

EU Risk Management Plan for Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 (Elasomeran, elasomeran/imelasomeran and elasomeran/davesomeran)

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP version number: 7.1

Data lock point for this RMP: 01 February 2023

Date of final sign off: 18 July 2023

Rationale for submitting an updated RMP:

Remove vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) as an important potential risk

Remove use in immunocompromised subjects as missing information

Remove interactions with other vaccines as missing information

Remove use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as missing information

Remove use in subjects with autoimmune or inflammatory disorders as missing information

Updated indication and posology for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older.

Update the indication and posology for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 months of age and older

Updated qualitative and quantitative composition for Spikevax bivalent Original/Omicron BA.4-5

Update epidemiology up to 01 February 2023

Update clinical exposure for study mRNA-1273-P204 (Booster dose Phase) as 10 µg Spikevax booster vaccine in this study for children 6 months to < 6 years of age

Include study mRNA-1273-P306 evaluating Spikevax bivalent Original/Omicron BA.1 in healthy children 6 months to < 6 years of age

Include study mRNA-1273-P920 evaluating safety outcomes for Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5)

Update study mRNA-1273-P203 to refer to open-label Part 3 that will evaluate the safety and immunogenicity of bivalent mRNA-1273.222 vaccine in COVID-19 vaccine-naïve 12 to <18 years old adolescents

Update special populations exposure up to 17 December 2022

Update post-authorisation exposure data up to 17 January 2023

Update study milestones for study mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901

Update pharmacovigilance plan to reflect administrative updates for mRNA-1273-P901, mRNA-1273-P910, mRNA-1273-P911 and mRNA-1273-P919

Update mRNA-1273-P910 as a study for characterising pericarditis

Summary of significant changes in this RMP:

Compared to the previously approved Spikevax, Spikevax bivalent Original/Omicron BA.1 and Spikevax bivalent Original/Omicron BA.4-5 European Union (EU) RMP version 6.3, this RMP version 7.1 has been updated:

To update the Products Overview (Part I) with the current indication and posology for Spikevax bivalent Original/Omicron BA.1 for individuals 6 years of age and older

To update the indication and posology for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older

To update the indication and posology for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 months of age and older

To update the qualitative and quantitative composition for Spikevax bivalent Original/Omicron BA.4-5

To update the products overview table in Module SI in line with the current SmPC

To update the epidemiology in Module SI with cumulative data through 01 February 2023

To update the indication in the Epidemiology for Spikevax bivalent Original/Omicron BA.4-5 for use in individuals 6 years of age and older

To update the indication in the Epidemiology section for Spikevax bivalent Original/Omicron BA.4-5 for use in individuals 6 months of age and older

To include clinical trial exposure for study mRNA-1273-P306 (Part 1 and Part 2)

To update the description of study mRNA-1273-P203 to refer to open-label Parts 2 and 3 in the clinical trial exposure section

To update the clinical trial exposure data for mRNA-1273-P204 (Booster dose Phase) as 10 µg Spikevax booster vaccine in this study for children 6 months to < 6 years of age

To update SIV.1 to highlight the areas of missing information that are no longer safety concerns

To update the exposure of special populations in SIV.3 with post-authorisation exposure data up to 17 January 2023

To update the paediatric exposure in SIV.3 to refer to the number of children 6 months to < 6 years of age administered the booster dose in mRNA-1273-P204

To update the post-authorisation exposure data in Module SV up to 13 January 2023

To update Module SVII.2 to justify the removal of VAED including VAERD as an important potential risk

To update Module SVII.2 to justify the removal of use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as missing information

To update Module SVII.3 to remove VAED including VAERD as an important potential risk and to remove use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as missing information

To update Module SVIII to remove VAED including VAERD, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns

To update Part III.1 to remove the COVID-19 / Vaccine Failure Questionnaire as a routine pharmacovigilance activity and to remove VAED including VAERD, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns

To update the pharmacovigilance plan (Parts III.2 and III.3), Annex 2 and Annex 3 to include studies mRNA-1273-P306 and mRNA-1273-P920

To update study milestones for studies mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901 in Part III.2, Part III.3 and Annex 2

To update the Summary Table of Additional Pharmacovigilance Activities in Part III.3 to highlight the removed safety concerns associated with the relevant studies

To update Part III.2, Part III.3 and Annex 2 to reflect administrative updates for studies mRNA-1273-P901, mRNA-1273-P910, mRNA-1273-P911 and mRNA-1273-P919

To update Risk Minimisation Measures (Parts V.1 and V.3) to remove VAED including VAERD, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes,

chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns

To update Summary of the Risk Management Plan (Part VI) to remove VAED including VAERD, use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as safety concerns

To update Part V.3 and Part VI to include mRNA-1273-P910 as a study for characterising pericarditis

To include studies mRNA-1273-P306 and mRNA-1273-P920 in the Summary of Risk Minimisation Measures as per Part III update

To update the indication for Spikevax bivalent Original/Omicron BA.4-5 for use in individuals 6 months of age and older in the Summary of the Risk Management Plan

To include studies mRNA-1273-P306 and mRNA-1273-P920 in the Summary of the Risk Management Plan as per Part III update

To update Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program in Annex 2 to highlight the removed safety concerns associated with the relevant studies

To update the protocol for mRNA-1273-P919 in Annex 3

To remove the COVID-19/Vaccine Failure Questionnaire in Annex 4

To update the list of references in Annex 7 associated with the updates in the RMP

RMP Module:	Significant Changes:
Part I Product Overview	<p>Updated current indication and posology for Spikevax bivalent Original/Omicron BA.1 for individuals 6 years of age and older.</p> <p>Updated indication and posology for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older.</p> <p>Updated indication and posology for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 months of age and older.</p> <p>Updated the qualitative and quantitative composition for Spikevax bivalent Original/Omicron BA.4-5.</p> <p>Updated the products overview table in line with the current SmPC.</p>
Part II Safety Specification	
Module SI Epidemiology of the indication(s) and target population(s)	<p>Updated indication for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 years of age and older.</p> <p>Updated indication for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 months of</p>

RMP Module:	Significant Changes:
	age and older. Updated with cumulative data through 01 February 2023.
Module SII Non-clinical part of the safety specification	No changes.
Module SIII Clinical trial exposure	Included clinical trial exposure for mRNA-1273-P306 Part 1 and Part 2. Updated the description of study mRNA-1273-P203 to refer to open-label Parts 2 and 3. Updated clinical trial exposure for mRNA-1273-P204 (Booster dose Phase).
Module SIV Populations not studied in clinical trials	Module SIV.1 updated to highlight the areas of missing information that are no longer safety concerns. Module SIV.3 updated with post-authorisation exposure data for the special populations up to 17 December 2022. Module SIV.3 updated with paediatric information relating to mRNA-1273-P204.
Module SV Post-authorisation experience	Updated with post-authorisation exposure data up to 17 January 2023.
Module SVI Additional EU requirements for the safety specification	No changes.
Module SVII Identified and potential risks	Module SVII.2 updated to justify the removal of VAED including VAERD as an important potential risk. Module SVII.2 updated to justify the removal of use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as missing information. Module SVII.3 updated to remove VAED including VAERD as an important potential risk and to remove use in immunocompromised subjects, interactions with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders as missing information.
Module SVIII Summary of the safety concerns	Updated to remove VAED including VAERD, 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.
Part III Pharmacovigilance plan	Part III.1 updated to remove the COVID-19/Vaccine Failure Questionnaire as a routine pharmacovigilance

RMP Module:	Significant Changes:
	<p>activity.</p> <p>Part III.1 updated to remove VAED including VAERD, 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.</p> <p>Parts III.2 and III.3 updated to include mRNA-1273-P306 and mRNA-1273-P920 as category 3 studies.</p> <p>Study milestones updated for studies mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901 in Parts III.2 and III.3.</p> <p>Part III.3 updated to highlight the removed safety concerns associated with the relevant studies.</p> <p>Parts III.2 and III.3 updated to incorporate administrative updates to studies mRNA-1273-P901, mRNA-1273-P910, mRNA-1273-P911 and mRNA-1273-P919.</p> <p>Updated Part III.3 to include pericarditis as a safety concern for mRNA-1273-P910.</p>
Part IV Plans for post-authorisation efficacy studies	No changes.
Part V Risk minimisation measures	<p>Parts V.1 and V.3 updated to remove VAED including VAERD, 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.</p> <p>Part V.3 updated to include mRNA-1273-P306 and mRNA-1273-P920.</p> <p>Part V.3 updated to include mRNA-1273-P910 for pericarditis.</p> <p>Part V.3 updated to change the CSR milestones for mRNA-1273-P301, mRNA-1273-P304 and mRNA-1273-P205 as per Part III update.</p>
Part VI Summary of the risk management plan	<p>Updated the indication for Spikevax bivalent Original/Omicron BA.4-5 for use in individuals 6 years of age and older.</p> <p>Updated the indication for Spikevax bivalent Original/Omicron BA.4-5 for individuals 6 months of age and older.</p> <p>Updated to remove VAED including VAERD, 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</p>

RMP Module:	Significant Changes:
	<p>inflammatory disorders as safety concerns.</p> <p>Updated to include mRNA-1273-P306 and mRNA-1273-P920.</p> <p>Updated to include mRNA-1273-P910 for pericarditis.</p> <p>Included mRNA-1273-P306 and mRNA-1273-P920 and updated study details for mRNA-1273-P901, mRNA-1273-P910 and mRNA-1273-P919 in Part II.C.2 as per Part III update.</p>
Part VII Annexes	<p>Annex 2 – Updated to include mRNA-1273-P306 and mRNA-1273-P920 as per Part III update.</p> <p>Updated mRNA-1273-P910 to include pericarditis as a safety concern.</p> <p>Updated mRNA-1273-P301, mRNA-1273-P304, mRNA-1273-P205, and mRNA-1273-P901 milestones as per Part III update.</p> <p>Updated to incorporate administrative changes to mRNA-1273-P901, mRNA-1273-P910, mRNA-1273-P911, and mRNA-1273-P919 as per Part III update.</p> <p>Updated the table to highlight the removed safety concerns associated with the relevant studies.</p> <p>Annex 3 – Updated to include mRNA-1273-P306 and mRNA-1273-P920 as per Part III update.</p> <p>Updated protocol for mRNA-1273-P919.</p> <p>Annex 4 – Removed the COVID-19/Vaccine Failure Questionnaire</p> <p>Annex 7 – Updated references.</p> <p>Annex 8 – Updated to reflect the changes made to the RMP.</p>

Other RMP versions under evaluation:

N/A

Details of the currently approved RMP:

Version number: 7.0

Approved with procedure: EMEA/H/C/PSUSA/00010897/202212

Date of approval (opinion date): 6 July 2023

EU QPPV name¹ : Marie-Pierre Caby-Tosi, EU QPPV

EU QPPV signature:

¹ EU QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website <http://www.ema.europa.eu>

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Moderna's EU QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Acronym	Definition
2019-nCoV	2019 novel coronavirus
Ab	Antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AI/ID	Autoimmune and/or inflammatory disease
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
BD	Booster dose
BLA	Biologics License Application
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMV	Cytomegalovirus
COVID-19	Disease caused by the novel 2019 coronavirus
CoV	Coronaviruses
CSR	Clinical Study Report
DLP	Data lock point
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERD	Enhanced respiratory disease
EU/EEA	European Union/European Economic Area
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
ICSR	Individual case safety report
Ig	Immunoglobulin
IM	Intramuscular(ly)
INN	International nonproprietary name
IP	Investigational product
IR	Incidence rate
IRR	Incidence rate ratio
IRT	Interactive response technology
KPSC	Kaiser Permanente Southern California
LPLV	Last participant last visit
LNP	Lipid nanoparticle
LSLV	Last subject last visit
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MedHx	Medical history
MERS	Middle East respiratory syndrome
MIS	Multisystem inflammatory syndrome
MIS-C	Multisystem inflammatory syndrome in children

Acronym	Definition
mRNA	Messenger ribonucleic acid
MSSR	Monthly Summary Safety Report
nAb	Neutralizing antibody(ies)
NHP	Nonhuman primate
NP	Nasopharyngeal
NPI	Nonpharmaceutical interventions
NTD	N-terminal domain
O/E	Observed to expected
PL	Patient leaflet
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PSUR	Periodic Safety Update Report
RBD	Receptor binding domain
RMP	Risk management plan
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
sBLA	Supplemental Biologic License Application
SCRI	Self-controlled risk interval
SmPC	Summary of Product Characteristics
SSR	Summary of Safety Report
TEAE	Treatment emergent adverse event
TESSy	The European Surveillance System
Th	T helper
TTO	Time to onset
VAED	Vaccine associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

Throughout the document, both elasomeran and mRNA-1273 (only for clinical trials titles) are used to identify the product.


Throughout the document, elasomeran/imelasomeran and mRNA-1273.214 are used to identify the bivalent vaccine Spikevax bivalent Original/Omicron BA.1.

