth, small for GA birth, stillbirth, or neonatal intensive care admission after COVID-19 vaccination during pregnancy. More specifically, a case-control study case-control study from Norwegian registries of 13 956 women with ongoing pregnancies (958 vaccinated) found adjusted odds ratios of 0.91 (0.75 to 1.10) for COVID-19 vaccination in the previous three weeks following a spontaneous abortion and 0.81 (0.69 to 0.95) for vaccination in the previous five weeks, showing no risk of early pregnancy loss after COVID-19

Missing information	Use in Pregnancy and While Breast-Feeding
	vaccination. Another important perinatal outcome of interest after maternal vaccination is risk of fetal anomalies. Given the importance of timing in pregnancy and risk of fetal anomalies, a large cohort study evaluated the association of COVID-19 vaccination during early pregnancy with risk of congenital fetal anomalies and found no difference in incidence of congenital anomalies among people who received at least one dose of COVID-19 vaccine versus unvaccinated people. Importantly, after control for potential confounders such as hemoglobin A1c level in the first trimester and age at delivery, vaccination within the highest risk period for teratogenicity was not associated with presence of congenital anomalies identified by ultrasonography (adjusted odds ratio 1.05, CI: 0.72 to 1.54). Additional studies have not found an increased risk of congenital anomalies among pregnant people received COVID-19 vaccines including elasomeran during pregnancy. There have also not been specific safety concerns identified for vaccinated breast-feeding women and/or their breastfed children. Epidemiological studies have not indicated any increased risk of side-effects in the mother or the breastfed child after vaccination with elasomeran, or decreased milk production. More specifically, a large series of 17,525 women vaccinated with a COVID-19 vaccine of which 6,815 were lactating women (2,596 received elasomeran), 7,809 pregnant, and 2,901 women of reproductive age planning to get pregnant, found that there was no difference in rate of AEs by vaccine type across all groups and the AEs were transient, mild and consistent with reactogenicity events. Regarding the side-effects among infants exposed to breastmilk from mothers who had been vaccinated with elasomeran, studies show no increased risk in short term adverse effects. In the large case series by [101] only 3% and 4.4% of breastfeeding mothers reported to have concerns about the infant after the first dose and second dose, respectively. Few infant events are reported; and the most common side-effects seen among nursing children are transient, non-serious poor sleep and irritability. Regarding impact of vaccination on breastmilk production, most studies have shown that only a small percentage of lactating vaccine recipients report a transient reduction in breastmilk production post-vaccination. The literature also demonstrates robust secretion and transfer of maternal SARS-CoV-2 antibodies (mainly Immunoglobulin (Ig) A and IgG) induced by vaccination through breast milk, and some studies have showed these antibodies have neutralizing activity indicating potential passive protection to the infant, although the effectiveness is not yet established. During the review period of this PBRER, the MAH received 206 pregnancy cases (802 events) with 64 serious cases (210 serious events) in individuals who received or had a medical history of maternal exposure to elasomeran. Five (5) cases reported a fatal outcome, and 69 cases were medically confirmed. A slightly lower proportion (31.1%) of cases during the review period were reported as "serious" compared to the cumulative period (35.4%). Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" in addition to known reactogenicity events and are reported as "serious" cases; See below in "Serious and Fatal Cases and Serious Pregnancy-related Events Elasomeran." Serious cases should be interpreted with caution as many do not meet the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding all events as serious in a given serious

Missing information	Use in Pregnancy and While Breast-Feeding
	case. The majority (73.0%) of pregnancy-specific cases occurred in the 25 to 39-year age group which is consistent with typical childbearing age and what has been seen in previous review periods. The most frequently reported PTs during the reporting period were reactogenicity events, consistent with the product safety profile and similar between the reporting period and the cumulative period. During the review period, 5 pregnancy cases were coded as fatal in individuals who received or had a medical history of maternal exposure to elasomeran. No safety concerns were identified from the review of serious and fatal cases received during the reporting period for the pregnancy subpopulation. During the review period, 10 serious pregnancy cases with a medical history of maternal exposure to elasomeran reported spontaneous abortion with 11 serious events. Of the 10 cases, 3 cases were medically confirmed, and no cases were coded as fatal. During the reporting period, 4 pregnancy cases that reported stillbirth were identified through medical review of cases that were coded as "fetal death" and/or "stillbirth." Overall, cases of stillbirth and spontaneous abortion received during the reporting period were similar to the cumulative period and no safety concerns were identified. During the review period, there were no pregnancy cases reporting events of myocarditis and/or pericarditis after receipt of elasomeran. During the reporting period, the pattern of the reports remained generally consistent when compared with the cumulative data. Review of serious pregnancy-specific events and non-pregnancy-specific events during the review period did not identify any safety concerns. Overall, cases of pregnancy-specific complications are temporally related with the administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Reported cases reflect obstetric events observed after administration of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Pregnancy-specific reports had limited information about past medical and obstetric history, GA at time of vaccination, onset of AE, diagnostics, treatment and/or outcome. Where data were available, noted confounding factors for spontaneous abortion/fetal deaths and complications of pregnancy included advanced maternal age, concomitant medications, comorbidities (such as hypothyroidism), previous relevant obstetric history, and congenital anomalies which predated the vaccination. Spontaneous abortion was the most frequently reported pregnancy-specific event; however, this is a relatively common occurrence in pregnancy, and no clear TTO cluster was identified. During the review period there were 5 cases reporting stillbirth (4 cases following vaccination with elasomeran and 1 case following a booster dose of elasomeran/imelasomeran). Considering that some cases had clear alternate etiologies, there is an absence of a clear TTO cluster, and published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth after COVID vaccination. There is insufficient evidence to support a causal relationship between elasomeran-containing vaccines and stillbirth. The MAH will continue to review and evaluate cases of spontaneous abortion, fetal death and stillbirth, using routine surveillance as well as PASS. Review of the 17 cases reporting congenital anomalies (15 cases following vaccination with elasomeran and 2 cases following a booster dose of

Missing information	Use in Pregnancy and While Breast-Feeding
	elasomeran/imelasomeran) during the reporting period did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with elasomeran-containing vaccines. Review of 6 serious cases received during the reporting period concerning children under 6 years of age who were exposed during gestation did not identify any unusual patterns or safety concerns. There were 2 pregnancy-related cases among adolescents received during the reporting period. Also, there continues to be a decreasing number of pregnancy-related cases following receipt of three or more doses of elasomeran (40 pregnancy cases reporting receipt of three or more doses of elasomeran). Overall, based on current available information there are no unusual patterns or pregnancy-related safety concerns identified among these subpopulations. During the reporting period, the MAH received 39 pregnancy cases reporting events after an exposure to a BD of elasomeran bivalent vaccines [25 cases reported an event after elasomeran/imelasomeran, and 14 cases reported an event after elasomeran/davesomeran]. Most events reflect expected reactogenicity. The most frequently reported pregnancy-specific event was "Maternal exposure during pregnancy." However, during this review period, the MAH received the first reports indicating pregnancy-specific adverse events/outcomes for elasomeran/imelasomeran. These events mark the first cases of fetal death or stillbirth and congenital anomaly associated with maternal exposure to a mother vaccinated with a BD of elasomeran/imelasomeran. No unusual patterns or pregnancy-specific safety concerns have been identified; MAH will continue to review cases that received the bivalent vaccines using routine surveillance. In-depth literature reviews performed have not identified any safety concerns for the use of elasomeran during pregnancy. Thus far, published literature has not identified any evidence of an increased risk of pregnancy, fetal or neonatal complications related to maternal immunization with elasomeran-containing vaccines. Furthermore, published literature have reported that there is transfer of maternal antibodies, reduction in COVID-19 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. This is acknowledgment that COVID-19 may be more serious and cause complications for both the mother and the fetus and published literature supports the favorable benefit/risk profile of maternal immunization with elasomeran-containing vaccines. Data continues to provide supporting evidence for the use of elasomeran-containing vaccines 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 elasomeran remains favorable. During the reporting period, the MAH received 53 lactation cases, of which 4 cases were among children under 6 years of age with exposure to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran via breastmilk. There were no reported fatalities. While vaccination can induce cytokines, which can be passed via breast milk, vaccination while 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. There were no lactation cases reported among the 12-17 age group during this reporting period and there were 5 lactation cases reporting receipt of third or

Missing information	Use in Pregnancy and While Breast-Feeding
	subsequent doses, with 60.0% reporting a lactation-specific event. Among the serious lactation-specific events, there was no clustering by dose or TTO and no concerning patterns or notable trends of events reported were identified. Reported events were mild and transient. The pattern of reports remained generally consistent during the reporting period when compared with the cumulative data. No new safety concerns were identified. Where duration and outcome are available, many of the events occur within 2 days after vaccination, and most events were mild/moderate, transient events where information is available. Both in the GSDB and in the literature, reports of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhea, and pyrexia are consistent with the safety profile of elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran or what is expected in the general population. 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 elasomeran remains favorable.
Anticipated risk/consequence of the missing information	Targeted populations of the indication will include women of childbearing potential, thus, the use of elasomeran in pregnant and breastfeeding women may happen. Pregnancy outcome data will be collected in enhanced pharmacovigilance. Two observational cohort pregnancy studies (mRNA-1273-P905 and mRNA-1273-P919, see Section 8) will inform on the risk of adverse outcome in women who were exposed to elasomeran during pregnancy. 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events for pregnancy using routine surveillance. The benefit-risk evaluation remains positive. 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran did not raise any safety issue of concern and the information provided does not support evidence of causality between elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran exposure. The MAH will continue to monitor events associated with breastfeeding women who receive elasomeran-containing vaccines and their children who are exposed to these vaccines through breast milk. The benefit-risk evaluation for this sub-population continues to remain positive.

Missing information	Long-Term Safety
Evidence source	Per protocols, the clinical development program has a safety follow-up period of 12 months in the ongoing Phase 1 study 20-0003, Phase 2a Study mRNA-1273-P201 and, 24 months in the Phase 3 study mRNA-1273-P301. In the Phase 3 Study mRNA-1273-P301 the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and

Missing information	Long-Term Safety
	Part B) was 183 days (range: 1 to 218 days), or approximately 6 months. The follow-up time is through Day 209 for the Phase 1 study DMID 20-0003 and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201. Study mRNA-1273-P904, the EU PASS, aims to carry out signal detection followed, if necessary, by safety evaluation of identified possible signals of Moderna vaccines targeting SARS-CoV-2 using routinely collected health data in secondary automated electronic data sources covering all or portions of the populations in Denmark, Italy, Norway, Spain, and the UK. The study population includes all persons with a record of at least one dose of Moderna vaccines targeting SARS-CoV-2 in each database between 06 Jan 2021 and 31 Dec 2022 and members of the database source population selected for each study design, including persons providing historical rates. The final data extraction is planned for 31 Mar 2023. Further, long-term outcomes of myocarditis following vaccination will be characterized in studies mRNA-1273-P910 and mRNA-1273-P911 (see Section 8).
Anticipated risk/consequence of the missing information	The long-term safety profile continues to be characterized through continued trial follow-up, active surveillance for safety, a European post-authorization safety study, and routine pharmacovigilance.

Missing information	Use in Immunocompromised subjects (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 a booster dose (Dose 4) and a second/ third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in immunocompromised individuals, especially now with the bivalent vaccines. The third dose of elasomeran recommended for immunocompromised patients is 100 ug dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 ug dose. 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 EURMP, was endorsed, and "*the PRAC Rapporteur considers that there is sufficient evidence to conclude that the gaps in knowledge regarding the safety of Spikevax when used in immunocompromised individuals have been adequately filled and can no longer be considered an area of missing information. Removal of 'use in immunocompromised subjects' from the RMP is endorsed.* *Regardless of the removal of the safety concern in the RMP, continued monitoring through routine pharmacovigilance as well as in the ongoing additional pharmacovigilance activities P304, P903 and P904 is warranted, as proposed by the MAH.* *Regarding the effectiveness in immunocompromised subjects, the studies P304 and P901 are ongoing and will remain in the pharmacovigilance plan.*"

Missing information	Use in Immunocompromised subjects (Safety concern in PBRER only)
	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, the review of post-approval/EUA data has not identified any patterns or specific safety concerns in immunocompromised individuals. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. Overall, the general pattern of commonly reported AEs in those considered immunocompromised individuals is comparable to the general population. Evaluation showed that the top five most frequently reported AEs in the immunocompromised population were representative of expected reactogenicity and were consistent with those seen in the general population. There were no clustering or trends observed after any dose. The pattern of events observed with elasomeran/imelasomeran or elasomeran/davesomeran compared to elasomeran in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in immunocompromised individuals after vaccination with elasomeran-containing vaccines. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. During the review period, there were no cases reported in immunocompromised children or adolescent subpopulations. 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 (1.1%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiology. After careful review of all new safety data received during the reporting period for the safety topic of Use in Immunocompromised individuals, the benefit-risk profile for elasomeran remains favorable. The Spikevax SmPC section 4.4 was updated to reflect that the use of elasomeran-containing vaccines in immunocompromised individuals is no longer a missing information, and no risk is associated with the use of elasomeran-containing vaccines in this population.