Throughout the document, elasomeran/davesomeran and mRNA-1273.222 are used to identify the bivalent vaccine Spikevax bivalent Original/Omicron BA.4-5.

Throughout the document, Spikevax bivalent is used to identify the bivalent vaccine Spikevax bivalent Original/Omicron BA.1.

Part I: Products Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Elasomeran, elasomeran/imelasomeran, and elasomeran/davesomeran
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Vaccine, other viral vaccines (J07BX03)
Marketing Authorisation Holder	MODERNA BIOTECH SPAIN, S.L. Calle del Príncipe de Vergara 132 Plt 12 Madrid 28002 Spain
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area	Spikevax, Spikevax bivalent/ Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5
Marketing authorisation procedure	Centralised
Brief description of the product	<p>Chemical class</p> <p>The mRNA drug substance in Spikevax 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 (Rozenski et al 1999; Karikó et al 2005). This nucleoside is included in elasomeran Drug Substance in place of the normal uridine base to minimise the indiscriminate recognition of the elasomeran mRNA by pathogen-associated molecular pattern receptors (e.g., toll-like receptors) (Desmet and Ishii 2021). The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure (Kozak 1991; Fechter and Brownlee 2005).</p> <p>Structure of mRNA</p>  <p>Abbreviations: mRNA, messenger RNA; PolyA, polyadenylated; UTR, untranslated region.</p> <p>Summary of mode of action</p> <p>Spikevax encodes for the prefusion stabilized spike glycoprotein of SARS-CoV-2. After intramuscular (IM; deltoid) injection, cells at the injection site take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The mRNA delivery system is based on the principle and observation that cells in vivo can take up mRNA, translate it, and express viral protein antigen(s) in the desired conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional spike glycoprotein that is inserted into the cellular membrane of the expressing cell(s).</p>

	<p>The spike glycoprotein is membrane bound, mimicking the presentation of natural infection.</p> <p>The expressed spike glycoprotein 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 glycoprotein results in functional antibody (Ab) and T-cell responses and in the generation of memory immune cell populations.</p> <p>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 (Omicron BA.1), each encapsulated into individual lipid nanoparticles, and co-formulated into a single drug product (Spikevax bivalent). After delivery, both mRNAs are delivered to cells in the body where the two distinct spike protomers, each of which represents one of the three components of the spike trimer, are expressed. After expression these spike protomers assemble into the spike trimer and both homotrimers as well heterotrimers (mixed protomers from the Wuhan spike and the Variant spike), form.</p> <p>The inclusion of both the original and the variant spikes in the vaccine are intended to broaden immunity. Inclusion of the Wuhan spike allows reactivation and boosting of memory immune cell populations, increasing immunity that was previously present. In addition, inclusion of the variant spike, which has novel functional epitopes present primarily on the receptor binding domain (RBD) and the N-terminal domain (NTD), allows new naïve immune populations to be engaged and new memory responses to be elicited. This likely broadens immunity not only to the spike antigens delivered but likely also against a broader diversity of spike proteins. Furthermore, the formation of heterotrimers with spike protomers from both the Wuhan and Variant spikes results in spike trimers that are able to flex more significantly than homotrimers, resulting in more presentation of the receptor binding domain in an “open” or “up” conformation, versus the “closed” conformation seen predominantly in homotrimers. In the open conformation, key sites of neutralization not exposed when the spike is closed are available, providing the immune system with more functional sites with which to engage.</p> <p>Important information about its composition</p> <p><u>Spikevax:</u> The active substance is mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 embedded in lipid nanoparticles (elasomeran)</p> <p><u>Spikevax bivalent Original/Omicron BA.1:</u> The active substances are mRNA encoding the prefusion stabilized spike glycoprotein of original SARS-CoV-2 embedded in lipid nanoparticles (elasomeran) and mRNA encoding the prefusion stabilized spike glycoprotein of SARS-CoV-2 Omicron variant (B.1.1.529) embedded in lipid nanoparticles (imelasomeran).</p> <p><u>Spikevax bivalent Original/Omicron BA.4-5:</u> The active substances are mRNA encoding the prefusion stabilised spike glycoprotein of original SARS-CoV-2 embedded in lipid nanoparticles (elasomeran) and mRNA encoding the prefusion stabilised 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 lipid nanoparticles (davesomeran).</p> <p>The other ingredients are SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG), trometamol, trometamol hydrochloride, acetic acid, sodium acetate, sucrose, water for injections.</p>
Hyperlink to the Product Information	Module 1

Indication(s) in the EEA	<p>Current:</p> <p>Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.</p> <p>Spikevax bivalent Original/Omicron BA.1 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19.</p> <p>Spikevax bivalent Original/Omicron BA.4-5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19.</p> <p>Proposed:</p> <p>Spikevax bivalent Original/Omicron BA.4-5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.</p>																						
Dosage in the EEA	<p>Current:</p> <p><i>Spikevax</i></p> <p>Spikevax posology for primary series, a third dose in severely immunocompromised and booster doses</p> <table><tr><th>Concentration</th><th>Vaccination type</th><th>Age(s)</th><th>Dose</th><th>Recommendations</th></tr><tr><td rowspan="5">Spikevax 0.2 mg/L dispersion for injection</td><td rowspan="2">Primary series</td><td>Individuals 12 years of age and older</td><td>2 (two) (0.5 mL each, containing 100 micrograms mRNA)</td><td rowspan="2">It is recommended to administer the second dose 28 days after the first dose</td></tr><tr><td>Children 6 through 11 years of age</td><td>2 (two) doses (0.25 mL each, containing 50 micrograms mRNA, which is half of the primary dose for individuals 12 years and older)</td></tr><tr><td rowspan="2">Third dose in severely immune-compromised individuals</td><td>Individuals 12 years of age and older</td><td>1 (one) dose of 0.5 mL, containing 100 micrograms mRNA</td><td rowspan="2">A third dose may be given at least 28 days after the second dose</td></tr><tr><td>Children 6 through 11 years of age</td><td>1 (one) dose of 0.25 mL containing 50 micrograms mRNA</td></tr><tr><td>Booster dose</td><td>Individuals 12 years of age and older</td><td>1 (one) dose of 0.25 mL, containing 50 micrograms mRNA</td><td>Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector</td></tr></table>	Concentration	Vaccination type	Age(s)	Dose	Recommendations	Spikevax 0.2 mg/L dispersion for injection	Primary series	Individuals 12 years of age and older	2 (two) (0.5 mL each, containing 100 micrograms mRNA)	It is recommended to administer the second dose 28 days after the first dose	Children 6 through 11 years of age	2 (two) doses (0.25 mL each, containing 50 micrograms mRNA, which is half of the primary dose for individuals 12 years and older)	Third dose in severely immune-compromised individuals	Individuals 12 years of age and older	1 (one) dose of 0.5 mL, containing 100 micrograms mRNA	A third dose may be given at least 28 days after the second dose	Children 6 through 11 years of age	1 (one) dose of 0.25 mL containing 50 micrograms mRNA	Booster dose	Individuals 12 years of age and older	1 (one) dose of 0.25 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector
Concentration	Vaccination type	Age(s)	Dose	Recommendations																			
Spikevax 0.2 mg/L dispersion for injection	Primary series	Individuals 12 years of age and older	2 (two) (0.5 mL each, containing 100 micrograms mRNA)	It is recommended to administer the second dose 28 days after the first dose																			
		Children 6 through 11 years of age	2 (two) doses (0.25 mL each, containing 50 micrograms mRNA, which is half of the primary dose for individuals 12 years and older)																				
	Third dose in severely immune-compromised individuals	Individuals 12 years of age and older	1 (one) dose of 0.5 mL, containing 100 micrograms mRNA	A third dose may be given at least 28 days after the second dose																			
		Children 6 through 11 years of age	1 (one) dose of 0.25 mL containing 50 micrograms mRNA																				
	Booster dose	Individuals 12 years of age and older	1 (one) dose of 0.25 mL, containing 50 micrograms mRNA	Spikevax may be used to boost individuals 12 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector																			

					vaccine at least 3 months after completion of the primary series.
Spikevax 0.1 mg/L dispersion for injection and Spikevax 50 micrograms dispersion for injection in pre-filled syringe*	Primary series†	Children 6 years through 11 years of age	2 (two) doses (0.5 mL each, containing 50 micrograms mRNA each)		It is recommended to administer the second dose 28 days after the first dose.
		Children 6 months through 5 years of age	2 (two) doses (0.25 mL each, containing 25 micrograms mRNA, which is half of the primary dose for children 6 years through 11 years of age)*		
	Third dose in severely immuno-compromised individuals‡	Children 6 years through 11 years of age	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA		A third dose may be given at least 28 days after the second dose.
		Children 6 months through 5 years of age	1 (one) dose of 0.25 mL, containing 25 micrograms mRNA		
	Booster dose	Individuals 12 years of age and older	1 (one) dose of 0.5 mL, containing 50 micrograms mRNA		Spikevax may be used to boost individuals 6 years of age and older who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine at least 3 months after completion of the primary series.
		Children 6 years through 11 years of age	1 (one) dose of 0.25 mL containing 25 micrograms mRNA*		
<p>*Do not use the pre-filled syringe to deliver a partial volume of 0.25 mL</p> <p>†For primary series for individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.</p> <p>‡For the third dose in severely immunocompromised individuals 12 years of age and older, the 0.2 mg/mL strength vial should be used.</p> <p><i>Spikevax bivalent Original/Omicron BA.1</i> <i>Individuals 12 years of age and older</i> The dose of Spikevax bivalent Original/Omicron BA.1 is 0.5 mL given intramuscularly.</p>					

Children 6 years through 11 years of age

The dose of Spikevax bivalent Original/Omicron BA.1 is 0.25 mL given intramuscularly.

There should be an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine. Spikevax bivalent Original/Omicron BA.1 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

Spikevax bivalent Original/Omicron BA.4-5*12 years of age and older*

The dose of Spikevax bivalent Original/Omicron BA.4-5 is 0.5 mL given intramuscularly.

Children 6 years through 11 years of age

The dose of Spikevax bivalent Original/Omicron BA.4-5 is 0.25 mL given intramuscularly.

There should be an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.4-5 and the last prior dose of a COVID-19 vaccine. Spikevax bivalent Original/Omicron BA.4-5 is only indicated for individuals who have previously received at least a primary vaccination course against COVID-19.

Proposed: Spikevax bivalent Original/Omicron BA.4-5 posology

Age(s)	Dose	Additional recommendations
Children 6 months through 4 years of age, without prior vaccination and no known history of SARS-CoV-2 infection	Two doses of 0.25 mL each, given intramuscularly*	Administer the second dose 28 days after the first dose. If a child has received one prior dose of Spikevax, one dose of Spikevax bivalent Original/Omicron BA.4-5 should be administered to complete the two-dose series.
Children 6 months through 4 years of age, with prior vaccination or known history of SARS-CoV-2 infection	One dose of 0.25 mL, given intramuscularly*	Spikevax bivalent Original/Omicron BA.4-5 should be administered at least 3 months after the most recent dose of a COVID 19 vaccine.
Children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly*	
Individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly	
Individuals 65 years of age and older	One dose of 0.5 mL, given intramuscularly	One additional dose may be administered at least 3 months after the most recent dose of a COVID-19 vaccine.