Missing information	Use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
Evidence source	Frail patients are considered at higher risk of complications due to coronavirus disease 2019 (COVID-19) infection including hospitalizations and deaths; and for this reason, are prioritized candidates for vaccination. Since frail subjects with unstable health conditions and comorbidities were excluded from the registration trials, ModernaTx, Inc. is characterizing safety through post-marketing routine monitoring of AEs in this special subpopulation. Frailty refers to a state of vulnerability to stressors characterized by a decreased physiological reserve, resulting in poor health outcomes compared to individuals of the same chronological age. Based on the final assessment report for PBRER#4 (Procedure no.: EMEA/H/C/PSUSA/00010897/202212, received after the DLP of this PBRER) the final recommendation regarding removal of use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., chronic obstructive pulmonary disease (COPD),

Missing information	Use in Frail Subjects with Unstable Health Conditions and Comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) (Safety concern in PBRER only)
	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., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular 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	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. 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 elasomeran/imelasomeran or elasomeran/davesomeran compared to elasomeran in this population was generally similar. Epidemiological studies have not indicated any significantly increased risk of side-effects in frail individuals after vaccination with elasomeran. Furthermore, they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations. The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events or safety concern. Cases with fatal outcome in the frail subpopulation in the reporting period (3.2%) were strongly confounded by multiple comorbidities and the advanced age in the elderly, that provided alternate etiology. 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 elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran in frail subpopulation. Information presented in those reports does not differ from the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. There was no published clinical literature that described new and potentially important safety information on the safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran 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 elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran 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 elasomeran in individuals with AI/ID, the MAH has been closely monitoring the safety profile of elasomeran in this population through routine Pharmacovigilance.

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders (Safety concern in PBRER only)
	Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/ effectiveness of the vaccine in AI/ID population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date. Countries have amended/approved an additional primary series dose (3rd Dose/Dose 3) in MedHx AI/ID patients to achieve an adequate, more robust immune response to vaccinations. Furthermore, countries are recommending a BD (Dose 4) and a second/third booster (Dose 5, for example, as authorized and recommended in the United States on 29 Mar 2022) after the three dose priming series in individuals with MedHx of AI/ID, especially now with the bivalent vaccines. The third dose of elasomeran recommended in individuals with known MedHx of AI/ID is 100 mcg dose, whereas the booster (either 4th dose for individuals with AI/ID, or 3rd dose for the general population) is a 50 mcg dose. Thus far, there have been no specific safety concerns for individuals with MedHx of AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran and have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general population receiving elasomeran. Based on the final assessment report for PBRER#4 (Procedure no.: EMEA/H/C/PSUSA/0001 0897/202212, 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 Jun 2023, the MAH considers the cases of MedHx AI/ID to be consistent with the known safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran, and the benefits for elasomeran far outweigh any possible vaccine-associated risks. Relevant literature findings to support the reporting period discuss the acceptable safety and benefit/risk profile of COVID vaccination among individuals with AI/ID. No new safety concerns were identified in the literature review concerning elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. In AI/ID patients with disease flares, there is a natural waxing and waning course, and there are no reliable referenced data on the background rates of respective flares especially given the number of various AI/ID diseases and how to accurately measure a flare. The identified flare cases did not demonstrate a safety concern for this reporting period. There have been reports of flares after many vaccines, including various COVID vaccines. Both health care providers and patients acknowledge the potential risk of flares after any vaccination, yet flares are not specifically described in any vaccine labels. At present, the global consensus is that the benefit of vaccination outweighs the potential risks of flares but should be discussed between patient and HCP. Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in

Missing information	Use in Subjects with Autoimmune or Inflammatory Disorders (Safety concern in PBRER only)
	general populations receiving elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran. For the fatal AI/ID cases, common comorbid conditions such as hypertension, Type 2 diabetes mellitus, COPD, arteriolosclerosis, hyperlipidemia, and chronic kidney disease are similar to those reported in the general population fatal reports. The MAH will continue to monitor events for AI/ID subjects using routine surveillance. The benefit-risk evaluation remains positive.

Missing Information	Interactions with other vaccines
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 Interaction with other vaccines as Missing Information from the EURMP, was endorsed, and that "*based on the cumulative evidence, the knowledge gaps regarding this area of missing information have been filled and interaction with other vaccines has not been shown to constitute an important risk. Therefore, it is no longer considered important in the context of the RMP and the PBRER. It should be removed from the PBRER list of safety concerns and an evaluation of new information on this topic in future PBRERs is not expected.*".	

16.5. Effectiveness of Risk Minimization (if applicable)

There are no additional risk minimization measures in place for elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran.

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy and Effectiveness Information

Epidemiology and Natural History of COVID-19 disease

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV). Coronaviruses infect humans, other mammals, and avian species, including livestock and companion animals. Four CoVs are causes of the common cold and represent the only significant CoVs to infect humans prior to the 21st century. Before 2019, novel coronaviruses had resulted in two major respiratory illness outbreaks during the 21st century: SARS, which occurred during 2002–04; and Middle East respiratory syndrome (MERS), which began in 2012 [102].

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 [103] [104]. The WHO declared COVID-19 a pandemic on 11 Mar 2020; however, by

that time, there was already widespread community transmission in many locations. As of 11 Jun 2023, over 767 million confirmed cases and 6.9 million deaths have been attributed to the COVID-19 pandemic globally [105]. Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [103] [104].

Globally, nearly 1.5 million new cases and 7300 deaths were reported between 15 May 2023 to 11 Jun 2023. At the regional level, all six WHO regions reported decreases in cases and deaths. Reported cases are not an accurate representation of infection rates due to the reductions in testing and due to continued reductions in reporting globally. During this 28-day period, only 59% (139 of 234) of countries and territories reported cases–a proportion that has been consistently declining since mid-2022. As of 11 Jun 2023, over 767 million confirmed cases and over 6.9 million deaths have been reported globally [105].

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids in three principal ways: 1) inhalation of respiratory droplets and aerosol particles; 2) deposition of respiratory droplets and aerosol particles on mucous membranes in the mouth, nose, or eye by direct splashes and/or sprays; and, 3) touching mucous membranes with hands that have been soiled either directly by respiratory fluids or indirectly by touching surfaces with virus on them [106]. Transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic individuals has also been documented and may account for an estimated 59% of transmission [107]. Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state, liver disease, obesity, pregnancy, sickle cell disease, SOT, and stroke or cerebrovascular disease [108]. Smokers and individuals with substance use disorders are also at increased risk for severe COVID-19 [108].

Most individuals with COVID-19 have mild symptoms or moderate illness. Approximately 10% to 15% of COVID-19 cases progress to severe disease, and approximately 5% become critically ill. Long-term sequelae in COVID-19 patients with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae [109] [110]. Myocardial injury has reported among patients with severe COVID-19 [111]. Additionally, some patients develop serious medical complications such as myocardial inflammation, ventricular dysfunction,

pulmonary function abnormalities, and acute kidney injury [112] [113] [114] [115] [116]. While more serious long-term health complications appear to be less common, they have individual, global health, and severe socioeconomic consequences.

Like all RNA viruses, SARS-CoV-2 is prone to mutation. Multiple viral variants have been detected, most of which appear to have little if any biological significance. However, a small number of 'variants of concern' (VOC) appear to influence SARS-CoV-2 transmissibility and possibly also host immune responses. Since the outbreak of the COVID-19 caused by the 2019 novel CoV began in Wuhan, in Dec 2019, the WHO proposed labels for global COVID-19 VOC and variants of interest (VOI) [117]. According to WHO, currently circulating VOC is the Omicron variant. Delta was originally documented in Oct 2020 in India and Omicron first documented in various countries in Nov 2021.

Among the 15 EU/EEA countries with an acceptable sequencing volume in the period from 13 May 2022 to 12 Jun 2022, the Omicron VOC remains the dominant variant circulating globally, accounting for 97% of sequences reported. Among Omicron lineages submitted, BA.2 represents 39%, while BA.2.12.1 represents 28%, BA.5 represents 6%, and BA.4 represents 3%. For epidemiological week 20 (15 May 2022 to 21 May 2022) and week 21 (22 May 2022 to 28 May 2022), there was a 4% decline in the number of BA.2 sequences, while there were increases of 4%, 3%, and 2% in BA.5, BA.2.12.1, and BA.4 sequences respectively.

The WHO current VOC are the Omicron subvariants. There are currently no circulating VOI listed by WHO; however, the European Center for Disease Prevention and Control lists BA.2.75 and its sub-lineages, BQ.1, XBB and its sub-lineages (excluding XBB1.5 and its sub lineages), XBB.1.5 as VOI as of 26 Jan 2023 [118]. Among the nine countries (Austria, Denmark, France, Germany, Italy, Latvia, Luxembourg, the Netherlands, and Sweden) with an adequate volume of sequencing or genotyping for weeks 1 to 2 (2 to 15 Jan 2023), the estimated distribution of VOC or VOI ranged from 48.4-76.0% in seven countries for BQ.1, 11.3-76.9% in nine countries for BA.5, 6.6-27.8% in eight countries for BA.2.75, 1.4-5.6% in six countries for XBB.1.5, 0.9-6.5% in seven countries for XBB, 0.3-15.3% in eight countries for BA.2, and 0.1-0.9% in eight countries for BA.4 [119].

In light of the widespread transmission of the Omicron VOC across the globe and the subsequent expected increased viral diversity, WHO has added a new category to its variant tracking system, termed "Omicron subvariants under monitoring" to signal to public HAs globally, which VOC lineages may require prioritized attention and monitoring. According to WHO, the main objective of this category is to investigate if these lineages may pose an additional threat to global public health as compared to other circulating viruses.

The general consensus reached amongst the regulators was aligned with WHO recommendation that an inclusion of an antigenically distinct variant, primarily Omicron (but to a lesser extent, Beta) should be considered as an additional component for a modified variant vaccine to be used going forward. The bivalent approach was favored over the monovalent approach however, a monovalent Omicron could also be considered.

At the request of FDA, based on the outcome of the 28 Jun 2022 Vaccines and Related Biological Products Advisory Committee (VRBPAC), the MAH developed a modified, bivalent booster, elasomeran/davesomeran (also referred to as ".222") vaccine, based on the addition of Omicron BA.4/BA.5 sublineage in combination with the prototype ancestral strain, 25 µg each, 50 µg total. The bivalent elasomeran/davesomeran (Original/ Omicron BA.4/BA.5) produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine.

As of 03 Mar 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 VOC, as these parental lineages are no longer circulating. ECDC will continue to categorize and report on specific SARS-CoV-2 sub-lineages in circulation that are relevantto the epidemiological situation. These additional variants of SARS-CoV-2 have been de-escalated based on at least one the following criteria: (1) the variant is no longer circulating, (2) the variant has been circulating for a long time without any impact on the overall epidemiological situation, (3) scientific evidence demonstrates that the variant is not associated with any concerning properties.

As of 17 Jun 2023, previously circulating VOCs and current Omicron subvariants under monitoring [117] are presented in Table 17.1 and Table 17.2:

Table 17.1 Previously circulating Variants of Concerns

WHOlabel	Pango lineages*	GISAID clade	Next strain clade	Additional amino acid changes monitored†	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	United Kingdom, Sep 2020	18 Dec 2020
Beta	B.1.351 B.1.351.2 B.1.351.3	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May 2020	18 Dec 2020
Gamma	P.1 P.1.1 P.1.2	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov 2020	11 Jan 2021

WHO label	Pango lineages*	GISAID clade	Next strain clade	Additional amino acid changes monitored*	Earliest documented samples	Date of designation
	P.1.4 P.1.6 P.1.7					
Delta	B.1.617.2 AY.1 AY.2 AY.3 AY.3.1	G/478K.V1	21A	+S:417N	India, Oct 2020	VOI: 04 Apr 2021 VOC: 11 May 2021
Omicron*	B.1.1.529	GRA/484A	21K, 21L 21M, 22A, 22B, 22C, 22D	+S:R346K +S:L452X +S:F486V	Multiple countries, Nov 2021	VUM: 24 Nov 2021 VOC: 26 Nov 2021

*Includes all descendent lineages.

Table 17.2 Omicron subvariants under monitoring

Pango lineage# (+ mutation)	GISAID clade	Next strain	Relationship to circulating VOC lineages	Spike genetic features	Earliest documented samples
BF.7*	GRA	22B	BA.5 sub lineage	BA.5 + S:R346T	24 Jan 2022
BQ.1$	GRA	22E	BA.5 sub lineage	BQ.1 and BQ.1.1: BA.5 + S:R346T, S:K444T, S:N460K	07 Feb 2022
BA.2.75§	GRA	22D	BA.2 sub lineage	BA.2.75: BA.2 + S:K147E, S:W152R, S:F157L, S:I210V, S:G257S, S:D339H, S:G446S, S:N460K, S:Q493R reversion CH.1.1: BA.2.75 + S:L452R, S:F486S	31 Dec 2021
XBBμ		22F	Recombinant of BA.2.10.1 and BA.2.75 sub lineages, i.e. BJ1 and BM.1.1.1, with a breakpoint in S1	BA.2+ S:V83A, S:Y144-, S:H146Q, S:Q183E, S:V213E, S:G252V, S:G339H, S:R346T, S:L368I, S:V445P, S:G446S, S:N460K, S:F486S, S:F490S XBB.1.5: XBB + S:F486P (see rapid risk assessment)	13 Aug 2022

Includes descendent lineages
* Additional mutations outside of the spike protein: N: G30-, S33F, ORF9b: M26-, A29I, V30L
$ additional mutation outside the spike protein: ORF1a: Q556K, L3829F, ORF1b: Y264H, M1156I, N1191S, N: E136D, ORF9b: P10F
§ additional mutations outside of the spike protein: ORF1a: S1221L, P1640S, N4060S, ORF1b: G662S, E: T11A
μ additional mutations outside of the spike protein: ORF1a: K47R, ORF1b: G662S, S959P, E: T11A, ORF8: G8*

Nature of the Benefit

As of 11 Jun 2023, over 767 million confirmed cases of SARS-CoV-2 and over 6.9 million deaths have been reported globally [105]. These figures are considered underestimates. As per estimates, COVID-19 deaths in 2021 imply a 1.7-year reduction in life expectancy at birth and a 1.1-year reduction in life expectancy at age 65 for the total US population relative to pre-pandemic levels [120]. Like other respiratory viruses, SARS-CoV-2 spreads efficiently. Indeed, the most recent circulating variants, Omicron and its sub lineages, have significantly enhanced transmissibility compared with the progenitor SARS-CoV-2 virus that was responsible for the start of the pandemic. Continued challenges in achieving global COVID-19 vaccine coverage, limitations in durability of vaccine protection, and viral evolution all contribute to the ongoing challenges in controlling this pandemic.

Elasomeran, an LNP-encapsulated mRNA vaccine expressing the prefusion stabilized spike glycoprotein, is enzymatically manufactured, directs vaccine antigen production in vivo, thus avoiding the need for the lengthy processes to optimize the production and in vitro characterization of the target antigen as required with traditional vaccines. This approach provides potential benefits in terms of reducing time from discovery to production. Additionally, production of the antigen in vivo likely mimics the expression of the antigen during the course of a natural infection.

mRNA does not interact with the genome, is nonreplicating, delivers only the genetic elements required for expression of the encoded protein, and is only a transient carrier of information and does not persist in the body.

During translation, mRNA serves as the template for the synthesis of the intended proteins. mRNA vaccines targeting SARS-CoV-2 represent the first vaccines employing this technology. They offer the potential to vaccinate against any encoded protein antigen with potential use in both prophylactic and therapeutic vaccines.

Moderna COVID-19 Vaccine is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 months of age and older.

Efficacy and immunogenicity against COVID-19 disease are currently being evaluated in 22 ongoing CTs including 12 sponsored by ModernaTx, Inc. Primary analysis for efficacy was demonstrated in adults 18 years and older in Study mRNA-1273-P301. The primary end point was the efficacy of the elasomeran vaccine in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second injection in the per protocol population, among participants who were seronegative at baseline."COVID-19 cases were defined as occurring in

participants who had at least two of the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if the participant was hospitalized) that was positive for SARS-CoV-2 by reverse-transcriptase–polymerase chain reaction (RT-PCR) test" [121]. Vaccine efficacy was assessed in the full analysis population (randomized participants who received at least one dose of mRNA-1273 or placebo), the modified intention-to-treat population (participants in the full analysis population who had no immunologic or virologic evidence of COVID-19 on day 1, before the first dose), and the per protocol population (participants in the modified intention-to-treat population who received two doses, with no major protocol deviations). Participants were evaluated in the treatment groups to which they were assigned. Vaccine efficacy was defined as the percentage reduction in the hazard ratio for the primary end point (mRNA-1273 vs. placebo). A stratified Cox proportional hazards model was used to assess the vaccine efficacy of mRNA-1273 as compared with placebo in terms of the percentage hazard reduction [121].

The primary efficacy endpoint in Study mRNA-1273-P301 was met, elasomeran prevented COVID-19 starting 14 days after the second injection of vaccine, based on a total of 95 adjudicated cases accrued (5 cases in the elasomeran group and 90 cases in the placebo group). For the primary analysis, 196 cases of COVID-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1,000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1,000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the elasomeran vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo. Findings were similar across key secondary analyzes, including assessment starting 14 days after dose 1 (225 cases with placebo, vs. 11 with elasomeran, indicating a vaccine efficacy of 95.2% [95% CI, 91.2 to 97.4]), and assessment including participants who were SARS-CoV-2 seropositive at baseline in the per protocol analysis (187 cases with placebo, vs. 12 with elasomeran; one volunteer assigned to receive elasomeran was inadvertently given placebo], indicating a vaccine efficacy of 93.6% [95% CI, 88.6 to 96.5]). Between days 1 and 42, seven cases of COVID-19 were identified in the elasomeran group, as compared with 65 cases in the placebo group.

A key secondary end point evaluated the efficacy of elasomeran at preventing severe COVID-19. Thirty participants in the trial had severe COVID-19; all 30 were in the placebo group (indicating vaccine efficacy of 100% [95% CI, could not be estimated to 1.0]), and one death among these participants was attributed to COVID-19. The vaccine efficacy to prevent COVID-19 was

consistent across subgroups stratified by demographic and baseline characteristics: age groups (18 to <65 years of age and ≥65 years), presence of risk for severe COVID-19, sex, and race and ethnic group (non-Hispanic White and communities of color). Among participants who were positive for SARS-CoV-2, by serologic or virologic testing, at baseline (337 in the placebo group and 343 in the elasomeran).

The mRNA-1273-P301 study population included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID-19. The efficacy of elasomeran was consistent for the primary efficacy endpoint in study participants with and without risk factors for severe COVID-19, in older and younger adults, in males and females, and in White participants and those from communities of color. There was a limited number of participants in each ethnic group in the subgroup analysis who contributed to the primary efficacy endpoint, and therefore efficacy analyzes were not performed for each specific racial and ethnic subgroup.

Importantly, analysis of the 04 May 2021 dataset also showed that elasomeran 100 µg was 98.2% effective in preventing severe COVID-19, with 106 adjudicated cases of severe COVID-19 in the placebo group and 2 adjudicated cases in the elasomeran group. Subgroup analyzes of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection. Additionally, elasomeran was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of elasomeran (VE of 92.8% based on Hazard Ratios).

Elasomeran also demonstrated protection against asymptomatic SARS-CoV-2 infection. The VE to prevent asymptomatic SARS-CoV-2 infection was 63.0% (95% CI 56.6%, 68.5%) and VE to prevent SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0% (95% CI 79.5%, 84.2%).

Study mRNA-1273-P301 demonstrated that the 100 µg dose level was highly immunogenic through Day 57 as measured by both bAb and nAb in both SARS-CoV-2 baseline-negative and baseline-positive individuals. In SARS-CoV-2 baseline-positive participants, antibody levels at Day 29 were similar to those observed at Day 57 in baseline-negative participants, indicating that the first injection of elasomeran acts like a booster in participants with previous SARS-CoV-2 infection.

The final efficacy analysis of the primary endpoint for Part A (04 May 2021) was performed on 799 adjudicated first occurrences of COVID-19 starting at least 14 days after the second injection in the Per protocol (PP) Set.

The follow-up period for the final blinded efficacy analysis provided a median of 148 days (approximately 5.3 months, where 1 month=28 days) from randomization to the PDV for participants who completed their PDV on or before the data cut-off date. Additionally, the median duration of follow-up from the PDV to the data cut-off was 67 days, during which time blinded follow-up continued for participants who did not complete their PDV on or before to the data cut-off. Together, these provide a total follow-up duration of approximately 7.6 months from randomization (or approximately 6.5 months from the second injection).

The results of this analysis were consistent with the results of the interim and primary efficacy analyzes, confirming persistent, high efficacy over a substantially larger case database and over the median 5.3-months blinded observation period of Part A. For the final efficacy analysis, the VE point estimate (95% CI) was 93.2% (91.0%, 94.8%; $p < 0.0001$) and the 95% CI was observed to be within the 95% CIs for the interim and primary efficacy analyzes. In the final analysis of efficacy (database lock of 04 May 2021), 108 participants had adjudicated severe COVID-19 starting 14 days after second injection in the PP Set (106 cases in the placebo group and 2 cases in the elasomeran group); the VE point estimate (95% CI) based on the hazard ratio was 98.2% (92.8%, 99.6%), confirming and extending the findings of the primary analysis of 25 Nov 2020 based on a median of 148 days (final analysis) versus 78 days (primary analysis) of efficacy follow-up after randomization. Among these participants, 3 deaths in the placebo group were attributed to COVID-19.

The observed efficacy in each subgroup was consistent with the high efficacy observed for the primary endpoint across the entire population, and the lower bound of the 95% CI of the individual subgroup analyzes exceeded 30%, one of the success criteria for the interim efficacy analysis. Results were consistent across subgroups (VE point estimates within the 95% CI for the overall dataset) stratified by age groups ($\geq$ 18 to < 65 years, $\geq$ 65 years, $\geq$ 65 years to < 75 years, and $\geq$ 75 years); age and health risk ($\geq$ 18 to < 65 years and not at risk, $\geq$ 18 to < 65 years and at risk, and $\geq$ 65 years), sex (male and female), ethnicity (Hispanic or Latino and not Hispanic or Latino); presence of risk for severe COVID-19 at screening; and race and ethnicity. With respect to the subgroup analysis for race and ethnicity, limited numbers of participants in each ethnic group contributed to the primary efficacy endpoint. Therefore, the race and ethnicity data were pooled into a "communities of color" group for this analysis to ensure that the subpopulations in the study

would be large enough for meaningful analysis. The VE of elasomeran across major demographic and baseline characteristic subgroups was consistent with that of the primary efficacy endpoint analysis.

Studies mRNA-1273-P201 and mRNA-1283-P101 provided evidence of persistence of immune response through Day 209, 6-months after the second injection of elasomeran, although antibody levels at Day 209 were lower than peak values.

The immunogenicity of the elasomeran vaccine was evaluated in DMID Study mRNA-1273-P101/20-0003/NCT04283461 and mRNA-1273-P201 and is supportive of the efficacy of the vaccine to prevent COVID-19 as demonstrated in the pivotal mRNA-1273-P301 Phase 3 study. In DMID Study mRNA-1273-P101/20-0003/NCT04283461 (Phase 1), 2 doses of 100 µg or higher generated the highest titers of neutralizing or binding antibody and this observation was the basis for selecting the 100-µg dose for use in the pivotal mRNA-1273-P301 Phase 3 study. Importantly, the antibody levels after 2 doses of elasomeran exceeded those in a pool of convalescent sera. Neutralizing activity was observed for the 100-µg elasomeran dose as of day 36, which was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata. Additionally, in DMID Study mRNA-1273-P101/20-0003, Th1-directed CD4+ T-cells were observed to be induced across age groups, with limited indication of a Th2-directed response and similar responses were observed among all age groups for the 100-µg dose. In the dose-confirming study, mRNA-1273-P201, generally comparable neutralizing and binding antibody responses were measured in the serum of participants who received either 50 µg or 100 µg doses of elasomeran administered 28 days apart.

Efficacy in adolescents 12 through 17 years of age

mRNA-1273-P203 is an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind, CT to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in adolescents ages 12 to 17 years in the US (NCT04649151). Participants with a known history of SARS-CoV-2 infection were excluded from the study.

A total of 3,732 participants were randomly assigned to receive doses of either 100 µg of mRNA 1273 vaccine or a placebo control in a 2:1 randomization ratio (2,773 participants aged ≥12 to < 16 years and 959 participants aged ≥ 16 to < 18 years.

An efficacy analysis was performed in 3,236 participants who received at least Dose 1 of either Moderna COVID-19 Vaccine (n=2,163) or placebo (n=1,073) and had a negative baseline

SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set). In the mITT set, 48.5% were female, 11.2% were Hispanic or Latino; 83.9% were White, 2.8% were African American, 6.3% were Asian, and 0.9% other races. Between participants who received Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as the presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive nasopharyngeal (NP) swab or saliva sample for SARS-CoV-2 by RT-PCR (reverse transcription polymerase chain reaction). Listed symptoms were fever (temperature > 38°C/≥ 100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.

There were 2 COVID-19 cases in the Moderna COVID-19 vaccine group and 13 cases in the placebo group, with a vaccine efficacy of 92.7% (95% CI of 67.8% to 99.2%) (Table 17.3).

Table 17.3 Efficacy analysis: COVID-19* in participants 12 to 17 years of age starting 14 days after Dose 1–modified intent-to-treat set

Moderna COVID-19 Vaccine			Placebo			% Vaccine efficacy (95% CI)†
Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	Participant (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	
2,163	2	3.828	1,073	13	52.473	92.7 (67.8, 99.2)

* COVID-19: Presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.
† Vaccine efficacy defined as 1 — ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Immunogenicity in adolescents 12 through 17 years of age

In mRNA-1273-P203, an analysis was conducted of SARS-CoV-2 50% neutralizing titers and seroresponse rates (SRR) 28 days after Dose 2 in a subset of adolescents aged 12 through 17 in mRNA-1273-P203 and in participants aged 18 through 25 in mRNA-1273-P301 (Part A) who had no immunologic or virologic evidence of prior COVID-19 at baseline. Non-inferior immune responses and SRR were demonstrated in a comparison of immune responses in adolescents aged 12 through 17 years compared with those of participants aged 18 through 25 (Table 17.4).