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

	Spikevax bivalent Original/Omicron BA.4-5 posology for immunocompromised individuals			
	Age(s)	Dose	Additional recommendations	
	Immunocompromised children 6 months through 4 years of age, without prior vaccination	Two doses of 0.25 mL, given intramuscularly*	A third dose in severely immunocompromised may be given at least 28 days after the second dose.	
	Immunocompromised children 6 months through 4 years of age, with prior vaccination	One dose of 0.25 mL, given intramuscularly*	Additional age-appropriate dose(s) may be administered in severely immunocompromised at least 2 months following the most recent dose of a COVID-19 vaccine at the discretion of the healthcare provider, taking into consideration the individual’s clinical circumstances.	
	Immunocompromised children 5 years through 11 years of age, with or without prior vaccination	One dose of 0.25 mL, given intramuscularly*		
Immunocompromised individuals 12 years of age and older, with or without prior vaccination	One dose of 0.5 mL, given intramuscularly			
*Do not use the single-dose vial or pre-filled syringe to deliver a partial volume of 0.25 mL.				
<i>Paediatric population</i>				
The safety and efficacy of Spikevax bivalent Original/Omicron BA.4-5 in children less than 6 months of age have not yet been established. No data are available.				
<i>Elderly</i>				
No dose adjustment is required in elderly individuals ≥65 years of age.				
Pharmaceutical form(s) and strengths	Current: Dispersion for injection White to off white dispersion (pH 7.0 - 8.0).			
	Qualitative and quantitative composition by strength and type of container			
	Strength	Container	Dose(s)	Composition per dose
	Spikevax 0.2 mg/mL dispersion for injection	Multidose vial (red flip-off cap)	Maximum 10 doses of 0.5 mL each	One dose (0.5 mL) contains 100 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

			Maximum 20 doses of 0.25 mL each	One dose (0.25 mL) contains 50 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
	Spikevax 0.1 mg/mL dispersion for injection	Multidose vial (blue flip-off cap)	5 doses of 0.5 mL each	One dose (0.5 mL) contains 50 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
			Maximum 10 doses of 0.25 mL each	One dose (0.25 mL) contains 25 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
	Spikevax 50 micrograms dispersion for injection in pre-filled syringe	Pre-filled syringe	1 dose of 0.5 mL For single-use only. Do not use the pre-filled syringe to deliver a partial volume of 0.25 mL.	One dose (0.5 mL) contains 50 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
Spikevax bivalent Original/Omicron BA.1 qualitative and quantitative composition				
	Strength	Container	Dose(s)	Composition per dose
	Spikevax bivalent Original/Omicron BA.1 (50 micrograms/50 micrograms)/mL dispersion for injection	Multidose 2.5 mL vial (blue flip-off cap)	5 doses of 0.5 mL each or 10 doses of 0.25 mL each	One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
		Multidose 5 mL vial (blue flip-off cap)	10 doses of 0.5 mL each or 20 doses of 0.25 mL each	One dose (0.25 mL) contains 12.5 micrograms of elasomeran and 12.5 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
	Spikevax bivalent Original/Omicron BA.1 25 micrograms/25 micrograms dispersion for injection	Single-dose 0.5 mL vial (blue flip-off cap)	1 dose of 0.5 mL each For single-use only	One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
	Spikevax bivalent Original/Omicron BA.1 25 micrograms/25 micrograms dispersion for	Pre-filled syringe	1 dose of 0.5 mL each For single-use only	

	injection in pre-filled syringe			
	Spikevax bivalent Original/Omicron BA.4-5 qualitative and quantitative composition			
	Strength	Container	Dose(s)	Composition per dose
	Spikevax bivalent Original/Omicron BA.4-5 (50 micrograms/50 micrograms)/mL dispersion for injection	Multidose 2.5 mL vial (blue flip-off cap)	5 doses of 0.5 mL each	One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of davesomeran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles). One dose (0.25 mL) contains 12.5 micrograms of elasomeran and 12.5 micrograms of davesomeran, a COVID 19 mRNA Vaccine (embedded in lipid nanoparticles).
	Spikevax bivalent Original/Omicron BA.4-5 25 micrograms/25 micrograms dispersion for injection	Single-dose 0.5 mL vial (blue flip-off cap)	1 dose of 0.5 mL each For single-use only.	One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of davesomeran, a COVID 19 mRNA Vaccine (embedded in lipid nanoparticles).
	Spikevax bivalent Original/Omicron BA.4-5 25 micrograms/25 micrograms dispersion for injection in pre-filled syringe	Pre-filled syringe	1 dose of 0.5 mL each For single-use only.	One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of davesomeran, a COVID 19 mRNA Vaccine (embedded in lipid nanoparticles).
	Proposed: Not applicable			
Vaccine construct and the formulation	<p>Elasomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (original).</p> <p>Imelasomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.1).</p> <p>Davesomeran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 (Omicron BA.4-5). The S proteins of the SARS-CoV-2 Omicron variant lineages BA.4 and BA.5 are identical.</p> <p>The other ingredients are SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate), Cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG), Trometamol, Trometamol hydrochloride, Acetic acid, Sodium acetate trihydrate, Sucrose, and Water for injections.</p>			

Is/will the product be subject to additional monitoring in the EU?	Yes.
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Part II: Safety Specification

Part II: Module SI – Epidemiology of the Indication and Target Population

Indication: Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older.

Spikevax bivalent Original/Omicron BA.1 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19.

Spikevax bivalent Original/Omicron BA.4-5 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 6 months of age and older.

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).

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 December 2019, and has spread globally ([WHO 2020a](#) and [WHO 2020b](#)). The World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020; however, by that time, there was already widespread community transmission in many locations. As of 25 January 2023, over 664,873,023 confirmed cases and 6,724,248 deaths have been attributed to the COVID-19 pandemic globally ([WHO 2023a](#)). Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions ([WHO 2020a](#) and [2020b](#)). WHO has continued to track Variants of Concern (VOC): current circulating VOCs as of 13 January 2023 are Omicron subvariants BF.7, BQ.1, BA.2.75, XBB, as well as additional sublineages ([WHO 2023b](#)).

Incidence of COVID-19 in Europe

Following the identification of SARS-CoV-2 and its global spread, large epidemics of COVID-19 occurred in Europe. By mid-March 2020, the WHO European Region had become the epicentre of the pandemic, reporting over 40% of globally confirmed cases. As of 25 January 2023, 32.4% of global mortality from SARS-CoV-2 was from the European Region ([WHO 2023a](#)).

The 14-day case notification rates collected by the European Centre for Disease Prevention and Control (ECDC) from 28 countries ranged from 11.0 to 611.6 per 100,000 population in the week 3 ending on 22 January 2023. This pooled rate has been decreasing for five weeks with rates per 100,000 population being <40 in twelve countries, 40–<100 in eight countries, 100–<300 in five countries (France, Germany, Italy, Luxembourg and Slovenia) and 300 or higher in three countries (Austria, Cyprus and Greece). No countries reported increases in incidence ([ECDC 2023a](#)).

During the same period (the week 3 ending on 22 January 2023), the 14-day COVID-19 death rate for the EU/EEA, based on data collected by ECDC from official national sources for 26 countries ranged from 0.0 to 34.3 per million population, with rates 20 or higher in five countries (Croatia, Greece, Latvia, Slovenia, and Sweden) ([ECDC 2023a](#)).

The below table presents key epidemiology indicators per country.

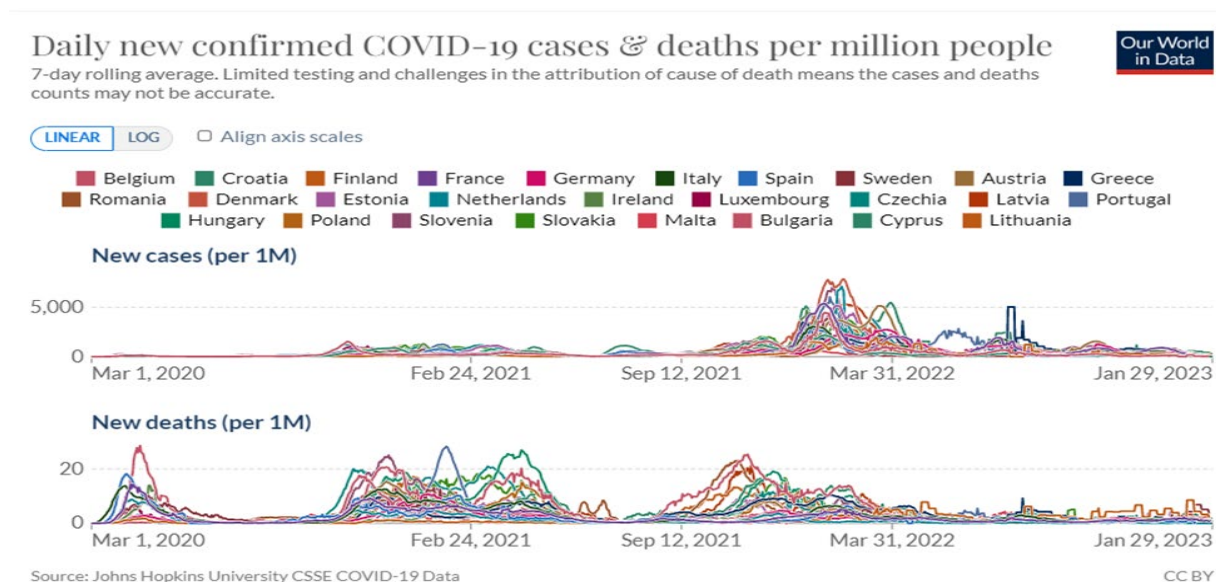
Table 2: 14-Day Case and Death Notification Rates in the EU/EEA (Week 3 ending 22 January 2023)

Country	Case Rate (14-day notification per 100,000 population)	Death Rate (14-day notification per million population)
EU/EEA (pooled)	110	8.3
Austria	322.5	9
Belgium	33.6	7.2
Bulgaria	23.6	5.5
Croatia	90.5	33
Cyprus	611.6	16.7
Czechia	35	5.5
Denmark	57.9	5.5
Estonia	51	15
Finland	33.6	12.8
France	115.2	13.9
Germany	181.3	3.4
Greece	551.4	34.3
Hungary	15.3	NA
Ireland	54	6.2
Italy	170.5	11.1
Latvia	23.3	24.8
Liechtenstein	56.3	0
Luxembourg	208.9	14.2
Malta	57.7	5.8
Netherlands	23.5	0
Norway	19.1	NA
Poland	11	3.2
Portugal	41.4	11.4
Romania	32.3	2.5
Slovakia	27.8	1.8
Slovenia	248.8	25.6
Spain	31.5	3.9
Sweden	54.8	24.8

NA= not available

Figure 1 displays the cases and deaths in the EU from 01 March 2020 to 29 January 2023 ([Mathieu 2023](#)). An overall improvement in the COVID-19 epidemiology was seen in 2023.

Figure 1: COVID-19 Cases and Deaths in the EU per Million People, 7-Day Rolling Average, 01 March 2020 to 29 January 2023



Variants of concern (VOC) and Variants of interest (VOI)

Since the outbreak of the COVID-19 caused by the 2019 novel CoV began in Wuhan, in December 2019, the WHO proposed labels for global COVID-19 variants of concern (VOC) and variants of interest (VOI) ([WHO 2022a](#)).

Delta was originally documented in October 2020 in India and Omicron first documented in various countries in November 2021. The WHO current VOC are the Omicron subvariants. There are currently no circulating VOI listed by WHO ([WHO 2022a](#)); however, the European Centre 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 variants of interest as of 26 January 2023 ([ECDC 2023b](#)). 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 January 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 ([ECDC 2023c](#)).

Age specific Case Notification rates

The 14-day case notification rate was significantly higher among elderly populations during the first 3 months of the pandemic. However, this shifted in late 2021 and early 2022, with younger age groups (<50 years old) having the highest case notification rate. This increase in notification rates in younger population groups can be explained by an increase in testing rates exacerbated by a relaxation of nonpharmaceutical interventions (NPIs) as older population groups achieve

vaccination including booster doses ([ECDC 2023d](#)). By the end of week 3 of 2023 (week ending 22 January 2023), pooled rates of case notification have continued to decrease following the small increases that were observed during December 2022 across all age groups ([ECDC 2023d](#)).

Incidence Among Adolescents in the EU/EEA

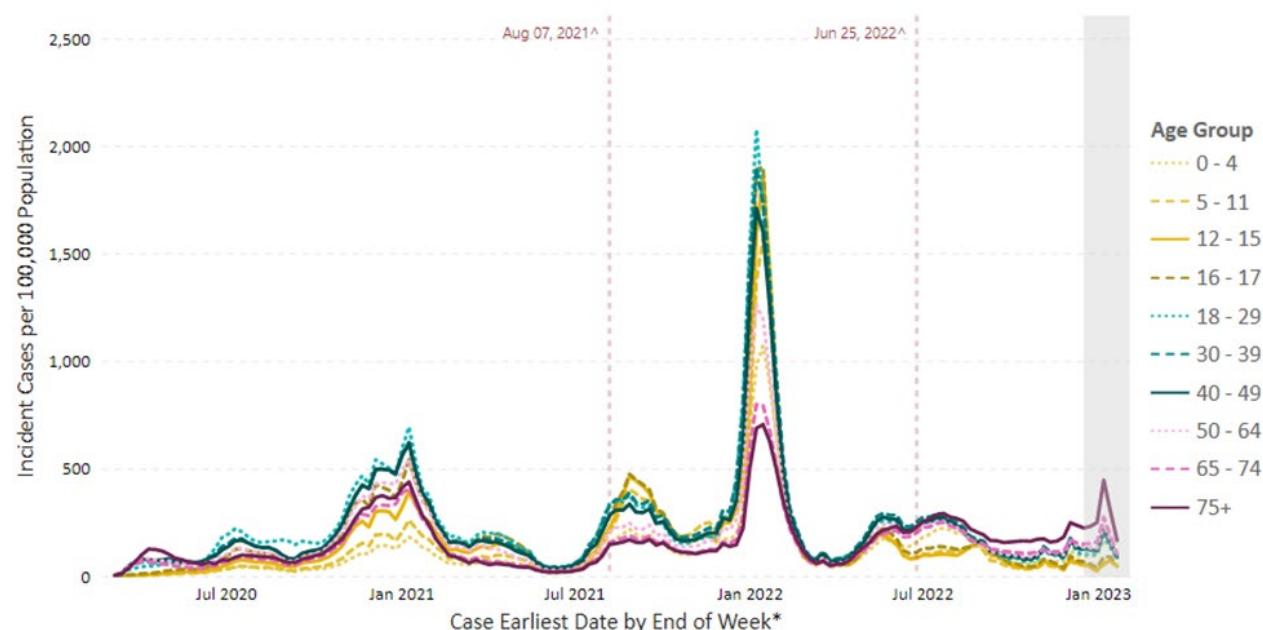
Country-level and pooled case-based data reported to The European Surveillance System (TESSy) in the EU/EEA countries indicate that case notification rates among adolescents have decreased after the peak in late 2021 and early 2022 ([ECDC 2023d](#)), which coincided with the predominant circulation of BA.1 variants ([Our World in Data 2023](#)).