Table 17.4 Summary of geometric mean titer and seroresponse rate–comparison of adolescents aged 12 through 17 to participants aged 18 through 25–per protocol immunogenicity subset

Assay	Time point	Moderna COVID-19 Vaccine		12 through 17 years/18 through 25 years	
		12 through 17 years n=340	18 through 25 years n=305		
		GLSM (95% CI)*	GLSM (95% CI)*	GMR (95% CI)†	Met Noninferiority objective (Y/N)‡
SARS-CoV-2 neutralization assay–ID50 (titer)§	28 days after Dose 2	1401.7 (1276.3, 1539.4)	1301.3 (1177.0, 1438.8)	1.08 (0.94, 1.24)	Y
		Seroresponse % (95% CI)	Seroresponse % (95% CI)	Difference in seroresponse rate % (95% CI)#	
		98.8 (97.0, 99.7)	98.6 (96.6, 99.6)	0.2 (-1.8, 2.4)	

GLSM = Geometric least squares mean
GMR = Geometric mean ratio
n = Number of subjects with non-missing data at the corresponding timepoint
* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
† The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in mRNA-1273-P203 and young adults in mRNA-1273-P301 [Part A]) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
‡ Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%.
§ SARS-CoV-2 50% inhibitory dose (ID50) neutralization titers were determined using a SARS-CoV-2 Spike-Pseudo-typed Virus Neutralization Assay. Quantification of SARS-CoV-2 neutralizing antibodies utilizes lentivirus particles expressing SARS-CoV-2 Spike protein on their surface and contains a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by relative luminescence units (RLU). Neutralization is measured as the serum dilution at which RLU is reduced by 50% (ID50) relative to mean RLU in virus control wells virus but after subtraction of mean RLU in cell control wells.
Seroresponse due to vaccination specific to pseudo virus neutralizing antibody ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits

Efficacy in children 6 through 11 years of age

The pediatric study is an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind, CT to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in children ages 6 through 11 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4,011 participants were randomized 3:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for effectiveness and safety until 1 year after the second dose.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cut-off date of 06 Oct 2021 was performed in 3,556 participants who received two doses (0.25 mL

at 0 and 1 month) of either the Moderna COVID-19 Vaccine (n=2,678) or placebo (n=878) and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to Treat Set [mITT]). Between participants who received the Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics. The median length of follow-up for efficacy for participants in the study was 50 days post Dose 1.

The efficacy information in children 6 through 11 years of age is presented in Table 17.5:

Table 17.5 Efficacy analysis: COVID-19 and SARS-CoV-2 infections in participants 6 through 11 years of age starting 14 days after dose 1–modified intent-to-treat set

	Moderna COVID-19 Vaccine N=2,672		Placebo N=877		% Vaccine Efficacy (95% CI)*
	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
COVID-19 Cases-Definition 1[a]	0	0	13	152.027	100.0 (89.3, NE)
COVID-19 Cases-Definition 2[b]	3	11.399	14	163.810	93.0 (75.1, 98.7)
SARS-CoV-2 Infections (regardless of symptoms)[c]	16	60.958	26	306.853	80.1 (61.5, 90.0)
Asymptomatic SARS-CoV-2 Infections[d]	13	49.529	12	141.625	65.0 (16.1, 85.3)

N = Number of participants at risk at 14 days after Dose 1 for specific efficacy endpoint.
NE = Not estimable
* Vaccine efficacy defined as 1-ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
[a] Participant must have experienced at least two of the following systemic symptoms: fever (≥38°C / ≥100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS- CoV-2 by RT-PCR.
[b] Presence of at least one symptom from a list of COVID-19 symptoms and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature >38°C / ≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.
[c] A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline binding antibody against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline.
[d] Absence of symptoms and infections as detected by RT-PCR or serology tests: absent of COVID-19 symptoms and at least 1 of the following: binding antibody level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.

Immunogenicity in children 6 through 11 years of age

An analysis evaluating SARS-CoV-2 50% neutralizing titers and SRR 28 days after Dose 2 was conducted in subset of children aged 6 through 11 (n=134) in the pediatric study and in participants aged 18 through 25 (n=296) in the adult study (NCT04796896). Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The GMR of the neutralizing antibody titers in children 6 through 11 years of age compared to the 18- to 25-year-olds was 1.5 (95% CI: 1.3, 1.8). The difference in seroresponse rate was 0.6% (95% CI: -2.8, 2.8). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

Clinical efficacy in children 6 months through 5 years of age

An ongoing Phase 2/3 study was conducted to evaluate the safety, tolerability, reactogenicity, and effectiveness of elasomeran in healthy children 6 months through 11 years of age. The study enrolled children in 3 age groups: 6 years through 11 years; 2 years through 5 years; and 6 months through 23 months.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cutoff date of 21 Feb 2022 was performed in 5,476 participants 6 months through 5 years of age who received two doses (at 0 and 1 month) of either elasomeran (n=4,105) or placebo (n=1,371) and had a negative baseline SARS-CoV-2 status (referred to as the Per Protocol Set for Efficacy). Between participants who received elasomeran and those who received placebo, there were no notable differences in demographics.

The median length of follow-up for efficacy post-Dose 2 was 71 days for participants 2 through 5 years of age and 68 days for participants 6 months through 23 months of age.

Vaccine efficacy in this study was observed during the period when the B.1.1.529 (Omicron) variant was the predominant variant in circulation.

Vaccine efficacy (VE) in Part 2 for the Per Protocol Set for Efficacy for COVID-19 cases 14 days or more after dose 2 using the "COVID-19 P301 case definition" (i.e., the definition employed in the pivotal adult efficacy study) was 36.8% (95% CI: 12.5, 54.0) for children 2 through 5 years of age and 50.6% (95% CI: 21.4, 68.6) for children 6 months through 23 months of age.

Immunogenicity in children 6 months through 5 years of age For children aged 2 years through 5 years of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n = 264; 25 micrograms) to those of young adults (n = 295; 100 micrograms) demonstrated a GMR of 1.014 (95% CI: 0.881, 1.167), meeting the noninferiority success criteria (i.e., lower

bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The geometric mean fold rise (GMFR) from baseline to Day 57 for these children was 183.3 (95% CI: 164.03, 204.91). The difference in seroresponse rates (SRR) between the children and young adults was -0.4% (95% CI: -2.7%, 1.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the SRR difference > -10%).

For infants and toddlers from 6 months through 23 months of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n = 230; 25 mcg) to those of young adults (n = 295; 100 mcg) demonstrated a GMR of 1.280 (95% CI: 1.115, 1.470), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The difference in SRR rates between the infants/toddlers and young adults was 0.7% (95% CI: -1.0%, 2.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the seroresponse rate difference > -10%).

Accordingly, the prespecified success criteria for the primary immunogenicity objective were met for both age groups, allowing efficacy of 25 micrograms to be inferred in both children 2 years through 5 years and infants and toddlers aged 6 months through 23 months (Table 17.6 and Table 17.7).

Table 17.6 Summary of geometric mean concentration ratio and seroresponse rate – comparison of individuals 6 months through 23 months of age to participants 18 years through 25 years of age –per-protocol immunogenicity set

		6 months through 23 months n=230	18 years through 25 years n=291	6 months through 23 months/18 years through 25 years	
Assay	**Time point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralization assay[c]	28 days after Dose 2	1 780.7 (1 606.4, 1 973.8)	1 390.8 (1 269.1, 1 524.2)	1.3 (1.1, 1.5)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		100 (98.4, 100)	99.3 (97.5, 99.9)	0.7 (-1.0, 2.5)	

GMC = Geometric mean concentration
n = number of participants with non-missing data at baseline and at Day 57
* Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ.
Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.

a The log-transformed antibody levels are analysed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
b Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%.
c Final geometric mean antibody concentrations (GMC) in AU/mL were determined using SARS-CoV-2 microneutralization assay.
d Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralizing antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.
e Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Table 17.7 Summary of geometric mean concentration ratio and seroresponse rate – comparison of individuals 2 years through 5 years of age to participants 18 years through 25 years of age – per protocol immunogenicity set

		2 years through 5 years n=264	18 years through 25 years n=291	2 years through 5 years/18 years through 25 years	
Assay	**Time point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralization assayc	28 days after Dose 2	1 410.0 (1 273.8, 1 560.8)	1 390.8 (1 262.5, 1 532.1)	1.0 (0.9, 1.2)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		98.9 (96.7, 99.8)	99.3 (97.5, 99.9)	-0.4 (-2.7, 1.5)	

GMC = Geometric mean concentration
n = number of participants with non-missing data at baseline and at Day 57
* Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ.
Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
a The log-transformed antibody levels are analysed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
b Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%.
c Final GMC in AU/mL were determined using SARS-CoV-2 microneutralization assay.
d Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralizing antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper- Pearson method.
e Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Immunogenicity in booster dose participants

mRNA-1273-P201 is an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the

Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series. In an open-label phase, 149 of those participants (Per Protocol Set) received a single BD (0.25 mL) at least 6 months after receiving the second dose in the primary series. A single BD (0.25 mL) was shown to be immunogenic at Day 29 post-BD and non-inferior to Day 57 immunogenicity of the primary series (two doses of 0.5 mL 1 month apart) in a subset of participants 18 years of age and older in mRNA-1273-P301.

Immunogenicity in participants 18 years of age and older–after elasomeran/imelasomeran BD (0.5 mL, 25 µg/25 µg)

The safety, reactogenicity, and immunogenicity of an elasomeran/imelasomeran BD are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 437 participants received the elasomeran/imelasomeran 50 µg BD, and 377 participants received the elasomeran (original) 50 µg BD.

Study P205 Part G evaluated the safety, reactogenicity and immunogenicity of elasomeran/imelasomeran when administered as a second BD to adults who previously received 2 doses of elasomeran (original) (100 µg) as a primary series and a BD of elasomeran (original) (50 µg) at least 3 months prior to enrolment. In P205 Part F, study participants received elasomeran/imelasomeran (50 µg) as a second BD and the Part F group serves as a within-study, non-contemporaneous comparator group to the elasomeran/imelasomeran group.

In this study, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). In the primary analysis, the original SARS-CoV-2 estimated neutralizing antibody geometric mean titre (GMT) and corresponding 95% CI was 6,422.3 (5990.1, 6885.7) and 5,286.6 (4,887.1, 5,718.9) 28 days after the elasomeran/imelasomeran and elasomeran (original) BDs, respectively. This GMT represents the ratio between response of elasomeran/imelasomeran versus elasomeran against the ancestral SARS-CoV-2 (D614G) strain. The GMR (97.5% CI) was 1.22 (1.08, 1.37) meeting the pre-specified criterion for noninferiority (lower bound of 97.5% CI ≥0.67).

The estimated Day 29 neutralizing antibody GMTs against Omicron, BA.1 were 2479.9 (2,264.5, 2,715.8) and 1,421.2 (1,283.0, 1,574.4) in the elasomeran/imelasomeran and elasomeran (original) booster groups, respectively, and the GMR (97.5% CI) was 1.75 (1.49, 2.04), which met the pre-specified superiority criterion (lower bound of CI >1).

In Study mRNA-1273-P205 Part G, all primary and key secondary immunogenicity objectives were met. mRNA 1273.214 50 µg elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2 (D614G) 28 days after BD administration as compared to a 50 µg BD of elasomeran [122]. The GMR (97.5% CI) for primary analysis population (participants with no prior infection) against the Omicron variant was 1.75 (1.49, 2.04) exceeding the recommended criteria [122]. Omicron neutralizing antibody responses were consistently higher in participants both with and without prior evidence of SARS-CoV-2 infection in the entire study population [GMR (97.5% CI) 1.79 (1.56, 2.04)]. The neutralizing antibody response against the ancestral SARS-CoV-2 (D614G) was also significantly higher with the 50-µg mRNA 1273.214, compared to 50 µg elasomeran, 28 days after the BD [GMR (97.5% CI): 1.22 (1.08, 1.37), primary analysis population], indicating that elasomeran/imelasomeran retained the neutralizing antibody response against the ancestral SARS-CoV-2. Additionally, 50 µg elasomeran/imelasomeran elicited potent neutralizing antibody against the Omicron BA.4 and BA.5 subvariants. Elasomeran/imelasomeran also elicited significantly higher binding antibody responses against multiple variants not contained in the vaccine, including Alpha, Beta, Gamma, and Delta (nominal alpha of 0.05). Therefore, elasomeran/imelasomeran provides an enhanced immune response against multiple variants.

On the basis of these results, the elasomeran/imelasomeran 50 µg elicited superior nAb responses against the Omicron subvariants BA.4, BA.5 compared with elasomeran 50 µg (nominal alpha of 0.05) and the BA.4, BA.5 nAb response was consistently higher in the elasomeran/imelasomeran group compared to the elasomeran group in participants with and without prior SARS-CoV-2.

Immunogenicity of a BD following primary vaccination with another authorized or approved COVID-19 vaccine in adults 18 years of age and older

Effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) BD in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous BD) is inferred from immunogenicity data supporting effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) BD administered following completion of a Moderna COVID-19 Vaccine primary series and from immunogenicity data from an independent Phase 1/2 open-label CT (NCT04889209) conducted in the United States that evaluated a heterologous BD (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to

receive a BD of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the BD and on Day 15 after the booster dose. A booster response to the Moderna COVID-19 Vaccine (0.5 mL) was demonstrated regardless of primary vaccination.

Immunogenicity in adult participants against the B.1.617.2 (Delta) variant

Serum samples were obtained from participants in mRNA-1273-P201 (Part B) pre-booster and on Day 29 post-booster. Results of the pseudovirion neutralization assay (PsVNA) against the B.1.617.2 (Delta) variant showed that administration of the Moderna COVID-19 Vaccine booster (50 µg) induced an 18-fold rise in neutralizing titers against the Delta variant compared with pre-booster levels (GMFR = 18.97; 95% CI, 16.72, 21.53; overall group, n = 295).