Country-level 14-day age-specific notification rates of new COVID-19 cases were available for 26 EU/EEA countries as of week 3 of 2023 (i.e., week ending 22 January 2023) in TESSy ([ECDC 2023d](#)). In children and adolescents < 15 years-old, the 14-day notification rates per 100,000 population ranged from 4.57 in Greece to 270.00 in the Netherlands. Among people aged 15-24 years, the 14-day notification rates per 100,000 population ranged from 7.35 in Spain to 258.92 in Austria.

Incidence of COVID-19 in the US

[Figure 2](#) below presents the trends in COVID-19 weekly cases per 100,000 population by age group from 01 March 2020 to 21 January 2023 from US CDC COVID Data Tracker ([CDC 2023a](#)). The older population saw slightly higher incidence than younger population in January 2023.

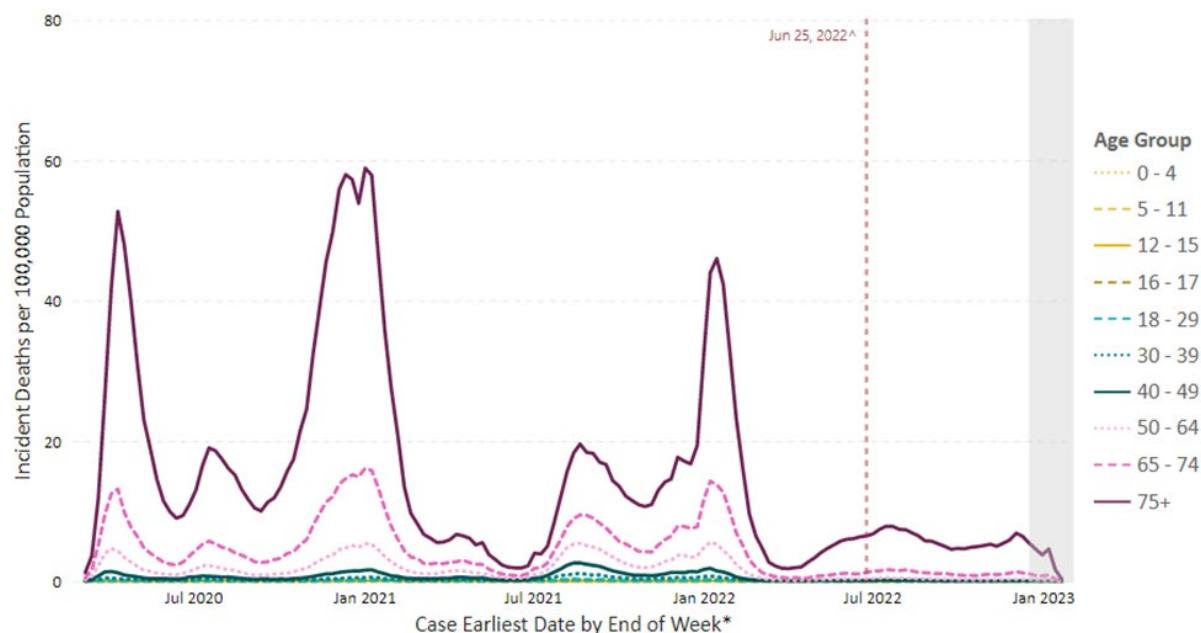
Figure 2: COVID-19 Weekly Cases (per 100,000 Population) by Age Group from 01 March 2020 to 21 January 2023 in the US (CDC)



^Case rates for South Dakota during the week ending 7 August 2021, and Texas during the week ending 25 June 2022, are reflective of a data reporting artifact. Surveillance data are provisional, and as additional clinical data becomes available, the case rates over time are subjective to change.

Figure 3 below presents the trends in COVID-19 deaths per 100,000 population by age group from 01 March 2020 to 21 January 2023. The death rates are still higher in the elderly age groups compared to the younger age groups (CDC 2023a).

Figure 3: COVID-19 Weekly Deaths per 100,000 Population by Age Group from 01 March 2020 to 21 January 2023 in the US (CDC)



^ The death rate for Texas during the week ending 25 June 2022 are reflective of a data reporting artifact.

As of 7 January 2023, the top three predominant VOC based on reported genomic sequencing results in the US were BQ.1.1 (34%), XBB.1.5 (26%), and BQ.1 (18%). The estimated proportion of XBB.1.5 was projected to increase to 61% by 28 January 2023 (CDC 2023f).

Risk Factors for severe COVID-19 outcomes

Age

Age has been identified as an independent risk factor for severe COVID-19 disease outcome (Booth 2021). Older adults (especially those ages 50 years and older) are more likely than younger people to be admitted into the hospital or intensive care for COVID-19, or die from SARS-CoV2 infection.

Medical conditions

According to the US CDC (CDC 2023b), many conditions were found to have a conclusive increased risk for at least one severe COVID-19 outcome in at least one published meta-analysis or systematic review or underwent the US CDC systematic review process: asthma, cancer,

cerebrovascular disease, chronic kidney disease, chronic lung diseases (bronchiectasis, COPD, interstitial lung disease, pulmonary embolism, and pulmonary hypertension), chronic liver diseases (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, and autoimmune hepatitis), cystic fibrosis, diabetes, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), mood disorders including depression, schizophrenia spectrum disorders, dementia, obesity, pregnancy and recent pregnancy, HIV (Human immunodeficiency virus), primary immunodeficiencies, solid organ or blood stem cell transplantation, use of corticosteroids or other immunosuppressive medications, smoking, disabilities including Down syndrome, and tuberculosis. Similar risk factors and risk groups were identified by ECDC ([ECDC 2023e](#)).

Main Existing Treatment Options

Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified and there is an urgent public health need for rapid development of novel prophylactic therapies, including vaccines to prevent the spread of this disease mainly of the new variants.

As of January 2023, six vaccines have been authorized for COVID prevention in the European Union including: Comirnaty[®] from BioNTech and Pfizer; Spikevax[®] from Moderna; Vaxzevria[®] from Astrazeneca, Jcovden from Janssen, Nuvaxovid[®] from Novavax, and VidPrevtyn Beta from Sanofi Pasteur. In addition, there are four adapted vaccines authorized for use in the EU, including: Comirnaty Original/ Omicron BA.1[®] from Pfizer, Comirnaty Original/Omicron BA.4-5[®] from Pfizer; Spikevax bivalent Original/Omicron BA.1[®] from Moderna, and Spikevax bivalent Original/ Omicron BA.4-5[®] from Moderna. There are other additional vaccines currently under rolling review (Sputnik V [Gam-COVID-Vac] from Gamaleya Institute), COVID-19 Vaccine HIPRA (PHH-1V) (from HIPRA Human Health S.L.U.), and COVID-19 Vaccine (Vero Cell) Inactivated from Sinovac ([EMA 2023](#)). The cumulative uptake of COVID-19 vaccines among adults (≥ 18 years old) as of week 3 of 2023 was 84.8% for at least one dose, 82.4% uptake of the primary course, and 65.4% uptake of first booster dose, and 16.9% uptake of second booster dose reported from 30 EU/EEA countries ([ECDC 2023c](#)). During the same period, 26.7% of paediatric population (< 18 years old) received at least one dose of COVID-19 vaccines.

In the US, two vaccines were approved (BLA): Comirnaty[®] from Pfizer (23 August 2021); and Spikevax[®] from Moderna (31 January 2022). Other vaccines authorized for emergency use include: Janssen COVID-19 vaccine, Novavax COVID-19 Vaccine Adjuvanted, Comirnaty Original/Omicron BA.4-5[®] from Pfizer; and Spikevax bivalent Original/Omicron BA.4-5[®] from Moderna ([FDA 2023](#)).

In addition, the following medicinal products have been authorized in the European Union: Kineret (anakinra), an immunosuppressive medicine; Paxlovid (nirmatrelvir/ritonavir), a protease inhibitor; Regkirona (regdanvimab), a monoclonal antibody medicine; RoActemra (tocilizumab), interleukin-6 inhibitor; Ronapreve (casirivimab/imdevimab), combination of two monoclonal antibodies; Veklury (remdesivir), an antiviral medication; Xevudy (sotrovimab), human neutralizing monoclonal antibody; and Evusheld (tixagevimab/ cilgavimab), combination of two recombinant human IgG1 monoclonal antibodies. Additionally, the marketing authorisation for

Lagevrio (molnupiravir), a medication that works by introducing errors into the SARS-CoV-2 virus' genetic code is under marketing authorization evaluation by the EMA ([EMA 2023](#)).

In the US, a variety of treatments have been authorized by FDA for Emergency Use ([FDA 2023](#)), such as antiviral drugs - Veklury (remdesivir) for adults and certain paediatric patients with COVID-19, Paxlovid (nirmatrelvir/ritonavir) and Lagevrio (molnupiravir) for patients with mild-to-moderate COVID-19; monoclonal antibodies - Actemra[®] (Tocilizumab), Sotrovimab, Bamlanivimab/etesevimab, and REGN-COV2 (casirivimab/imdevimab); immune modulators - Olumiant (baricitinib) and Actemra (tocilizumab) for certain hospitalised adults with COVID-19; and COVID-19 convalescent plasma with high titres of anti-SARS-CoV-2 antibodies in patients with immunosuppressive disease or receiving immunosuppressive treatment.

Natural History of COVID-19 in the Unvaccinated Population

Current evidence suggests that SARS-CoV-2 is primarily transmitted via direct contact or person-to-person via respiratory droplets by coughing or sneezing from an infected individual (whether symptomatic or not). Airborne transmission may be possible during certain medical procedures and in indoor, crowded and poorly ventilated environments ([WHO 2020c](#)). Common symptoms of COVID-19 include fever and cough, and other symptoms can include shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. In comparison to ancestral SARS-CoV-2, Delta and Omicron BA.1 have shorter incubation periods, estimated as approximately 3.7-4 days for Delta and approximately 3-3.4 days for Omicron BA.1. Higher infectious viral loads were detected in patients infected with Delta than in patients infected with Omicron BA.1 or ancestral SARS-CoV-2 ([Puhach 2022](#)). Overall patterns of shedding dynamics are conserved between SARS-CoV-2 variants. Infected children appear to shed SARS-CoV-2 virus with nasopharyngeal viral loads comparable to or higher than those in adults ([Heald-Sargent 2020](#); [DeBiasi 2021](#)). The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥ 30 breaths/min, $SpO_2 \leq 93\%$, $PaO_2/FiO_2 < 300$ mmHg, and/or lung infiltrates $> 50\%$ within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure) ([Chowdhury 2020](#)). The abnormalities seen in computed tomography of the chest also vary, but the most commonly observed are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course. Imaging may be normal early in infection and can be abnormal in the absence of symptoms. The circulating variants of SARS-CoV-2 evolves rapidly with different transmissibility and virulence. The Omicron variant, like other variants, is made up of several lineages and Sublineages, and share similar systems to previous variants. However, Omicron spreads more easily than earlier variants, including the Delta variant, and tends to cause less severe illness and death in general ([CDC 2023c](#); [Wolter 2022](#)).

Common laboratory findings of COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferases, C-reactive protein, D-dimer,

ferritin, and lactate dehydrogenase. While COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac, dermatologic, hematological, hepatic, neurological, renal, and other complications ([Gavriatopoulou 2020](#)). Thromboembolic events also occur in patients with COVID-19, with the highest risk in critically ill patients.

The understanding of immunity against SARS-CoV-2 is still incomplete. Binding antibodies (bAb and neutralizing antibodies (nAb) to SARS-CoV-2 have been shown to develop in most individuals between day 10 and day 21 after infection ([Ni 2020](#); [Seydoux 2020](#); [To 2020](#)). Reviews of the published literature indicate that most patients develop IgG seropositivity and nAb following primary infection with SARS-CoV-2 in > 91% and > 90% of cases, respectively. T-cell responses against the SARS-CoV-2 spike protein have been characterised and correlate well with immunoglobulin (Ig) G and IgA Ab titres in COVID-19 patients, which has important implications for vaccine design and long-term immune response ([Braun 2020](#); [Grifoni 2020](#); [Weiskopf 2020](#)). In general, more people were tested positive for infection-induced SARS-CoV-2 antibodies in US and Europe by 2022, with the highest seroprevalence in the paediatric population ([Clarke 2022](#); [Castilla 2022](#); [Kislaya 2023](#)). During December 2021 to February 2022, the overall seroprevalence of infection-induced antibodies in US increased from 33.5% to 57.7%, with the highest seroprevalence in February 2022 among children under 12 years old (75.2%), followed by 74.2% in children aged 12-17 years, 63.7% in adults aged 18-49 years, 49.8% in adults aged 50-64 years, and 33.2% in adults aged ≥65 years ([CDC 2023d](#)). Similarly, during 26 April to 03 June 2022 the overall seroprevalence of infection-induced antibodies in Navarre, Spain was approximately 59% and decreased with advancing age, with the highest seroprevalence in children aged 5–17 years old (85%) ([Castilla 2022](#)). In Portugal, although the overall seroprevalence of infection-introduced antibodies was lower (27.3%) during 27 April to 08 June 2022, a steep increase (12–30%) in N IgG seroprevalence was also observed for all age groups from the last survey in October–December 2021 ([Kislaya 2023](#)).