In the overall mRNA-1273-P201 (Part B) group (n = 293), the pre-booster neutralizing antibodies (nAb) GMT for the Delta variant was 42.27 (95% CI: 37.19, 48.04; n=293) and 28 days post-booster, the GMT was 803.51 (95% CI: 731.42, 882.70; n = 295). Over 90% of booster recipients in the overall group (92.2%; 95% CI: 88.5, 95.0%; n = 293) met the definition of a seroresponse for the Delta variant (using a 4-fold increase from pre-booster baseline).

Administration of the 50 µg elasomeran prototype booster resulted in robust increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 µg had a GMFR of 20.89 (95% CI: 17.54, 24.87); those primed with 100 µg had a GMFR of 17.28 (95% CI: 14.38, 20.77), showing the consistency in responses regardless of priming dose.

Additional analyzes of Delta variant nAb GMT by age group have been conducted. nAb responses in older adults are numerically similar to those observed in the younger groups (749.94 vs. 822.98).

The GMFR (Day 29 post-booster: pre-booster) achieved by Moderna COVID-19 Vaccine booster, measured by the Delta pseudovirus assay (18.97; 95% CI: 16.72, 21.53), points to the ability of the prototype vaccine booster to enhance a breadth of nAb responses, including against the highly transmissible Delta variant. Just as the Moderna COVID-19 Vaccine booster generated enhanced nAb levels against the original strain (GMFR 15.06 [95% CI: 13.43, 16,89]), it also was able to broaden, and increase nAb levels against Delta variant.

Immunogenicity in children against the B.1.617.2 (Delta) variant

Additional data on the immunogenicity of the Moderna COVID-19 Vaccine against the Delta variant comes from the pediatric study. Serum samples were obtained at baseline and on Day 57 from participants 6 to <12 years of age.

In the per protocol immunogenicity subset (n=134), the baseline nAb GMT against Delta (measured by PsVNA ID50) in children 6 years to < 12 years old was below the LLOQ; 28 days after 2 doses of 50 μg of the Moderna COVID-19 Vaccine, serum nAb GMT was 756.46 (95% CI: 650.99, 878.77). Furthermore, 99.3% of children met the definition of seroresponse against the Delta variant. The GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant.

Study mRNA-1273-P204 is an ongoing Phase 2/3 study conducted to evaluate the safety, tolerability, reactogenicity, and effectiveness of elasomeran in healthy children 6 months through 11 years of age. The study enrolled children in 3 age groups: 6 years through 11 years; 2 years through 5 years; and 6 months through 23 months.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cut-off date of 21 Feb 2022 was performed in 5,476 participants 6 months through 5 years of age who received two doses (at 0 and 1 month) of either elasomeran (n=4,105) or placebo (n=1,371) and had a negative baseline SARS-CoV-2 status (referred to as the Per Protocol Set for Efficacy). Between participants who received elasomeran and those who received placebo, there were no notable differences in demographics.

The median length of follow-up for efficacy post Dose 2 was 71 days for participants 2 through 5 years of age and 68 days for participants 6 months through 23 months of age.

Vaccine efficacy in this study was observed during the period when the B.1.1.529 (Omicron) variant was the predominant variant in circulation.

For children aged 2 years through 5 years of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n = 264; 25 micrograms) to those of young adults (n=295; 100 μg) demonstrated a GMR of 1.014 (95% CI: 0.881, 1.167), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The GMFR from baseline to Day 57 for these children was 183.3 (95% CI: 164.03, 204.91). The difference in SRR between the children and young adults was -0.4% (95% CI: -2.7%, 1.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the SRR difference > -10%).

For infants and toddlers from 6 months through 23 months of age, comparison of Day 57 nAb responses in this Part 2 Per Protocol Immunogenicity Subset (n=230; 25 μg) to those 24 of young adults (n=295; 100 μg) demonstrated a GMR of 1.280 (95% CI: 1.115, 1.470), meeting the noninferiority success criteria (i.e., lower bound of the 95% CI for GMR ≥ 0.67; point estimate ≥ 0.8). The difference in SRR rates between the infants/toddlers and young adults was 0.7% (95% CI: -1.0%, 2.5%), also meeting the noninferiority success criteria (lower bound of the 95% CI of the seroresponse rate difference > -10%).

Accordingly, the pre-specified success criteria for the primary immunogenicity objective were met for both age groups, allowing efficacy of 25 μg to be inferred in both children 2 years through 5 years and infants and toddlers aged 6 months through 23 months (Table 17.8 and Table 17.9).

Table 17.8 Summary of geometric mean concentration ratio and seroresponse rate–comparison of individuals 6 months through 23 months of age to participants 18 years through 25 years of age–per protocol immunogenicity set

		6 months through 23 months n=230	18 years through 25 years n=291	6 months through 23 months/18 years through 25 years	
Assay	**Time point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralization assay[c]	28 days after Dose 2	1 780.7 (1 606.4, 1 973.8)	1 390.8 (1 269.1, 1 524.2)	1.3 (1.1, 1.5)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		100 (98.4, 100)	99.3 (97.5, 99.9)	0.7 (-1.0, 2.5)	

GMC = Geometric mean concentration
n = number of participants with non-missing data at baseline and at Day 57
* Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
[a] The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
[b] Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%.
[c] Final GMC in AU/mL were determined using SARS-CoV-2 microneutralization assay.
[d] Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralizing antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.
[e] Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Table 17.9 Summary of geometric mean concentration ratio and seroresponse rate–comparison of individuals 2 years through 5 years of age to participants 18 years through 25 years of age – per protocol immunogenicity set

		2 years through 5 years n=264	18 years through 25 years n=291	2 years through 5 years/ 18 years through 25 years	
Assay	**Time point**	**GMC (95% CI)***	**GMC (95% CI)***	**GMC ratio (95% CI)[a]**	**Met noninferiority objective (Y/N)[b]**
SARS-CoV-2 neutralization assay[c]	28 days after Dose 2	1 410.0 (1 273.8, 1 560.8)	1 390.8 (1 262.5, 1 532.1)	1.0 (0.9, 1.2)	Y
		Seroresponse % (95% CI)[d]	**Seroresponse % (95% CI)[d]**	**Difference in seroresponse rate % (95% CI)[e]**	
		98.9 (96.7, 99.8)	99.3 (97.5, 99.9)	-0.4 (-2.7, 1.5)	

GMC = Geometric mean concentration
n = number of participants with non-missing data at baseline and at Day 57
* Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
a The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (participants 6 months through 5 years of age and young adults) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
b Noninferiority is declared if the lower bound of the 2-sided 95% CI for the GMC ratio is greater than 0.67, with a point estimate of >0.8 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%, with a point estimate of >-5%c Final GMC in AU/mL were determined using SARS-CoV-2 microneutralization assay.
d Seroresponse due to vaccination specific to SARS-CoV-2 RVP neutralizing antibody concentration at a subject level is defined in protocol as a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.
e Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits

From the study mRNA-1273-P204, VE in Part 2 for the Per Protocol Set for Efficacy for COVID-19 cases 14 days or more after dose 2 using the "COVID-19 P301 case definition" (i.e., the definition employed in the pivotal adult efficacy study) was 36.8% (95% CI: 12.5, 54.0) for children 2 through 5 years of age and 50.6% (95% CI: 21.4, 68.6) for children 6 months through 23 months of age.

Important endpoints that support the benefit

Primary Efficacy Endpoints: efficacy of the mRNA-1273 vaccine in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second injection in the per protocol population, among participants who were seronegative at baseline.

Secondary Efficacy Endpoints: efficacy of mRNA-1273 in the prevention of severe COVID-19 as defined by one of the following criteria: respiratory rate of 30 or more breaths per minute; heart

rate at or exceeding 125 beats per minute; oxygen saturation at 93% or less while the participant was breathing ambient air at sea level or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg; respiratory failure; ARDS; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or a need for vasopressors); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; or death.

Primary Immunogenicity endpoints:

From mRNA-1273-201:

1. Immunogenicity of elasomeran by measure of specific binding antibody levels
2. Immunogenicity of elasomeran by measure of specific neutralizing antibody levels

From Study mRNA-1273-P101/20-0003:

- Immunogenicity of elasomeran measured by IgG ELISA to SARS-CoV-2 spike protein

From Study mRNA-1273-P204:

- Immunogenicity of elasomeran 3 by measure of specific neutralizing antibody levels and the seroconversion rate

Evidence of Efficacy and Effectiveness in authorized indications:

The primary analysis of efficacy (data cut 25 Nov 2020) included a total of 196 adjudicated COVID-19 cases in the per protocol population, which exceeded the target total number of cases (151) specified in the protocol. This was an increase from the 95 cases observed at the first interim analysis data cut-off on 11 Nov 2020. After Day 1 and through 25 Nov 2020, a total of 269 COVID-19 cases were identified, with an incidence of 79.7 cases per 1,000 person-years (95% CI, 70.5 to 89.9) among participants in the placebo group with no evidence of previous SARS-CoV-2 infection. For the primary analysis, 196 cases of COVID-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1,000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1,000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the elasomeran vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo.

17.2. Newly Identified Information on Efficacy and Effectiveness

Three-month antibody persistence of elasomeran/imelasomeran booster vaccine against COVID-19.

Participants in Study P205 Part G were sequentially enrolled to receive 50 ug of elasomeran (n = 376) or elasomeran/imelasomeran (n = 437) as second BD. In participants with no pre-booster incidence of SARS-CoV-2, elasomeran/imelasomeran elicited Omicron BA.1-neutralizing antibody titres (observed GMT) that were significantly higher (964.4 [834.4, 1114.7]) than those of elasomeran (624.2 [533.1, 730.9]) and similar between boosters against ancestral SARS-CoV-2 at three months.

Immunogenicity in participants 18 years of age and older–after elasomeran/davesomeran BD (0.5 mL, 25 ug/25 ug)

The safety, reactogenicity, and immunogenicity of an elasomeran/davesomeran BD are evaluated in an ongoing Phase 2/3 open-label study in participants 18 years of age and older (mRNA-1273-P205). In this study, 511 participants received the elasomeran/davesomeran 50 ug BD, and 376 participants received the elasomeran 50 ug BD.

Study P205 Part H evaluated the safety, reactogenicity and immunogenicity of elasomeran/davesomeran when administered as a second BD to adults who previously received 2 doses of elasomeran (100 ug) as a primary series and a first BD of elasomeran (50 ug). In P205 Part F, study participants received elasomeran (50 ug) as a second BD and the Part F group serves as a within-study, non-contemporaneous comparator group to the elasomeran/davesomeran group.

In this study, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). In the primary analysis, the original SARS-CoV-2 estimated neutralizing antibody GMT and corresponding 95% CI was 87.9 (72.2, 107.1) and 2324.6 (1921.2, 2812.7) 28 days after the elasomeran/davesomeran and elasomeran BDs, respectively. The Day 29 GMR for elasomeran Original/Omicron BA.4-5 ug BD versus the elasomeran 50 ug booster dose was 6.29 (5.27, 7.51), meeting the pre-specified criterion for superiority (lower bound of CI >1).

The estimated neutralizing antibody GMTs (95% CI) against Omicron BA.4/BA.5 adjusted for pre-booster titre and age group were 2747.3 (2399.2, 3145.9) and 436.7 (389.1, 490.0) 28 days after elasomeran/davesomeran and elasomeran booster doses, respectively, and the GMR (95% CI) was 6.29 (5.27, 7.51), meeting the pre-specified criterion for non-inferiority (lower bound of CI >0.667).

Primary Series Effectiveness (Study mRNA-1273-P901)

Study P901 is an ongoing observational cohort study conducted within Kaiser Permanente Southern California (a large, integrated health care system serving a diverse population of over 4.5 million members) in the US to estimate the real-world VE of mRNA-1273 in preventing SARS-CoV-2 infection (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality). This study was initiated on 28 Jan 2021 and has resulted in several analyses assessing the real-world effectiveness of mRNA-1273 over time during the SARS-CoV-2 pandemic [123] [124] [11] [125].

A test-negative case-control analysis to evaluate mRNA-1273 VE against SARS-CoV-2 variants and assess its effectiveness against the delta variant by time since vaccination was conducted within Study P901 [123]. Individuals with a SARS-CoV-2 positive test sent for whole genome sequencing or a negative test from 1 Mar 2021 to 27 Jul 2021 were included. Test-positive cases were matched 1:5 to test-negative controls. The analysis included 8,153 test-positive cases and their matched controls. The two-dose VE was 86.7% (95% CI: 84.3%, 88.7%) against infection with the delta variant, 98.4% (95% CI: 96.9%, 99.1%) against alpha, 90.4% (95% CI: 73.9%, 96.5%) against mu, 96%-98% against other identified variants, and 79.9% (95% CI: 76.9%, 82.5%) against unidentified variants (that is, specimens that failed sequencing). The VE against hospital admission with the delta variant was 97.5% (95% CI: 92.7%, 99.2%). The VE against infection with the delta variant declined from 94.1% (95% CI: 90.5%, 96.3%) 14-60 days after vaccination to 80.0% (95% CI: 70.2%, 86.6%) 151-180 days after vaccination. Waning was less pronounced for non-delta variants. The VE against delta infection was lower among people aged ≥ 65 years (75.2% [95% CI: 59.6%, 84.8%]) than those aged 18-64 years (87.9% [95% CI: 85.5%, 89.9%]).