Various studies indicate that most patients mount an immune response following a SARS-CoV-2 infection, but that this immunity may wane over time. More recent studies found that antibody titres peak between 3 to 4 weeks after infection and remain relatively stable up to 4 months after infection ([Gudbjartsson 2020](#)). Neutralizing activity also starts to decline after 1 to 3 months from symptom onset, as recently reported in a series of longitudinal studies on convalescent patients ([Baden 2021](#); [Beaudoin-Bussi res 2020](#); [Long 2020](#); [Perreault 2020](#); [Pr vost 2020](#)). The longevity of the Ab response to SARS-CoV-2 is still to be determined, but it is known that Ab levels to other CoVs wane over time (range: 12 to 52 weeks from the onset of symptoms) and homologous reinfections have been documented ([Wu 2007](#); [Kellam 2020](#)). Reinfection by SARS-CoV-2 under endemic conditions would likely occur with medians ranged from 16 to 22 months after peak antibody response through natural infection ([Townsend 2021](#); [Townsend 2022](#)). Several observational studies report that at least two exposures to S protein, through vaccination and/or infection, provide a degree of protective immunity ([Goldberg 2022](#); [Andeweg 2022](#); [Babouee Flury 2022](#); [Hansen 2023](#); [Chin 2022](#)), but the protection against wanes with increasing time since the last immunity-conferring event. A systematic review and meta-analysis of 65 studies from 19 different countries showed protection from re-infection from ancestral, alpha, and delta variants declined over time but remained at 78.6% (95% uncertainty interval [UI] 49.8–93.6) at 40 weeks, while protection against re-infection by the omicron BA.1 variant declined more rapidly and was estimated at 36.1% (24.4–51.3) at 40 weeks. On the other hand, protection against severe disease

remained high for all variants, with 90.2% (95% UI 69.7–97.5) for ancestral, alpha, and delta variants, and 88.9% (84.7–90.9) for omicron BA.1 at 40 weeks ([Team 2022](#)). Most children and adolescents appear to have asymptomatic or non-severe symptomatic SARS-CoV-2 infections ([Viner 2020](#); [Forrest 2022](#)). SARS-CoV-2-related death in children and adolescents is rare ([Smith 2022](#)). However, COVID-19 can lead to severe outcomes in children and adolescents ([Marks 2022](#); [Shi 2022](#); [Preston 2021](#)). For example, coinciding with increased circulation of the Omicron variant in US, COVID-19–associated hospitalisation rates among children and adolescents aged 0–17 years in late December 2021 was about four times that of the Delta variant peak, yet the proportions of hospitalised children and adolescents requiring ICU admission (Delta = 27.8%; Omicron = 20.2%) or IMV (Delta = 6.3%; Omicron = 2.3%) were significantly lower during the Omicron period ([Marks 2022](#)). Most common chronic conditions associated with hospitalised paediatric patients are diabetes, gastrointestinal, neurological, cardiac, and pulmonary diseases, specifically asthma and obesity, but some of these conditions may not be necessarily causally associated with COVID-19 ([Forrest 2022](#); [Bailey 2021](#)).

Multisystem inflammatory syndrome (MIS) is a rare but serious condition associated with COVID-19 in which different body parts become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs. It can affect people who are younger than 21 years old (MIS-C) and adults 21 years and older (MIS-A) ([CDC 2023e](#)). The usual duration between acute infection and onset of MIS-C symptoms is two to 12 weeks ([Dufort 2020](#); [Ahmad 2021](#)). In contrast to acute COVID-19 infection in children, MIS-C appears to be a condition of higher severity with 68% of cases having required critical care support ([Radia 2021](#)). MIS shares features with other paediatric inflammatory syndromes such as Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome.

Post-acute sequelae of SARS-CoV-2 are characterised by a wide range of persistent symptoms such as fatigue, dyspnoea, chest pain, cognitive impairment, and sleeping disturbances that can last weeks, months or even years after infection ([Davis 2023](#); [Soriano 2022](#)). Studies show that around 10-20% of people infected by SARS-CoV-2 may go on to develop symptoms that have been diagnosed as “long COVID”. It is estimated that more than 17 million people across the WHO European Region may have experienced some form of post-COVID symptom persistence during the first two years of the pandemic (2020/21) ([WHO 2023c](#)). However, the exact numbers of those living with “long COVID” is uncertain, partly because of a lack of consensus of a case definition ([Soriano 2022](#)). A systematic review and meta-analysis by ECDC indicate that the risk of post COVID-19 condition may be higher amongst individuals who experience more severe COVID-19 disease ([ECDC 2022](#)). Current and future risks to populations for post COVID-19 condition in the context of increased levels of vaccination and hybrid immunity remain unknown.

Part II: Module SII – Nonclinical Part of the Safety Specification

Table 3 summarises the key nonclinical findings and their relevance to safety in humans. In summary, the nonclinical package, which consisted of both studies performed with elasomeran and with mRNA vaccines formulated in the same SM-102 lipid nanoparticle (LNP) vaccine matrix to support elasomeran use in human, shows no important identified or potential risks. A developmental and reproductive study with elasomeran in female Sprague-Dawley rats was completed in December 2020 with no adverse findings.

Table 3: Key Safety Findings From Nonclinical Studies and Relevance to Human Use

Study Type	Important Nonclinical Findings	Relevance to Human Use
Safety pharmacology and toxicology		
Vaccine enhanced disease and specific ERD studies	<p>Several nonclinical studies (e.g., disease pathology, immunoprofiling) in several species have been generated to address the theoretical risk of disease enhancement with elasomeran. In summary, vaccination with elasomeran generated a balanced ratio of IgG1 to IgG2a in mice, indicating a Th2-biased response is not observed. Robust neutralizing antibodies were induced post-vaccination in mice, hamsters, and NHPs following vaccination with elasomeran, with the indication of a Th1 dominant T-cell profile in mouse and NHP models. T-cell response was not measured in hamsters. This strengthens the argument that disease enhancement similar to that observed with previous RSV and measles vaccines is unlikely to be observed. After challenge, viral load and levels of replicating virus were measured in both the nasal passages and lungs of mice, hamsters, and NHPs. In animals vaccinated with higher doses of elasomeran, complete protection was observed. In animals dosed with low levels of elasomeran, some level of protection was evident, with no indications of increased viral load, demonstrating that ERD is not occurring. In addition, lung histopathology analyses after viral challenge in mice, hamsters, and NHPs post-vaccination is also reassuring, as these animals did not have evidence of enhanced disease.</p> <p>See further description below in text.</p>	<p>These nonclinical results show a lack of vaccine-enhanced pulmonary pathology post - challenge with elasomeran in relevant animal species.</p> <p>In addition, the clinical Phase 3 mRNA-1273-P301 study was designed to assess the risk of enhanced disease through continuous unblinded monitoring of cases by the DSMB with prespecified rules for determining harm based on an imbalance in cases unfavourable to elasomeran as defined in the analysis plan.</p> <p>As a result of these assessments, no safety concerns have been identified.</p>
Pharmacokinetics and Drug Metabolism		
Distribution Study	<p>A biodistribution study was performed with mRNA-1647, an mRNA-based vaccine against human cytomegalovirus also formulated in SM-102-containing LNPs. As observed with other IM-delivered vaccines, the highest mRNA concentrations were</p>	<p>The biodistribution of mRNA-based vaccines formulated in LNPs is consistent with administration of IM drug products and distribution via the lymphatics. mRNA does not</p>

Study Type	Important Nonclinical Findings	Relevance to Human Use
	<p>observed at the injection site of the male rat followed by the proximal (popliteal) and distal (axillary) lymph nodes, consistent with distribution via the lymphatic system. These tissues, as well as spleen and eye, had tissue-to-plasma AUC ratios > 1.0. Overall, only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues (ie, lung, liver, heart, kidney, axillary distal lymph nodes [bilateral pooled], proximal popliteal and inguinal lymph nodes [bilateral pooled], spleen, brain, stomach, testes, eye, bone marrow femur [bilateral pooled], jejunum [middle region], and injection site muscle), and the mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen where it persisted in general 5 days.</p>	<p>persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen where it persisted in general 5 days.</p>
Repeat-dose toxicity studies		
<p>Evaluation of mRNA vaccines formulated in the same SM-102 LNP vaccine matrix) in rat administered IM at doses ranging from 9 to 150 µg/dose once every 2 weeks for up to 6 weeks.</p>	<p>Clinical observations included generally dose-dependent erythema and edema at the injection site and transient increases in body temperature at 6 hours postdose returning to baseline 24 hours postdose were observed at ≥ 9 µg/dose. These observations resolved or were considered resolving within 72 hrs.</p> <p>There were clinical chemistry and hematology changes consistent with inflammatory responses (ie, increases in white blood cells, neutrophils, eosinophils, and decreased lymphocytes); minimal coagulation changes consisting of a slightly increased activated partial thromboplastin time and an associated increase in fibrinogen were observed.</p> <p>Clinical chemistry results indicated a decrease in albumin, increase in globulin, and a corresponding decrease in albumin/globulin ratio.</p> <p>In general, clinical pathology changes were dose-dependent and transient.</p> <p>Consistent with other indicators of systemic inflammation in response to vaccine administration, transient cytokine increases were observed at ≥ 9 µg/dose at 6 hours postdose including interferon gamma, monocyte chemoattractant protein-1, and macrophage inflammatory protein 1alpha. Increased cytokine/chemokines were generally resolved by the end of the 2-week recovery period.</p> <p>Macroscopic and microscopic changes were observed and included skin thickening at the</p>	<p>Review of the toxicology data found evidence of dose-dependent treatment-related effects at the injection site and systemic inflammatory responses to administration to the LNP.</p> <p>Clinical findings such as increased body temperature, injection site pain, other inflammation related findings</p> <p>In ongoing clinical Phase 1 and 2a studies with elasomeran, evaluation of safety clinical laboratory values of Grade 2 or higher revealed no patterns of concern. In the clinical Phase 3 mRNA-1273-P301 study, solicited local and systemic adverse reactions in the 7 days following administration, increased following the second dose. Solicited local adverse reactions, primarily injection site pain, were common.</p>

Study Type	Important Nonclinical Findings	Relevance to Human Use
	<p>injection site and enlarged lymph nodes. These observations were correlated with microscopic changes that included mixed cell inflammation at the injection site; increased cellularity and mixed cell inflammation in the lymph nodes. Additionally, decreased cellularity in the splenic periarteriolar lymphoid sheath; increased myeloid cellularity in the bone marrow; and hepatocyte vacuolation and Kupffer cell hypertrophy was occasionally observed in the liver. Changes were generally reversing by the end of the 2-week recovery period.</p>	
Other Nonclinical Toxicology Studies		
Evaluation of elasomeran at repeat doses, non-GLP immunogenicity rat study with non-terminal endpoints	<p>Elasomeran-related clinical signs were consistent with previous GLP toxicology studies on other mRNA-based vaccines. At doses ≥ 30 ug/dose observations included transient dose-dependent injection site edema with or without hindlimb impairment were observed at approximately 24 hours postdose and generally resolved within 7 days after dose administration. Clinical pathology associated with inflammation were observed and included increased neutrophils, eosinophils, and/or globulin. Other mild elasomeran-related changes observed at 30, 60, and/or 100 $\mu\text{g}/\text{dose}$ consisted of decreased red cell mass, reticulocytes, and lymphocytes and increased creatinine, triglyceride, cholesterol, and/or glucose.</p> <p>In general, these changes are consistent with the results from the previous GLP rat toxicity studies conducted with other mRNAs formulated in the SM-102 LNP.</p>	
Reproductive/development	<p>A developmental and reproductive toxicity study was performed with elasomeran in female Sprague-Dawley rats in December 2020 with no adverse findings noted. Elasomeran was at the clinical dose of 100 $\mu\text{g}/\text{dose}$. There were no maternal effects on mating and fertility, ovarian/uterine examinations, natural delivery or litter assessments. Further, there were no fetal and/or pup effects on in-life parameters, gross pathology, fetal sex, external or visceral assessments, or skeletal malformations. Non-adverse, common skeletal variations consisting of wavy ribs and increase nodules were observed at 100 $\mu\text{g}/\text{dose}$. The no observed adverse effect level is 100 μg, which on a mg/kg basis, provides a 137-fold safety</p>	<p>The risk for adverse pregnancy outcomes after exposure is unknown in humans, but nonclinical findings do not suggest a specific risk. Pregnancy is an exclusion criterion in the ongoing clinical trials.</p>

Study Type	Important Nonclinical Findings	Relevance to Human Use
	margin to 60-kg woman.	
Genotoxicity	<p>SM-102, the novel lipid used in the elasomera LNP formulation, was evaluated in as an individual agent in a bacterial reverse mutation (Ames) test and an in vitro micronucleus test in human peripheral blood lymphocytes. The results for SM-102 were negative. In addition, in vivo genotoxicity risk was assessed in a GLP-compliant rat micronucleus test using an mRNA-based vaccine formulated in SM-102-containing LNPs (mRNA-1706), the same formulation as elasomera. SM-102 induced a minimal, statistically significant increases in MIEs in male rats at both 24 and 48 hours and in female rats at 48 hours only; however, there was no clear dose response, and the increases were generally weak and associated with minimal bone marrow toxicity.</p> <p>A second, non-GLP, in vivo genotoxicity study was conducted using NPI luciferase mRNA in SM-102 containing LNPs. In this study, there was no significant increase in the incidence of micronuclei.</p> <p>The results of these two studies led to an equivocal result. Given the observed increases in body temperature observed in toxicology studies it is likely that drove the slight increases observed in micronuclei formation at high systemic (intravenous) doses. Overall, the genotoxic risk to humans is considered to be low due to minimal systemic exposure following IM administration, limited duration of exposure, and negative in vitro results.</p>	Nonclinical findings suggest that the risk to humans after IM administration is low, due to minimal systemic exposure and negative in vitro results.
Carcinogenicity	No carcinogenicity studies have been performed with elasomera.	N/A

CMV = cytomegalovirus; DSMB = data safety monitoring board; ERD = enhanced respiratory disease; GLP = Good Laboratory Practice; IgG = immunoglobulin G; IM = intramuscular; LNP = lipid nanoparticle; MIE = micronucleated immature erythrocytes; NHP = nonhuman primate; NPI = nascent peptide imaging; RSV = respiratory syncytial virus; Th = T-helper.

Vaccine-associated Disease Enhancement

There was a theoretical concern over the potential for vaccine associated disease enhancement in recipients of SARS-CoV-2 vaccines. The concern was that a SARS-CoV-2 vaccine could theoretically cause enhanced disease and specifically enhanced respiratory disease (ERD) in vaccines that were subsequently exposed to wild-type SARS-CoV-2. The potential for vaccination against SARS-CoV-2 to be associated with disease enhancement was a theoretical concern, given similar observations with other respiratory viruses in general, and in animal models of some highly pathogenic CoVs. This concern has been triggered by preclinical work on SARS-CoV and

MERS-CoV vaccines (Czub 2005; Deming 2006; Bolles 2011), the experience with feline infectious peritonitis virus and vaccines in cats (Takano 2008; Pedersen 2009; Pedersen 2012), and enhanced disease seen with respiratory syncytial virus, measles (Kim 1969; Polack 2007), and dengue vaccines in humans (Smatti 2018). Importantly, vaccine-associated disease enhancement has not been seen following SARS or MERS vaccines given to humans, albeit the number of people who received these experimental vaccines remains very small.

These events were associated either with macrophage-tropic CoVs susceptible to Ab-dependent enhancement of replication or with vaccine antigens that induced Ab with poor neutralizing activity and Th2-biased responses. The Vaccine Research Center of the NIH and the Sponsor performed nonclinical studies in mice, hamsters, and nonhuman primates (NHPs) to evaluate dose-ranging responses to elasomeran (immunogenicity), high-dose virus SARS-CoV-2 challenge (protection), and to address the theoretical concern of ERD mediated by vaccine-induced Ab responses and/or T helper (Th) 2 directed T-cell responses observed with other vaccines against viral respiratory diseases. These studies demonstrated that elasomeran is immunogenic in all species assessed, showing a dose-dependent response in IgG binding Ab titres and a significant correlation between bAb and nAb activity. In addition, antigen-specific T-cell responses were observed in studies in mice and in the NHP study. Th1-directed CD4+ and CD8+ T-cell responses were measured post boost in animals that were vaccinated with elasomeran. Direct measurement of Th1-directed responses in mice and NHPs, indirect measurement of IgG 2a/c/IgG1 Ab subclasses in mice, and the high levels of nAb in all species lessens concerns regarding disease enhancement associated with administration of elasomeran.

In addition to measurements of the immune response, mice, NHPs, and hamsters were challenged with high-dose SARS-CoV-2 virus. In these studies, dose levels of elasomeran that were predicted to be optimal (fully protective) and suboptimal (subprotective) were included. At higher doses, mice and NHPs were fully protected from viral replication in both lungs and nasal passages. At subprotective dose levels, animals either remained fully protected in the lungs or had reduced viral burden post-challenge versus control animals. There were no observations of increased viral load in vaccinated animals at protective or subprotective dose levels, which further supports that elasomeran does not drive enhanced disease. Lung histopathology assessments were performed to verify reduction of inflammation, immune complex deposition, and immune cell invasion in response to viral challenge in vaccinated animals versus placebo animals. In animals vaccinated with both optimal and suboptimal dose levels, histopathological evaluation of the lungs of mice and NHPs confirms the lack of ERD. This was demonstrated by the presence of minimal inflammation and lack of significant neutrophilic-associated alveolar disease or eosinophil-dominant inflammatory response measured, which have historically been associated with vaccine-associated ERD. In contrast, moderate to severe inflammation was elicited by SARS-CoV-2 infection in phosphate-buffered saline control animal groups, which often involved the small airways and the adjacent alveolar interstitial (Corbett 2020). These nonclinical disease pathology and immune profiling studies show immune signatures not predicted to associate with ERD and a lack of vaccine-enhanced viral replication or pulmonary pathology after challenge with SARS-CoV-2 in relevant animal species.

To further address the risk of enhanced disease, peripheral blood mononuclear cells were obtained from study participants in the Phase 1 study and restimulated to assess the cytokine profile post vaccination. The intracellular cytokine profile of the CD4+ and CD8+ T cells reflected a Th1-

rather than a Th2-directed response ([Jackson 2020](#)). These results were reassuring since the risk of enhanced disease has been previously associated with a Th2-directed immune response. In Study mRNA-1273-P301, prespecified harm rules designed to detect an imbalance in cases of COVID-19 or severe COVID-19 were not met. Most importantly, after a median follow-up of 2 months after the second dose of vaccine, the majority of COVID-19 cases occurred in participants who received placebo rather than elasomeran ([Baden 2021](#)), confirming no clinical evidence for vaccine enhanced disease following vaccination with elasomeran.

A conclusion of safety concerns for elasomeran based on nonclinical data is summarised in [Table 4](#).

Table 4: Conclusions on Safety Concerns Based on Nonclinical Data

Safety Concerns
Important identified risks: Not applicable
Important identified risks: Not applicable
Missing information: Not applicable

Part II: Module SIII – Clinical Trial Exposure

Seven clinical trials of elasomeran are ongoing and two clinical trials are completed as reported below. Two of the nine studies are sponsored by DMID of NIAID and include a dose-ranging Phase 1 safety and immunogenicity study 20-0003 (Phase 1 mRNA-1273-P101) and 21-0002 to evaluate safety and immunogenicity of a SARS-CoV-2 variant mRNA1273.351 in naïve and previously vaccinated adults. Study 20-0003 is completed. The remaining six ongoing studies are a Phase 2/3 safety, reactogenicity, and efficacy study in healthy adolescents ages 12 to < 18 years including an evaluation of the immunogenicity and safety of elasomeran booster and bivalent mRNA-1273.222 vaccine given as 2 primary doses (mRNA-1273-P203); a Phase 2/3, two-part, dose-escalation (open-label), age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of elasomeran SARS-CoV 2 vaccine in healthy children 6 months to less than 12 years of age including an evaluation of the immunogenicity and safety of elasomeran booster (mRNA-1273-P204); a Phase 3b, open-label, safety and immunogenicity study of SARS-CoV-2 elasomeran vaccine in adult solid organ transplant recipients and healthy controls (mRNA-1273-P304); a pivotal Phase 3 efficacy, safety, and immunogenicity study (mRNA-1273-P301); a Phase 2/3 8-part open-label study to evaluate the immunogenicity and safety of mRNA vaccine boosters for SARS-CoV-2 variants (mRNA-1273-P205); and a Phase 3, open-label, safety and immunogenicity 2-part study of mRNA-1273.214 vaccine in healthy children 6 months to less than 6 years of age (mRNA 1273 P306).

The second completed study is a dose-confirming Phase 2a safety and immunogenicity study (mRNA-1273-P201).

Table 5: Summary of vaccination groups by dose (µg) in the ongoing studies P301 (Part A), P203 (Part 1A, Part 1B and Part 1C), and P204 (Part 1, Part 2, and Part Booster Dose), and completed studies P201 (Part A) and (P101) 20-0003

Study	Dose					
	10 µg	25 µg	50 µg	100 µg	250 µg	Total
20-0003 (Phase 1 P101)	0	35	35	35	15	120
P201 Part A (Phase 2a)	0	0	200	200	0	400
P301 Part A (Phase 3)	0	0	0	15184	0	15184
P203 Parts 1A and 1B (Phase 2/3)	0	0	0	2486	0	2486
P203 Part 1C (Phase 2/3)	0	0	1346	0	0	1346
P204 Part 1 (Phase 2/3) ¹	0	219	535	371	0	1125
P204 Part 2 (Phase 2/3) ¹	0	4792	3007	0	0	7799
P204 Booster Dose (Phase 2/3) ¹	145	1294	0	0	0	1439

Note: Does not include DMID NIAID sponsored phase 1 study 21-0002 a Phase 1 open label study to evaluate safety and immunogenicity of prototypes and modified SARS-CoV-2 vaccines in naïve and previously vaccinated adults and mRNA-1273-P204

¹Includes children 6 months to < 12 years of age

Source:

Tables 2A-2C in Safety Summary Report Protocol 20-0003: Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (elasomeran) in Healthy Adults 26 October 2020; mRNA-1273-P201 (Part A) study Table 14.1.6.1 (Data extraction date: 11 June 2021); mRNA-1273-P203 study Table 14.1.6.1.4.2 (Data extraction date: 31 Jan 2022) and Table 14.1.1.1.5 (Data extraction date: 16 May 2022); mRNA-1273-P301 (Part A) study Table 14.1.6.2.1 (Data extraction date: 04 May 2021); mRNA-1273-P204 study Part 1 Table 14.1.5.1

and Part 2 [Table 14.1.5.2](#) (Data extraction date: 10 November 2021 and 21 February 2022), and Booster Dose [Table 14.1.6.5.1](#) (Data extraction date: 23 May 2022) and [Table 14.1.6.1](#) (Data extraction date: 18 August 2022).

Table 6: Summary of Vaccination groups by dose (µg) in the ongoing open label studies P301 (Part B), P304, P205 (Part A, Part G, Part F Cohort 2, and Part H 2nd Booster), P306 (Part 1 and Part 2), and completed study P201 (Part B)

Study	Dose			
	10 µg	50 µg	100 µg	Total
P201 Part B	0	173	171	344
P301 Part B	0	0	27832	27832
P304	0	0	138	138
P205 Part A (Phase 2/3) ¹	0	300	595	895
P205 Part G (Phase 2/3) ²	0	437	0	437
P205 Part F Cohort 2 (Phase 2/3) ³	0	377	0	377
P205 Part H 2 nd booster (Phase 2/3) ⁴	0	400	0	400
P306 Part 1	0	179	0	0
P306 Part 2	539	0	0	0

Note:

1 Part A includes mRNA-1273.211

2 Part G includes mRNA-1273.214

3 Part F includes Cohort 2 - mRNA-1273

4 Part H includes mRNA-1273.222. The planned number of participants is 400 and enrolment is currently ongoing.

Source:

mRNA-1273-P201 (Part B) study [Table 14.1.1.1](#) (Data extraction date 23 November 2021); mRNA-1273-P304 study (Data from ongoing trial as of 17 Dec 2021); mRNA-1273-P301 (Part B) study [Table 14.1.3.2.2](#) (Data extraction date: 04 May 2021)); mRNA-1273-P205 study Part A [Table 14.1.3.1](#) (Data extraction date: 02 February 2022); mRNA-1273-P205 study Part G/Part F (Cohort 2) [Table 14.1.1.8](#) (Data extraction date: 27 April 2022); mRNA-1273-P205 Part H [Table 10](#) Protocol Amendment 8 dated 01 August 2022; mRNA-1273-P306 study Part 1 [Table 14.1.3.2.1](#) (Data extraction date: 05 December 2022) and Part 2 [Table 14.1.3.2.2](#) (Data extraction date: 05 December 2022).