Another test-negative case–control analysis to evaluate mRNA-1273 VE against infection and hospitalization with Omicron or Delta was conducted within Study P901 [125]. Individuals with a SARS-CoV-2 positive test sent for whole genome sequencing or a negative test from 06 Dec 2021 to 31 Dec 2021 were included. Test-positive cases were matched 1:2 to test-negative controls. The analysis included 26,683 test-positive cases with variants determined by S gene target failure status (16% Delta and 84% Omicron). The two-dose VE against Omicron infection at 14–90 days was 44.0% (95% CI: 35.1%, 51.6%) but declined quickly.

An analysis conducted within Study P901 estimated the VE of receipt of 2 doses (primary series) of 100 µg mRNA-1273 versus unvaccinated individuals [124]. Individuals receiving 2 doses of mRNA-1273 ≥ 24 days apart (18 Dec 2020 to 31 Mar 2021) were 1:1 matched with randomly

selected unvaccinated individuals, with follow-up through 30 Jun 2021. This analysis included 352,878 recipients of 2 doses of mRNA-1273 matched to 352,878 unvaccinated individuals. The VE against COVID-19 diagnosis was 87.4% (99.3% CI: 84.8%, 89.6%). The VE against COVID-19 hospitalization and hospital death was 95.8% (99.3% CI: 90.7%, 98.1%) and 97.9% (99.3% CI: 66.9%, 99.9%), respectively. The VE was higher against symptomatic (88.3% [98.3% CI: 86.1%, 90.2%]) than asymptomatic COVID-19 (72.7% [98.3% CI: 53.4%, 84.0%]), but was generally similar across age, sex, and racial/ethnic subgroups. The VE among individuals with history of COVID-19 ranged from 8.2% to 33.6%. The most prevalent variants were Delta (47.1%), Alpha (21.4%), Gamma (11.4%), Epsilon (4.3%), and Iota (4.3%) among vaccinated individuals and Alpha (41.2%), Epsilon (18.2%), Delta (11.0%) and Gamma (8.6%) among unvaccinated individuals.

Booster Effectiveness (Study P901)

Tseng et al observed that the three-dose VE was 93.7% (95% CI: 92.2%, 94.9%) and 86.0% (95% CI: 78.1%, 91.1%) against Delta infection and 71.6% (95% CI: 69.7%, 73.4%) and 47.4% (95% CI: 40.5%, 53.5%) against Omicron infection at 14–60 days and >60 days, respectively [125]. The three-dose VE was 29.4% (95% CI: 0.3%, 50.0%) against Omicron infection in immunocompromised individuals. The three-dose VE against hospitalization with Delta or Omicron was >99% across the entire study population. Receipt of three doses of mRNA-1273 demonstrated high, durable VE against Delta infection but lower effectiveness against Omicron infection, particularly among immunocompromised people. However, VE of three doses of mRNA-1273 remained high against hospitalization with Delta and Omicron variants.

An analysis conducted within Study P901 estimated the rVE of receipt of 3 doses (2-dose primary series [100 µg mRNA-1273] plus booster [50 µg mRNA-1273]) versus 2 doses (primary series only) of mRNA-1273 among immunocompetent individuals [11]. Immunocompetent individuals who received a BD of mRNA-1273 from 20 Oct 2021 through 31 Dec 2021 were matched 1:1 to randomly selected 2-dose mRNA-1273 recipients and followed up through 31 Jan 2022. This analysis included 431,328 mRNA-1273 booster dose vaccinated individuals matched to 431,328 2-dose mRNA-1273 vaccinated individuals. In this analysis, IR of symptomatic SARS-CoV-2 infection, COVID-19 hospitalization and COVID-19 related hospital death rates were lower in individuals who had received a BD of mRNA-1273 as compared with individuals who had received only the primary series. The rVE of a 50 µg mRNA-1273 BD was 61.3% (95% CI: 60.5%, 62.2%) for SARS-CoV-2 infection, 89.0% (95% CI: 86.2%, 91.2%) for COVID-19 hospitalization, and 96.0% (95% CI: 68.0%, 99.5%) for COVID-19 hospital death. Relative VE

estimates against SARS-CoV-2 infection did not differ substantially by age, sex, race/ethnicity, pregnancy status, chronic disease, and infection history sub-groups (ranging from 55.6% to 66.7%). Relative VE against SARS-CoV-2 infection decreased from 67.1% (0 to <1 month of follow-up) to 30.5% (2 to <3 months). For COVID-19 hospitalization, rVE decreased from 91.2% (0 to <1 month) to 78.7% (2 to <3 months). Results from the analysis for rVE of a BD of mRNA-1273 were consistent with those from Study P301 and demonstrated that SARS-CoV-2 infection rates and COVID-19 rates were lower in boosted versus non-boosted individuals who had received only the 2-dose mRNA-1273 primary series.

17.3. Characterization of Benefits

From the study mRNA-1273-P205, the primary immunogenicity analysis was based on the primary immunogenicity set which includes participants with no evidence of SARS-CoV-2 infection at baseline (pre-booster). The Day 29 GMR for elasomeran/imelasomeran 4-5 ug BD versus the elasomeran 50 ug BD was 6.29 (5.27, 7.51), meeting the pre-specified criterion for superiority (lower bound of CI >1).

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR AUTHORIZED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

As a result of the outbreak of COVID-19 caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) that began in Wuhan, Hubei Province, China in December 2019, and that soon started to spread globally, the WHO declared COVID-19 a pandemic on 11 Mar 2020. Widespread community transmission of SARS-CoV-2 was soon reported in the Americas, Europe, Africa, and Southeast Asia. Soon the world mobilized and sustained a historic response to the COVID-19 pandemic as it became a health and an economic crisis that disrupted every single segment of the population shattering lives, business, and our day-to-day life.

As of 17 Jun 2023, more than 1.3 billion doses of elasomeranare estimated to have been distributed to 91 countries and more than 772 million doses administered. North America, Europe, and Asia accounted for approximately 89% of elasomeran doses distributed and approximately 84% of elasomeran doses administered. More than 127 million BDs of elasomeran/imelasomeran are estimated to have been distributed to 41 countries and more than 70 million doses administered. Europe, the UK, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. More than 110 million BDs of elasomeran/davesomeran are estimated to have been distributed to 25 countries and more than

60 million doses to have been administered. The United States, Canada, Europe, and Asia accounted for >99% of all doses distributed and administered. Low- and middle-income countries [126] are estimated to account for approximately 13% of the doses distributed globally and approximately 13% of doses administered.

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

Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 404,120,202 individuals received a first dose, 311,160,321 received a second dose, 190,540,777 received a third dose, and 78,503,483 received a fourth dose, with third and fourth doses including both original elasomeran and elasomeran/imelasomeran and elasomeran/davesomeran booster dose formulations.

In Nov 2021, the Omicron variant (B.1.1.529; BA.1) emerged as the most antigenically divergent variant to date with > 30 mutations in the spike protein [127]. While less pathogenic as compared to the delta variant, the Omicron variant was significantly more transmissible than previous variants [128] [129], [130]. As a result, soon after its emergence, Omicron rapidly became the dominant circulating variant worldwide [131]. While incident cases, hospitalizations, and deaths increased in the US during the Omicron wave, individuals who received mRNA-based vaccines, such as mRNA-1273, had lower rates of these outcomes based on data reported to the US CDC. The 2-dose mRNA-1273 primary series, along with the use of a BD, has been shown to be effective against COVID-19 and hospitalization due to COVID-19 caused by SARS-CoV-2 variants, including Alpha, Beta, Delta, Gamma, and Omicron. However, the effectiveness of the original vaccine formulations appeared to be reduced with respect to infections with the Omicron variant [123] [125].

Furthermore, after the Omicron (BA.1) variant's discovery, additional subvariants of Omicron had been identified, including BA.1.1, BA.2, BA.2.12.1, BA.2.13, BA.2.75, BA.3, BA.4, BA.4.6, BA.5, and had demonstrated increased transmissibility and immune escape versus the original strain, resulting in additional waves of COVID-19 infection dominated by these subvariants. The morbidity and mortality associated with COVID-19 caused by antigenically divergent variants such as Omicron and the decreased effectiveness of mRNA-1273 against Omicron infection

created the need to develop a booster with enhanced immunogenicity in order to confer improved protection against COVID-19 and help decrease the burden on hospitals and healthcare systems [132] [133].

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 public health emergency of international concern (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 Public Health Emergency (PHE) for COVID-19, declared under Section 319 of the Public Health Service (PHS) Act, to expire at the end of the day on 11 May 2023."

Throughout the first half of 2023, global public health agencies and vaccine regulators met to align the criteria used and the vaccine strain composition recommendations and have generally aligned around a common recommendation for the 2023-2024 COVID-19 vaccine formulation. Members of the ICMRA including WHO met on 08 May 2023 and the WHO TAG-CO-VAC met on 11-12 May 2023 and issued a statement on 18 May 2023 (WHO 2023b). In both meetings the conclusion was that there is a need to update the COVID-19 vaccine composition. Both groups concluded that the SARS-CoV-2 virus had evolved, diverging from the ancestral strain as well as the variant included in the currently authorized bivalent vaccines. As of the time of their meeting in May 2023, since XBB.1 descendent sublineages predominated SARS-CoV-2 circulation globally, the conclusion of these bodies was that monovalent XBB-containing vaccines, such as XBB.1.5, could be considered a reasonable choice for the 2023-2024 formulation to enhance vaccine-induced immune responses to circulating SARS-CoV-2 variants. This recommendation was based on current epidemiology and the high level of immunity already present against the ancestral virus and previously circulating SARS-CoV-2 subvariants.

On 06 Jun 2023, the ECDC and the EMA issued a statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants. Similar to the WHO TAG-CO-VAC statement, ECDC/EMA recommended a monovalent vaccine composition as suitable to ensure adequate immunogenicity against circulating SARS-CoV-2 variants in both primed and naïve individuals, and XBB.1.5 was considered a reasonable choice to increase the breadth of immunity also against XBB descendent lineages [119].

On 15 Jun 2023, the FDA VRBPAC voted unanimously in favor of recommending an update of the COVID-19 vaccines to a monovalent XBB-lineage for the 2023–2024 formulation. Based on the totality of evidence, FDA has advised manufacturers who will be updating their COVID-19 vaccines, that they should develop vaccines with a monovalent XBB.1.5 composition [134].

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. The clinical course of vaccine-associated cases of myocarditis and pericarditis appears generally favourable; those individuals who are hospitalized have lengths of stay of around 2 to 4 days on average. Analysis of post-authorization safety data has shown that this identified risk of myocarditis and pericarditis is generally within 7 days following vaccination against COVID-19 in people aged 12 to 40 years, particularly young people under 30 years old. 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.

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. Overall, evaluation of data received during this reporting period of those patients receiving a 3rd dose or a BD (Original) shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series, as it had been described in the literature.

There is also evidence of chronic sequelae known as "long COVID-19" in children and adults even after mild infection; this includes fatigue, muscle and joint pain, insomnia, concentration difficulties, respiratory problems, persistent anosmia and ageusia, and cardiac palpitations that may persist 6 months or more after infection [135].

As the pandemic continues, it is evident that the vaccination coverage in pediatric and adolescent populations has not reached the level in adults, leaving a group of individuals vulnerable to both COVID-19 as well as severe COVID-19 and sequelae.

18.2. Benefit-Risk Analysis Evaluation

There is an established safety profile of 3 or more doses of elasomeran, from data in clinical studies and post licensure data with more than 1.3 billion doses of elasomeran distributed, and more than 774 million doses estimated to have been administered globally as of 17 Jun 2023. Further, bivalent booster (elasomeran/imelasomeran and elasomeran/davesomeran) safety has been demonstrated in adults including young adults (18 to < 25 years) in clinical studies and post-authorization settings, where approximately more than 13 million doses have been administered.

The efficacy of mRNA-1273 to prevent COVID-19 was confirmed after administration of a primary series to adults 18 years and older in the pivotal Phase 3 study, Study P301 Part A. Data from Part A, the randomized placebo-controlled phase of the study, supported the US EUA (authorization on 18 Dec 2020) and BLA (approval on 31 Jan 2022). Results from P301A demonstrated VE of 93.2% (95% CI: 91.0, 94.8; $p < 0.0001$) for a total of 799 adjudicated COVID-19 cases, confirming persistent, high efficacy with a large case database over a median 5.3-month blinded observation period [136]. P301A results also demonstrated that mRNA-1273 was immunogenic, as indicated by increased nAb and bAb levels 1 month after first dose (Day 29) and 1 month after second dose (Day 57). Effectiveness in adolescents and children 6 months and older was inferred by immunobridging, and favorable point estimates also were observed.

While the efficacy of the primary series was previously demonstrated, the emergence of highly transmissible and antigenically divergent SARS-CoV-2 variants such as Delta and Omicron contributed to breakthrough infection among vaccinated individuals [125], thereby prompting the authorization of first and second BDs of 50 µg mRNA-1273 to confer enhanced protection. Immunogenicity and real-world effectiveness studies have demonstrated the ability of boosters to protect against novel variants; however, the ongoing genetic evolution of the SARS-CoV-2 virus necessitated the development of booster vaccine formulations to target immunity to new variants and further enhance clinical effectiveness against circulating variants.