Study 20-0003 (Phase 1)

The open-label dose-finding Phase 1 safety and immunogenicity study ([NCT04283461](#)) enrolled 120 healthy adults 18 years of age and older to receive either 25 µg, 50 µg, 100 µg, or 250 µg of elasomeran. Participants received 2 doses of elasomeran given intramuscularly (IM) 28 days apart and were followed up until Day 394. Participants in the trial were offered the option to participate in a substudy in which they would receive a third elasomeran vaccination, administered via an IM injection at a dosage of 100 µg/0.5 mL, given 6 to 12 months after receipt of their second vaccination in the main study. Substudy participants were followed for safety, reactogenicity, and immunogenicity endpoints through 12 months post third vaccination (Substudy Day 366). The study is completed.

Table 7: Participant Exposure by Gender in the Completed 20-0003 Study

Gender	Males	Females	Total
Number of participants	61	59	120

Source: [Tables 2A-2C](#) in Safety Summary Report Protocol 20-0003: Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (elasomeran) in Healthy Adults 26 October 2020.

Table 8: Participant Exposure by Age in the Completed 20-0003 Study

Age (years old)	18-55	56-70	≥ 71	Total
Number of participants	60	30	30	120

Source: [Tables 2A-2C](#) in Safety Summary Report Protocol 20-0003: Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (elasomeran) in Healthy Adults 26 October 2020.

Table 9: Participant Exposure by Race/Ethnic Group in the Completed 20-0003 Study

Race/Ethnicity	Participants (n)
American Indian or Alaska Native	1
Asian	5
Native Hawaiian or Other Pacific Islander	0
Black	3
White	109
Multiracial	1
Unknown	1
Total	120

Source: [Tables 2A-2C](#) in Safety Summary Report Protocol 20-0003: Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (elasomeran) in Healthy Adults 26 October 2020.

Table 10: Summary of Vaccination Groups by Dose, Age Category, and Gender in the Completed 20-0003 Study

Elasomeran dose	25 µg	50 µg	100 µg	250 µg
All participants 18-55 years of age	15 (9 males; 6 females)	15 (9 males, 6 females)	15 (7 males, 8 females)	15 (6 males, 9 females)
All participants 56-70 years of age	10 (3 males, 7 females)	10 (5 males, 5 females)	10 (5 males, 5 females)	0
All participants ≥71 years of age	10 (8 males, 2 females)	10 (6 males, 4 females)	10 (3 males, 7 females)	0

Source: [Tables 2A-2C](#) in Safety Summary Report Protocol 20-0003: Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (elasomeran) in Healthy Adults 26 October 2020.

As of 17 Mar 2021, in study 20-0003 the subjects in Cohorts 1 through 5,7,8 and 10 through 12 have completed Study Milestones Day 209 (±7 days) visit (6 months after second vaccination).

mRNA-1273-P201 (Phase 2a)

The mRNA-1273-P201 is a completed three-part, Phase 2a study: Part A, Part B, and Part C. Part A is a randomized, placebo-controlled dose-confirming Phase 2a safety and immunogenicity study ([NCT04405076](#)) that enrolled 600 healthy adults 18 years of age and older in the US. Study participants were randomized 1:1:1 to receive placebo, elasomeran 50 µg, or elasomeran 100 µg. The study is divided into 2 cohorts by age, Cohort 1 with 300 participants (≥ 18 to < 55 years old)

and Cohort 2 with 300 participants (≥ 55 years old). Participants received 2 doses of elasomeran or placebo given IM 28 days apart and were followed up until Day 394. Part A, blinded Phase comprised a Participant Decision Clinic Visit (initiation of Part B) or Day 394 (Month 13), whichever was earlier.

Part B was designed to offer participants who received placebo in Part A of this study the option to receive 2 injections of open label elasomeran. Participants who received 1 or 2 doses of 50 μg or 100 μg elasomeran in Part A were offered a single booster dose of elasomeran (50 μg) in Part B.

Part C was a proof-of-concept rollover study of approximately 60 participants who were enrolled in Moderna's Phase 3 mRNA-1273-P301 study, have already been unblinded, and have previously received 2 doses of elasomeran at least 6 months earlier. Upon enrolment into Part C of this study, they received a single IM injection of mRNA-1273.351 (20 μg or 50 μg) or elasomeran/mRNA-1273.351 mixture (50 μg total) at least 6 months after receiving the second vaccination in the mRNA-1273-P301 study.

Table 11: Duration of Exposure in the Completed mRNA-1273-P201 Study (Part A)

Duration of Exposure	Dose		
	Elasomeran 50 μg	Elasomeran 100 μg	Total
Number of Participants, n (%)	200 (100)	200 (100)	400 (100)
Received First Injection	200 (100)	200 (100)	400 (100)
Received Second Injection	195 (97.5)	198 (99.0)	393 (98.3)
≥ 49 Days Since First Injection	197 (98.5)	200 (100)	397 (99.3)
≥ 56 Days Since First Injection	197 (98.5)	200 (100)	397 (99.3)
≥ 28 Days Since Second Injection	195 (97.5)	198 (99.0)	393 (98.3)
< 28 Days Since Second Injection	0	0	0
≥ 28 and < 56 Days Since Second Injection	2 (1.0)	0	2 (0.5)
≥ 56 Days Since Second Injection	193 (96.5)	198 (99.0)	391 (97.8)
Study Duration from First Injection (Days)			
Mean (Standard Deviation)	242.4 (38.38)	245.1 (28.30)	243.8 (33.7)
Median	245.0	246.0	245.0
Quartile 1, Quartile 3	229.0, 259.5	228.5, 260.0	229.0, 260.0
Minimum, Maximum	30, 346	58, 360	30, 360

Source: mRNA-1273-P201 Table 14.1.6.1 (Data extraction date: 11 June 2021).

Table 12: Age Group and Gender in the Completed mRNA-1273-P201 Study (Part A)

Age Group, N	Dose		
	Elasomeran 50 µg	Elasomeran 100 µg	Total
Adult, 18 – 64 years	150	157	307
Elderly, 65-74 years	42	37	79
Elderly, 75-84 years	6	5	11
Elderly, 85 + years	2	1	3
Gender			
Male	63	76	139
Female	137	124	261

Source: mRNA-1273-P201 Tables 14.1.6.2.1 and 14.1.6.2.3 (Data extraction date: 11 June 2021).

Table 13: Participant Race in the Completed mRNA-1273-P201 Study (Part A)

Race, N	Dose		
	Elasomeran 50 µg	Elasomeran 100 µg	Total (N)
White	188	188	376
Black or African American	5	8	13
Asian	2	2	4
American Indian or Alaska Native	2	1	3
Native Hawaiian or Other Pacific Islander	1	0	1
Multiple	1	0	1
Other	1	1	2

Source: mRNA-1273-P201 Table 14.1.6.2.4 and Table 14.1.6.1 (Data extraction date: 11 June 2021).

Table 14: Participant Ethnicity in the Completed mRNA-1273-P201 Study (Part A)

Ethnicity	Dose		
	Elasomeran 50 µg	Elasomeran 100 µg	Total (N)
Hispanic or Latino	15	16	31
Not Hispanic or Latino	184	184	368
Not Reported	1	0	1

Source: mRNA-1273-P201 Table 14.1.6.2.5 and Table 14.1.6.2.1 (Data extraction date: 11 June 2021).

Table 15: Participants in the Completed mRNA-1273-P201 Open label Study (Part B)

	Elasomeran Dose	
	50 ug (N= 200) n (%)	100 ug (N=200) n (%)
Number of Participants (N)		
Received First Open-Label Injection	173 (86.5)	171 (8)
Received second Open-Label Injection	0	0

Source: mRNA-1273-P201 (Part B) [Table 14.1.1.1](#) (Data extraction date 23 November 2021).

Table 16: Participant Age Group in the Completed mRNA-1273-P201 Study (Part B)

	Elasomeran Booster Dose	
	50 ug (N= 173)	100 ug (N= 171)
Age group, N		
Age ≥ 18 years and age < 55 years	80	82
Age ≥ 55 years	93	89

Source: mRNA-1273-P201 (Part B) [Table 14.1.1.1](#) (Data extraction date 23 November 2021).

Table 17: Participant Gender in the Completed mRNA-1273-P201 Study (Part B)

	Elasomeran Booster Dose	
	50 ug (N= 173)	100 ug (N= 171)
Gender, N		
Male	49	67
Female	124	104

Source: mRNA-1273-P201 Part B [Table 14.1.3.7.1](#) (Data extraction date 23 November 2021).

Table 18: Participant Race in the Completed mRNA-1273-P201 Study (Part B)

	Elasomeran Booster Dose	
	50 ug (N= 173)	100 ug (N=171)
Race, n (%)		
White	164 (94.8)	164 (95.9)
Black or African American	3 (1.7)	5 (2.9)
Asian	2 (1.2)	1 (0.6)
American Indian or Alaska Native	1 (0.6)	1 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.6)	0
Multiracial	1 (0.6)	0
Other	1 (0.6)	0

Source: mRNA-1273-P201 Part B [Table 14.1.3.7.1](#) (Extraction Date: 23 November 2021).

Table 19: Participant Ethnicity in the Completed mRNA-1273-P201 Study (Part B)

Ethnicity, n (%)	Elasomeran Booster Dose	
	50 µg (N= 173)	100 µg (N=171)
Hispanic or Latino	10 (5.8)	10 (5.8)
Not Hispanic or Latino	162 (93.6)	161 (94.2)
Not Reported	1 (0.6)	0

Source: mRNA-1273-P201 Part B Table 14.1.3.7.1 (Extraction Date: 23 November 2021).

A total of 60 participants who received 2 primary doses of elasomeran (100 µg) in mRNA-1273-P301 were selected to enter the mRNA-1273 variant booster phase (Part C) of the mRNA-1273-P201 study and assigned to study treatment: 20 participants to the 50 µg mRNA-1273.351 group (Cohort 1), 20 participants to the 50 µg elasomeran/mRNA-1273.351 group (Cohort 2), and 20 participants to the 20 µg mRNA-1273.351 group (Cohort 3) (Table 20 to Table 23).

Table 20: Participants in the Completed mRNA-1273-P201 Open label Study (Part C)

Number of Participants (N)	mRNA-1273.351 50 µg (Cohort 1) (N=20) n (%)	Elasomeran/ mRNA-1273.351 50 µg (Cohort 2) (N=20) n (%)	mRNA-1273.351 20 µg (Cohort 3) (N=20) n (%)
Received booster dose	20 (100)	20 (100)	20 (100)

Source: mRNA-1273-P201 Part C Table 14.1.1.1.2 (Extraction Date: 23 November 2021).

Table 21: Participant Age and Gender in the Completed mRNA-1273-P201 Study (Part C)

Age at Enrollment of mRNA-1273-P301 Study (Years)	mRNA-1273.351 50 µg (Cohort 1) (N=20)	Elasomeran/ mRNA-1273.351 50 µg (Cohort 2) (N=20)	mRNA-1273.351 20 µg (Cohort 3) (N=20)
Mean (SD)	53.9 (12.65)	55.6 (14.78)	47.5 (13.20)
Median	56.5	54.5	50.0
Min, Max	27, 70	28, 79	26, 67
Gender, n (%)			
Male	11 (55.0)	12 (60.0)	5 (25.0)
Female	9 (45.0)	8 (40.0)	15 (75.0)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.

Source: mRNA-1273-P201 Part C Table 14.1.3.12 (Extraction Date: 23 November 2021).

Table 22: Participant Race in the Completed mRNA-1273-P201 Study (Part C)

Race, n (%)	mRNA-1273.351 50 µg (Cohort 1) (N=20)	Elasomeran/ mRNA-1273.351 50 µg (Cohort 2) (N=20)	mRNA-1273.351 20 µg (Cohort 3) (N=20)
White	19 (95.0)	19 (95.0)	20 (100)
Black or African American	0	0	0
Asian	1 (5.0)	0	0
American Indian or Alaska Native	0	1 (5.0)	0
Native Hawaiian or Other Pacific Islander	0	0	0
Multiracial	0	0	0
Other	0	0	0
Not Reported	0	0	0
Unknown	0	0	0

Source: [mRNA-1273-P201 Part C Table 14.1.3.12](#) (Extraction Date: 23 November 2021).