Studies conducted for a 50 µg mRNA-1273 booster (including the original mRNA-1273 booster and the variant-containing bivalent vaccines mRNA-1273.222 and mRNA-1273.214) elicits enhanced immune responses against SARS-CoV-2 compared to those elicited by the primary series, and consistent responses were observed across adolescents, younger adults, and older adults. Additionally variant-containing bivalent boosters elicit superior immune responses to the variant in the vaccine compared with the original mRNA-1273 booster, and enhanced responses are observed in both younger and older adults, and regardless of prior SARS-CoV-2 status, and

variant-containing bivalent boosters induce immune responses that are durable, and cross neutralize divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted individuals, and rates of COVID-19, hospitalized COVID-19 and hospitalized COVID-19 death are lower in boosted versus non-boosted individuals [124] [125].

Vaccine effectiveness data show that despite the epitope divergence from the original strain, elasomeran continues to protect adults against severe outcomes associated with Omicron, including hospitalization and death (VE ~ 80%) [125]. Although severe COVID-19-related outcomes are rare in children, one case of MIS-C and one case of long COVID were observed in placebo recipients in the 2 to 5 and 6-to-11-year age groups, respectively. Data from the Omicron wave continue to show that the vast majority of hospitalizations are occurring in unvaccinated individuals [137] [138] [139] [140].

The tolerability and safety of elasomeran in the pediatric age groups was evaluated across each age group in a total of > 10,800 adolescents, children, toddlers, and infants who received at least 1 dose of elasomeran. Elasomeran in these age groups was generally safe, well tolerated, and no new safety signals were identified. The overall safety profile of two doses of elasomeran observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as PMS. The profile of elasomeran in children is also consistent with other routinely administered pediatric vaccines for the respective age groups. Across all pediatric age groups, the AE profile of elasomeran in the pediatric populations is characterized primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration. Across all 4 age groups fever ≥ 40°C was the only Grade 4 solicited systemic AR reported in more than 1 participant. Febrile seizure was reported in 1 participant proximal to vaccination, but the event, along with a number of the Grade 4 fevers were associated with evidence of co-existing viral infections.

Evaluation of the post-marketing safety information included in the GSDB for children <18 years of age showed that the safety profile for the elasomeran vaccines is comparable to that observed during the clinical studies for the vaccines, and that the safety data evaluated as of 17 Jun 2023 does not indicate any changes in the benefit-risk profile of elasomeran. Overall, most cases were non-serious. When serious, these cases often had serious events reported once that did not demonstrate any unusual patterns or groupings by medical concept. The most frequently reported MedDRA PTs in children < 18 years of age were Product administered to patient of inappropriate age followed by Pyrexia and Headache. The observed safety profile of the use of elasomeran

vaccines in the subpopulation of infants 0-5 months of age and children 6 months to 17 years of age continues to support a positive benefit-risk assessment.

A review of the post-authorization data received during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. A large proportion of the myocarditis and pericarditis events received were reported as either resolved or resolving. Data also indicates that the short term (<3 months) course and outcome of myocarditis and pericarditis following vaccination is milder and less severe than myocarditis or pericarditis in general.

Evaluation of the cumulative information for reports of myocarditis and/or pericarditis following exposure to elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy does not indicate a safety issue and cases of myocarditis and pericarditis in this subpopulation are consistent with the known safety profile of elasomeran. Similar to myocarditis and pericarditis events, overall, most of the myocarditis and pericarditis events reported in pregnancy were resolved or resolving at the time the report was received.

Based on the data presented in this PBRER, elasomeran administered as two 100 µg doses (for individuals >12 years of age), two 50 µg doses (for individuals 6 to 11 years of age), or two 25 µg doses (for individuals 6 months to 5 years of age) given 28 days apart or as a third 100 µg/ 50 µg/25 µg dose for immunocompromised individuals, respectively, including a 50 µg BD at least 6 months after primary vaccination against SARS-CoV-2 for individuals >12 years of age, is a highly effective vaccine and capable of restoring nAbs to levels observed following receipt of the primary series. This is true as well against emerging VOCs, with the use of the bivalent vaccines elasomeran/ imelasomeran or elasomeran/davesomeran, providing an attribute that can be used to help contain the pandemic, along with an acceptable safety profile for the prevention of COVID-19.

Post-authorization safety data collected in the GSDB show that elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran are well tolerated, and the safety profiles are similar to that observed during the MAH's clinical studies.

Considering the available safety and efficacy data from the 12 clinical studies presented herein, and the ongoing post-authorization surveillance, the MAH considers that the known and potential benefits outweigh the known and potential risks for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran.

Risks associated with elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran are

considered adequately managed with the product labels. An RMP is in place with ongoing studies including the continuation of the ongoing pivotal trial, Study mRNA-1273-P301, and other observational studies to further characterize important risks. Routine pharmacovigilance will monitor for potential new ARs.

Because the purpose of vaccination is different from that of treatment of infection, the focus of this section is on vaccines only. In addition to many vaccines that remain under development, several vaccines against COVID-19 are currently available for use under various regulatory provisions in countries around the world, as follows:

- mRNA-based vaccines: Pfizer-BioNTech Comirnaty (BNT162b2); Comirnaty Original/ Omicron BA.1® from Pfizer, Comirnaty Original/Omicron BA.4-5® from Pfizer; Moderna COVID-19 Vaccine SPIKEVAX (elasomeran; the subject of this application) SPIKEVAX bivalent Original/Omicron BA.1®, and SPIKEVAX bivalent Original/ Omicron BA.4-5® both from ModernaTx, Inc.
- Viral vector, nonreplicating: Adenovirus vaccine: AstraZeneca (Vaxzevria/Covishield); Janssen Vaccines (Johnson & Johnson) (JNJ-78436735; Ad26.COV2.S).
- Recombinant adenovirus vaccines: VidPrevtyn Beta from Sanofi Pasteur, Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik V (rAd26 and rAd5); Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik Light (rAd26); CanSino Biologics Convidicea (PakVac, Ad5-nCov).
- Inactivated vaccines: Sinovac (CoronaVac); Beijing Institute of Biological Products (BBIBP-CorV); Bharat Biotech Indian Council of Medical Research (ICMR), Ocugen, ViroVax (Covaxin); Wuhan Institute of Biological Products, China National Pharmaceutical Group (WIBP-CorV); Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products (CoviVac); Research Institute for Biological Safety Problems (QazVac); Minhai Biotechnology Co, Kangtai Biological Products Co. Ltd. (Unnamed vaccine candidate); Shifa Pharmed Industrial Group (CovIran Barekat); Chinese Academy of Medical Sciences, Institute of Medical Biology (Unnamed vaccine candidate).
- Peptide vaccine: Federal Budgetary Research Institution State Research Center of Virology and Biotechnology (EpiVacCorona).
- Recombinant vaccine: Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences (ZF2001).

- Protein subunit vaccine: Center for Genetic and Engineering Biotechnology (Abdala); Medigen Vaccine Biologics, Dynavax (MVC-COV1901).
- Conjugate vaccine: Finlay Institute of Vaccines, Pasteur Institute (Soberana 02).

Table 18 1. Benefit-Risk Evaluation Table

Decision Factors	Evidence/ Uncertainties	Conclusions
Analysis of Condition/ Disease	An outbreak of COVID-19 caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in Dec 2019, and the disease quickly spread globally. The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 Jan 2020 and declared COVID-19 a pandemic on 11 Mar 2020. Of major public health concern is whether immunity to early pandemic strains, developed via vaccination (or natural infection), confers protection against newly circulating variants. Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults but develop symptomatic COVID-19 primary infection at significantly lesser rates and rarely develop severe disease. It also became clear that a fraction of children develops a life-threatening hyperinflammatory state 4–6 weeks after infection with primary COVID-19 termed Multisystem Inflammatory Syndrome in Children (MIS-C). In Nov of 2021, the Omicron variant (B.1.1.529; BA.1) emerged as the most antigenically divergent variant to date with >30 mutations in the spike protein [127]. Omicron shares antibody escape site mutations with the Beta variant and it also exhibits transmissibility advantages [141] [142] [143]. Globally, nearly 1.5 million new cases and 7300 deaths were reported in the last 28 days (15 between 15 May 2023 to 11 Jun 2023). The Omicron variant has become the epidemiologically dominant variant in multiple countries since 2022 and Omicron subvariants with additional spike protein mutations (BA.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, BN.1 and XBB.1) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). The European Center for Disease Prevention and Control lists BA.2.75 and its sub-lineages, BQ.1, XBB and its sub-lineages (excluding XBB1.5 and its sub-	COVID-19 disease is a pandemic and a public health emergency. Evidence suggests that immunity against COVID-19 is waning worldwide and may contribute to reinfection or breakthrough infections from the original virus strain or escape variants. Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults but develop symptomatic COVID-19 primary infection at significantly lesser rates. Complications are rare but may be severe (e.g., MIS-C). The Omicron variant has become the epidemiologically dominant variant in multiple countries in 2022. Omicron subvariants with additional spike protein mutations (BA.2, BA.2.12.1, BA.4, BA.5, BQ.1.1, BN.1 and XBB.1) have been associated with ongoing waves of infection, following the initial wave of Omicron (BA.1). Evaluation of COVID-19 incidence over time indicates marked increases in children ages 0 to 4 years old during the Delta and Omicron variant waves. After the onset of the Omicron wave, the demographics of hospitalized patients with COVID-19 shifted to younger age groups. • On 04 May 2023, the WHO Director-General in agreement with the recommendation provided by the International Health Regulations (2005) (IHR) Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, announced that "…COVID-19 is now

Decision Factors	Evidence/ Uncertainties	Conclusions
	lineages), XBB.1.5 as VOI as of 26 Jan 2023 [119]. Among the nine countries (Austria, Denmark, France, Germany, Italy, Latvia, Luxembourg, the Netherlands, and Sweden) with an adequate volume of sequencing or genotyping for weeks 1 to 2 (2 to 15 Jan 2023), the estimated distribution of VOC or VOI ranged from 48.4-76.0% in seven countries for BQ.1, 11.3-76.9% in nine countries for BA.5, 6.6-27.8% in eight countries for BA.2.75, 1.4-5.6% in six countries for XBB.1.5, 0.9-6.5% in seven countries for XBB, 0.3-15.3% in eight countries for BA.2, and 0.1-0.9% in eight countries for BA.4 [119]. On 04 May 2023, the WHO Director-General in agreement with the recommendation provided by the International Health Regulations (2005) (IHR) Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, announced that "…COVID-19 is now an established and ongoing health issue which no longer constitutes a PHEIC." Additionally, on 09 May 2023, the Department of HHS in the US, stated that "Based on current COVID-19 trends, the Department of HHS is planning for the federal PHE for COVID-19, declared under Section 319 of the PHS Act, to expire at the end of the day on 11 May 2023.	an established and ongoing health issue which no longer constitutes a PHEIC."
Medical Need for Treatment of Condition/ Disease	As of 11 Jun 2023, over 767 million confirmed cases and 6.9 million deaths have been attributed to the COVID-19 pandemic globally. Globally, nearly 1.5 million new cases and 7300 deaths were reported in the last 28 days (15 between 15 May 2023 to 11 Jun 2023 [105]. Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [144,145]. Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults [146] [147] [148]. However, COVID-19 can also lead to severe outcomes in children and adolescents [149] [150]. As of 17 Jun 2023, confirmed COVID-19 mortality has surpassed 1.1 million deaths in the US. Comparison of apparent case fatality rates from early in the pandemic	Since Dec 2020, elasomeran and other COVID-19 vaccines have been available under EUA, conditional approvals, and full approval worldwide. As of 17 Jun 2023, more than 1.3 billion doses of elasomeran, 128 million doses of elasomeran/imelasomeran, and 217 million dose of elasomeran/ davesomeran have been distributed; more than 774 million doses of elasomeran, more than 70 million doses of elasomeran/ imelasomeran, and more than 119 million doses of elasomeran/ davesomeran are estimated to have been administered. Elasomeran is approved and/or authorized in numerous countries throughout the world for adults (≥18

Decision Factors	Evidence/ Uncertainties	Conclusions
	(acknowledging the limitations of such data) showed that the risk of death from COVID-19 was higher among the elderly and among individuals with certain pre-existing health conditions. Among all fatal cases, 75% had one of the listed pre-existing conditions. The most common was cardiac disorder, diabetes, and cancer malignancy. Two-thirds (67.8%) of all severe hospitalizations were in patients with one of the listed pre-existing conditions. Elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. The bivalent elasomeran/davesomeran (Original/ Omicron BA.4/BA.5) produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine.	years age), adolescents (12 to < 18 years of age), and children (6 months to < 12 years of age) as a two dose primary series. Additionally, approvals and/or authorizations for additional doses in special populations (e.g., immunocompromised) and/or as a BD, including authorization for two bivalent vaccines (elasomeran/imelasomeran, and elasomeran/davesomeran) 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 04May2021 dataset showed that elasomeran 100 µg was 98.2% effective in preventing severe COVID-19. Subgroup analyzes of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection. Elasomeran was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of elasomeran (VE of 92.8% based on HR). Multiple studies from the US and other countries have demonstrated high	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 203 and 204 the co-primary immunogenicity objectives were met in all age groups, demonstrating noninferiority to young adults (18 to 25 years of age)

Decision Factors	Evidence/ Uncertainties	Conclusions
	effectiveness of a 2 dose COVID-19 mRNA vaccination series against SARS-CoV-2 infection (including both symptomatic and asymptomatic infections) caused by the original and variant strains and sequelae including severe disease, hospitalization, and death. Real-world effectiveness studies report COVID-19 mRNA vaccine effectiveness ranging from 86-89% for SARS-CoV-2 infection, 65-92% for asymptomatic infections, 85 to 97% for symptomatic disease, 87 to 98% for hospitalization or severe disease, and 97% effectiveness against death depending on the population studied and geographic region. Data from both P201 Part A and P301 Part A studies support persistence of immunogenicity and effectiveness through at least 6 months. Results from the P301 final blinded analysis were consistent with results of the interim and primary analyzes, confirming persistence of high rates of efficacy over a median of 5.3-month blinded observation period. Administration of a BD of elasomeran of 50 µg at least 6 months after administration of the second of 2 doses of the primary series greatly enhanced immune responses compared to pre-boost levels showing within 2 weeks nAb responses against these variants a 32- to 44-fold rise compared to the pre-booster titers. Across the full pediatric program, the effectiveness of elasomeran was demonstrated from 6 months to 17 years. In Studies 203 and 204 the pre-specified co-primary immunogenicity objectives were met in all age groups, demonstrating noninferiority to young adults (18 to 25 years of age) in the pivotal efficacy trial, Study 301. The GMT ratio of nAb titers as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a two dose primary series (two doses of 100 µg in adolescents, two doses of 50 µg elasomeran in older children and two doses of 25 µg of elasomeran in younger children and infants/toddlers). mRNA 1273.214 50 µg elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2 (D614G) 28 days after BD administration as compared	in the pivotal efficacy trial, Study 301. The GMT ratio of nAb titers as compared to young adults ranged from 1.01 through 1.28, showing a consistent immune response after a two dose primary series (two doses of 100 µg in adolescents, two doses of 50 µg elasomeran in older children and two doses of 25 µg of elasomeran in younger children and infants/toddlers). Vaccine effectiveness data show that despite the epitope divergence from the original strain, elasomeran continues to protect adults against severe outcomes associated with Omicron, including hospitalization and death (VE ~ 80%) [125]. Elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. Supportive data from the first bivalent vaccine (mRNA-1273.211) demonstrate a durable neutralizing antibody response to multiple variants, suggesting improved antibody persistence with bivalent vaccines. The bivalent elasomeran/davesomeran 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

Decision Factors	Evidence/ Uncertainties	Conclusions
	to a 50-µg BD of elasomeran [122] elasomeran/imelasomeran elicited a superior neutralizing antibody response against Omicron and a non-inferior antibody response against the ancestral SARS-CoV-2, 28 days after immunization, regardless of pre-booster SARS-CoV-2 infection, as well as a potent neutralizing antibody response against the Omicron BA.4 and BA.5 subvariants. The bivalent elasomeran/davesomeran produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine. Studies conducted for a 50 µg mRNA-1273 booster (including the original mRNA-1273 booster and the variant-containing bivalent vaccines mRNA-1273.222 and mRNA-1273.214) elicits enhanced immune responses against SARS-CoV-2 compared to those elicited by the primary series, and consistent responses were observed across adolescents, younger adults, and older adults. Additionally variant-containing bivalent boosters elicit superior immune responses to the variant in the vaccine compared with the original mRNA-1273 booster, and enhanced responses are observed in both younger and older adults, and regardless of prior SARS-CoV-2 status, and variant-containing bivalent boosters induce immune responses that are durable, and cross neutralize divergent SARS-CoV-2 strains. COVID-19 IR are lower in boosted versus non-boosted individuals, and rates of COVID-19, hospitalized COVID-19 and hospitalized COVID-19 death are lower in boosted versus non-boosted individuals.	monovalent vaccine. • Variant-containing bivalent boosters elicit superior immune responses to the variant in the vaccine compared with the original elasomeran booster. • Enhanced responses are observed in both younger and older adults, and regardless of prior SARS-CoV-2 status. • Variant-containing bivalent boosters induce immune responses that are durable, and cross neutralize divergent SARS-CoV-2 strains.
Key Risks	The safety of elasomeran in controlled clinical studies is based largely on data from Study mRNA-1273-P301, which was a 2-part Phase 3 study: Part A, the blinded Phase was a randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and	In the ongoing CTs for elasomeran the most common solicited local AR was pain, and the most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. The majority of the solicited local and systemic ARs

Decision Factors	Evidence/ Uncertainties	Conclusions
	immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS-CoV-2 infection. Part B, the open-label observational Phase was designed to offer participants who received placebo in Part A of this study and who met EUA eligibility an option to request 2 doses of mRNA-1273 vaccine and remain on study. Cumulatively, 53,983 subjects are estimated to be have been exposed to either mRNA-1273, or its variants (mRNA 1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.214, mRNA 1273.222, mRNA 1273.617.2, mRNA-1273.529, mRNA-1273.231 and mRNA 1273.815), and participants exposed to mRNA-1273 in conjunction to mRNA-1283 (including its variants mRNA-1283.211) or mRNA-1010 or mRNA-1345, or co-administration with mRNA-1010 or co-administration with mRNA 1345 in the mRNA clinical development program sponsored by ModernaTx, Inc. The total count of 53,983 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). Till DLP, 16,507 subjects were exposed to mRNA 1273 in CTs sponsored by licensing partners. Out of 16,507 subjects, 1,280 subjects were exposed to mRNA 1273 in CTs sponsored by DMID, 1,534 subjects from a CT sponsored by GSK, 17 subjects from a CT sponsored by NCI, 19 subjects from a CT sponsored by UCLA, 12,340 subjects from a CT sponsored by SAMRC, 1,012 subjects from CTs sponsored by MSD, and 305 subjects from a CT sponsored by University of Southampton. Cumulatively, 3,290 subjects were enrolled in investigator-initiated trials. The type, incidence, and severity of ARs and TEAEs reported with elasomeran in CTs were consistent with the CT data previously submitted in support of authorization. No unexpected safety findings were identified. Solicited local and systemic ARs were more common in participants who received mRNA 1273 compared with those who received placebo after both the first and second doses.	occurred within the first 2 days after administration of mRNA 1273 and generally persisted for 1 to 3 days. Overall, in the Phase 1/2/3 ongoing CTs no new clinically significant abnormalities or new safety risks were identified beyond those already included in the CCDS/ IB. Tolerability and safety of elasomeran evaluated across each age group in a total of > 10,800 adolescents, children, toddlers, and infants who received at least 1 dose of mRNA-1273 was generally safe, well tolerated, and no new safety signals were identified. The overall safety profile of two doses of elasomeran observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as PMS. The profile of elasomeran in children is also consistent with other routinely administered pediatric vaccines for the respective age groups. Across all pediatric age groups, the AE profile of elasomeran in the pediatric populations is characterized primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration. Across all 4 age groups fever ≥ 40°C was the only Grade 4 solicited systemic AR reported in more than 1 participant. Febrile seizure was reported in 1 participant proximal to vaccination, but the event, along with a number of the Grade 4 fevers were associated with evidence of co-existing viral infections. Anaphylaxis has been reported in individuals who have received the Modema 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.

Decision Factors	Evidence/ Uncertainties	Conclusions
	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 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	Since Jul 2021, myocarditis and pericarditis have been considered as an important identified risks that may occur following vaccination against COVID-19 with a messenger RNA vaccine, especially in young men. Available data suggest that the course of myocarditis and pericarditis following vaccination is typically milder than viral myocarditis or pericarditis and is self-limited. The clinical course of cases of myocarditis and pericarditis appears generally favorable; those individuals who are hospitalized have lengths of stay of around 2 to 4 days on average. A review of the post-authorization data received during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. Evaluation of data received during this reporting period of those patients receiving a 3rd dose or a BD, shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series. To date, based on the data from ongoing trials, and post-authorization safety information, the general safety profile of elasomeran continues to appear well tolerated and with an acceptable safety profile.

Decision Factors	Evidence/ Uncertainties	Conclusions
	safety signals were identified. The overall safety profile of two doses of mRNA-1273 observed in Studies 203 and 204 was consistent with the known safety profile to date observed in the pivotal Study 301 as well as PMS. The profile of mRNA-1273 in children is also consistent with other routinely administered pediatric vaccines for the respective age groups. Across all pediatric age groups, the AE profile of mRNA-1273 in the pediatric populations is characterized primarily by transient local injection site and systemic reactions, Grade 1 to Grade 2 in severity, and of 2 to 3 days in duration. Across all 4 age groups fever ≥ 40°C was the only Grade 4 solicited systemic AR reported in more than 1 participant. Febrile seizure was reported in 1 participant proximal to vaccination, but the event, along with a number of the Grade 4 fevers were associated with evidence of co-existing viral infections. No confirmed cases of myocarditis or pericarditis were reported in Studies 203 and 204. Cases involving myocarditis/pericarditis received during this reporting period were consistent with the known safety profile of elasomeran. A review of the data received cumulatively and during this reporting period showed a continuous decreasing trend in the number of reported cases, with events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second of the vaccine, with a TTO less than 7 days. The same pattern was observed for cases reported after receiving a 3rd or more doses of elasomeran (Original). Overall, evaluation of data received during this reporting period of those patients receiving a 3rd dose or a BD shows an increased risk of myocarditis in adults that appears attenuated compared to the risk following the second dose of the primary series, as it had been described in the literature. Evaluation of the cumulative information for reports of myocarditis and/or pericarditis following exposure to elasomeran or elasomeran/imelasomeran and elasomeran/davesomeran during pregnancy does not indicate a safety issue and cases of	

Decision Factors	Evidence/ Uncertainties	Conclusions
	myocarditis and pericarditis in this subpopulation are consistent with the known safety profile of elasomeran. Similar to myocarditis and pericarditis events, overall, most of them yocarditis and pericarditis events reported in pregnancy were resolved or resolving at the time the report was received. Passive and observational surveillance information shows that the clinical profile of patients experiencing myocarditis/ pericarditis following exposure to a COVID-19 mRNA vaccine result in events with a relatively short period of hospitalization, most cases follow an uncomplicated clinical course and complete resolution of symptoms is rapidly achieved, and can be effectively treated with a standard medication treatment with ibuprofen and colchicine, without any CMR-detectable consequence [151].	

19. CONCLUSIONS AND ACTIONS

Overall, the cumulative evidence on the safety and efficacy for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran, fully supports the indications as described in the RSI, authorized as a suspension for injection for active immunizations to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older, or a BD in individuals 6 years of age and older, and individuals 12 years of age and older, respectively.

Clinical trial data and the results of the post-authorization non interventional study (NIS) conducted to date support the positive safety and efficacy profile of mRNA-1273, mRNA-1273.214, and mRNA-1273.222.

During the reporting period, 4 validated signals were closed as refuted by the MAH; Amenorrhea (Re-evaluation), Diarrhea (re-evaluation), Idiopathy inflammatory myopathy/Myositis, Pemphigus and pemphigoid, and 2 validated signals were ongoing; IgA Nephropathy flares, and Sensorineural hearing loss.

A Spikevax RMP version 7.0 was submitted during the reporting period along with PBRER#4 within procedure EMEA/H/C/PSUSA/00010897/202212 to propose removal of the following safety concerns:

- Important potential risk: VAED including VAERD
- Missing information: Use in immunocompromised subjects, Interaction with other vaccines, Use in frail subjects with unstable health conditions and co-morbidities (e.g. COPD, diabetes, chronic neurological disease, cardiovascular disorders) and Use in subjects with autoimmune or inflammatory disorders.

The evaluation of the PBRER#4 was still ongoing at the end of the reporting period.

The data included in this PBRER#5 does not indicate any changes in the benefit-risk profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. The safety profile of elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran is closely monitored on a continuous basis and the analysis of the data contained within this report supports the current RSI (CCDS v16.0, dated 03 Jan 2023) for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran. Examination of the data contained within this report further supports the conclusion that the overall benefit-risk balance for elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran continues to be positive and remains unchanged.

20. APPENDICES TO THE PBRER

Appendix 1 Reference Safety Information

Appendix 2 Worldwide Marketing Authorization status

Appendix 3 Cumulative Summary Tabulations of Serious AEs from Clinical Trials

Appendix 4 Cumulative and Interval Summary Tabulations of Serious and Non-Serious Adverse Reactions from Post-marketing Data Sources

Appendix 5 Tabular Summary of Safety Signals and Signal Evaluation Reports

Appendix 6 Listing of all MAH-Sponsored Interventional Trials with the Primary Aim of Identifying, Characterizing, or Quantifying a Safety Hazard or Confirming the Safety Profile of the Medicinal Product

Appendix 7 Listing of all the MAH-sponsored Non-interventional Studies with the Primary Aim of Identifying, Characterizing, or Quantifying a Safety Hazard; Confirming the Safety Profile of the Medicinal Product; or Measuring the Effectiveness of Risk Management Measures

Appendix 8 List of the Sources of Information Used to Prepare the PBRER

Appendix 9 EU Regional Appendices

Appendix 10 US Regional Appendices

Appendix 11 Canada Regional appendix

Appendix 12 Other Appendices Supporting PBRER

Appendix 13 Literature search strategies