Table 23: Participant Ethnicity in the Completed mRNA-1273-P201 Study (Part C)

Ethnicity, n (%)	mRNA-1273.351 50 µg (Cohort 1) (N=20)	Elasomeran/ mRNA-1273.351 50 µg (Cohort 2) (N=20)	mRNA-1273.351 20 µg (Cohort 3) (N=20)
Hispanic or Latino	0	1 (5.0)	1 (5.0)
Not Hispanic or Latino	20 (100)	19 (95.0)	19 (95.0)
Not Reported	0	0	0
Unknown	0	0	0

Source: [mRNA-1273-P201 Part C Table 14.1.3.12](#) (Extraction Date: 23 November 2021).

mRNA-1273-P203 (Phase 2/3)

Part 1 of Phase 2/3 study (mRNA-1273-P203) is a 3-part (Part A, Part B and Part C) study of the safety, reactogenicity, and efficacy of elasomeran in healthy adolescents ages 12 to < 18 years. Part 1A is a randomized, observer-blind, placebo-controlled study of adolescents randomly assigned 2:1 to receive either 2 injections of 100 µg of elasomeran vaccine or 2 injections of placebo control each given 28 days apart. Part 1B is an open-label observational phase designed to offer participants who received placebo in Part 1A of the study and who meet the EUA eligibility criteria an option to request and receive elasomeran. The study enrolled a total of 2486 participants who received elasomeran vaccine. In Part 1C, all study participants were offered elasomeran as a 50 µg booster and a total of 1346 participants 12 years to < 18 years of age who completed the 100 µg elasomeran primary series received a 50 µg elasomeran booster dose.

Part 2 of mRNA-1273-P203 is an open-label design. The study will evaluate the safety, reactogenicity, and effectiveness of a 50 µg primary series of mRNA-1273 SARS CoV 2 vaccine in healthy adolescents 12 to < 18 years of age. Part 3 (open-label, single-arm design) will evaluate the safety, reactogenicity, and effectiveness of a 2-dose 50 µg primary series of mRNA-1273.222 SARS-CoV-2 vaccine, administered 6 months apart, in approximately 500 healthy adolescents 12 to <18 years of age.

Table 24: Duration of Exposure in Parts 1A and 1B of the Ongoing mRNA-1273-P203 Study (12 Years to < 18 Years)

Duration of Exposure, n (%)	Elasomeran (N=2486)
Received First Injection	2486 (100)
Received Second Injection	2480 (99.8)
≥ 7 Days Since First Injection	2486 (100)
≥ 35 Days Since First Injection	2480 (99.8)
≥ 56 Days Since First Injection	2458 (98.9)
≥ 7 Days Since Second Injection	2474 (99.5)
≥ 28 Days Since Second Injection	2457 (98.8)
≥ 56 Days Since Second Injection	2439 (98.1)
≥ 84 Days Since Second Injection	2419 (97.3)
≥ 112 Days Since Second Injection	2406 (96.8)
≥ 140 Days Since Second Injection	2398 (96.5)
≥ 168 Days Since Second Injection	2376 (95.6)
≥ 196 Days Since Second Injection	2340 (94.1)
≥ 224 Days Since Second Injection	2301 (92.6)
≥ 252 Days Since Second Injection	2267 (91.2)
≥ 280 Days Since Second Injection	2198 (88.4)
≥ 308 Days Since Second Injection	1424 (57.3)
≥ 336 Days Since Second Injection	349 (14.0)
≥ 364 Days Since Second Injection	33 (1.3)
Study Duration from First Injection (Days)	
Mean (Standard Deviation)	330.6 (57.07)
Median	342.0
Quartile 1, Quartile 3	326.0, 356.0
Minimum, Maximum	30, 419

Source: mRNA-1273-P203 Table 14.1.6.1.4.2 (31 Jan 2022).

Table 25: Age Group and Gender in Parts 1A and 1B of the Ongoing mRNA-1273-P203 Study (12 Years to < 18 Years)

Characteristic	Elasomeran (N=2486)
Age Group, N	
≥ 12 years and < 16 years	1838
≥ 16 years and < 18 years	648
Gender, N	
Male	1283
Female	1203
Total	2486

Source: [mRNA-1273-P203 Table 14.1.3.13.1](#) (31 Jan 2022).

Table 26: Participant Race in Parts 1A and 1B of the Ongoing mRNA-1273-P203 Study (12 Years to < 18 Years)

Characteristic	Elasomeran (N=2486)
Race, N	
White	2084
Black or African American	83
Asian	142
American Indian or Alaska Native	12
Native Hawaiian or Other Pacific Islander	3
Multiple	118
Other	27
Not Reported	11
Unknown	6
Total	2486

Source: [mRNA-1273-P203 Table 14.1.3.13.1](#) (31 Jan 2022).

Table 27: Participant Ethnicity in Parts 1A and 1B of the Ongoing mRNA-1273-P203 Study (12 Years to < 18 Years)

Characteristic	Elasomeran (N=2486)
Ethnicity, N	
Hispanic or Latino	280
Not Hispanic or Latino	2186
Not Reported	19
Unknown	1
Total	2486

Source: mRNA-1273-P203 Table 14.1.3.13.1 (31 Jan 2022).

Table 28: Duration of Exposure in the Ongoing mRNA-1273-P203 Study (Part 1C, Booster Dose) (12 Years to < 18 Years)

Duration of Exposure, n (%)	Placebo- elasomeran -Booster (N=18)	Elasomeran- Booster (N=1346)	Total (N=1364)
Received Booster	18 (100)	1346 (100)	1364 (100)
< 168 Days	13 (72.2)	0	13 (1.0)
≥ 168 and < 196 Days	5 (27.8)	0	5 (0.4)
≥ 196 and < 224 Days	0	0	0
≥ 224 and < 252 Days	0	0	0
≥ 252 and < 280 Days	0	10 (0.7)	10 (0.7)
≥ 280 and < 308 Days	0	529 (39.3)	529 (38.8)
≥ 308 and < 336 Days	0	427 (31.7)	427 (31.3)
≥ 336 and < 364 Days	0	243 (18.1)	243 (17.8)
≥ 364 and < 392 Days	0	115 (8.5)	115 (8.4)
≥ 392 and < 420 Days	0	19 (1.4)	19 (1.4)
≥ 420 Days	0	3 (0.2)	3 (0.2)
Time on Study from Dose 1 of mRNA-1273 (Days)			
Mean (SD)	208.7 (11.50)	460.7 (16.55)	457.4 (33.16)
Median	210.0	456.0	456.0
Q1, Q3	204.0, 217.0	448.0, 470.0	448.0, 470.0
Min, Max	169, 221	347, 524	169, 524
Person-years from Dose 1 of mRNA-1273 [3]	10.3	1697.9	1708.2
Time Since Primary Series Dose 2 to Booster (Days) [1]			
Mean (SD)	157.3 (26.00)	321.5 (27.55)	319.3 (33.29)
Median	158.0	316.0	315.0
Q1, Q3	155.0, 169.0	300.0, 338.0	299.0, 337.0
Min, Max	63, 184	274, 422	63, 422
Follow-Up Time on Study After Booster (Days)			
Mean (SD)	21.3 (13.05)	109.2 (23.08)	108.0 (25.07)
Median	21.0	117.0	116.0
Q1, Q3	18.0, 22.0	98.0, 125.0	96.0, 125.0
Min, Max	4, 64	2, 141	2, 141
< 28 Days	16 (88.9)	19 (1.4)	35 (2.6)
≥ 28 Days	2 (11.1)	1327 (98.6)	1329 (97.4)
≥ 28 and < 56 Days	1 (5.6)	38 (2.8)	39 (2.9)
≥ 56 Days	1 (5.6)	1289 (95.8)	1290 (94.6)
≥ 84 Days	0	1174 (87.2)	1174 (86.1)
≥ 112 Days	0	736 (54.7)	736 (54.0)
≥ 140 Days	0	4 (0.3)	4 (0.3)
Person-years from Booster [2]	1.1	402.3	403.4

Source: mRNA-1273-P203 Table 14.1.6.5.1 (16 May 2022).

Table 29: Age Group and Gender in the Ongoing mRNA-1273-P203 Study (Part 1C, Booster Dose) (12 Years to < 18 Years)

Characteristic	Placebo-elasomeran-Booster (N=18)	Elasomeran-Booster (N=1346)	Total (N=1364)
Age Group, n (%)			
16 to <18 years	4 (22.2)	267 (19.8)	271 (19.9)
12 to <16 years	14 (77.8)	1079 (80.2)	1093 (80.1)
Gender, n (%)			
Female	10 (55.6)	655 (48.7)	665 (48.8)
Male	8 (44.4)	691 (51.3)	699 (51.2)

Source: mRNA-1273-P203 Table 14.1.3.14.1 (16 May 2022).

Table 30: Participant Race in the Ongoing mRNA-1273-P203 Study (Part 1C, Booster Dose) (12 Years to < 18 Years)

Characteristic	Placebo-elasomeran-Booster (N=18)	Elasomeran-Booster (N=1346)	Total (N=1364)
Race, n (%)			
American Indian or Alaska Native	0	7 (0.5)	7 (0.5)
Asian	0	66 (4.9)	66 (4.8)
Black	0	43 (3.2)	43 (3.2)
Native Hawaiian or Other Pacific Islander	0	1 (<0.1)	1 (<0.1)
White	18 (100)	1140 (84.7)	1158 (84.9)
Other	0	10 (0.7)	10 (0.7)
Multiracial	0	71 (5.3)	71 (5.2)
Not reported	0	4 (0.3)	4 (0.3)
Unknown	0	4 (0.3)	4 (0.3)

Source: mRNA-1273-P203 Table 14.1.3.14.1 (16 May 2022).

Table 31: Participant Ethnicity in the Ongoing mRNA-1273-P203 Study (Part 1C, Booster Dose) (12 Years to < 18 Years)

Characteristic	Placebo-elasomeran-Booster (N=18)	Elasomeran-Booster (N=1346)	Total (N=1364)
Ethnicity, n (%)			
Hispanic or Latino	8 (44.4)	171 (12.7)	179 (13.1)
Not Hispanic or Latino	10 (55.6)	1164 (86.5)	1174 (86.1)
Not reported	0	11 (0.8)	11 (0.8)

Source: mRNA-1273-P203 Table 14.1.3.14.1 (16 May 2022).

mRNA-1273-P204 study

A Phase 2/3, two-part, dose-escalation (open-label), age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and

effectiveness of elasomeran SARS-CoV 2 vaccine in healthy children 6 months to less than 12 years of age.

The study population was evaluated in 3 discrete age groups (6 years through 11 years, 2 years to < 6 years, and 6 months to < 2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of elasomeran in the primary series. The study has two parts. Part 1 is the open-label, dose-escalation, age de-escalation phase. Part 2 is the randomized, observer-blind, placebo-controlled expansion phase which evaluated the selected dose of elasomeran.

In total, 751 children 6 years to < 12 years of age were treated in Part 1 (380 elasomeran 50 µg and 371 elasomeran 100 µg) and 4002 children 6 years to < 12 years of age were treated in Part 2 (3007 elasomeran 50 µg and 995 placebo) ([Table 32](#) to [Table 39](#)). Participants in Part 1 are distinct from those in Part 2.

Following evidence of enhanced effectiveness of the adult booster dose (BD), study mRNA-1273-P204 was amended to offer a BD (elasomeran, 25 µg) to all children enrolled in the 6 through 11 years age group, which could be administered starting 6 months post-dose 2 of the primary series. A total of 1,294 participants received a 25 µg BD in the Booster Dose Phase of the study.

Table 32: Summary of Study Duration by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Duration of Exposure	Elasomeran 50 µg (N=380)	Elasomeran 100 µg (N=371)	Total (N=751)
≥ 7 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 35 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 56 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 7 days since second injection, n (%)	379 (99.7)	371 (100)	750 (99.9)
≥ 28 days since second injection, n (%)	379 (99.7)	371 (100)	750 (99.9)
≥ 56 days since second injection, n (%)	379 (99.7)	370 (99.7)	749 (99.7)
Study duration from dose 1, days			
Median (min, max)	175.0 (149, 241)	170.0 (76, 204)	173.0 (76, 241)
Study duration from dose 2, days			
Median (min, max)	146.0 (0, 212)	141.0 (41, 174)	143.0 (0, 212)

Abbreviations: max = maximum; min = minimum.

Percentages are based on the number of participants in the Part 1 Safety Set,

Source: [Study mRNA-1273-P204 Table 14.1.5.1](#)

Data from ongoing trial as of 10 November 2021

Table 33: Summary of Blinded Study Duration in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Duration of Exposure	Elasomeran 50 µg (N=3007)	Placebo (N=995)	Total (N=4002)
Received first injection, n (%)	3007 (100)	995 (100)	4002 (100)
Received second injection, n (%)	2990 (99.4)	971 (97.6)	3961 (99.0)

Duration of Exposure	Elasomeran 50 µg (N=3007)	Placebo (N=995)	Total (N=4002)
≥ 7 days since first injection, n (%)	3007 (100)	995 (100)	4002 (100)
≥ 56 days since first injection, n (%)	2995 (99.6)	986 (99.1)	3981 (99.5)
≥ 7 days since second injection, n (%)	2990 (99.4)	971 (97.6)	3961 (99.0)
≥ 28 days since second injection, n (%)	2981 (99.1)	966 (97.1)	3947 (98.6)
≥ 56 days since second injection, n (%)	1066 (35.5)	218 (21.9)	1284 (32.1)
Study duration from dose 1, days			
Median (min, max)	83.0 (29, 94)	79.0 (14, 94)	82.0 (14, 94)
Study duration from dose 2, days			
Median (min, max)	52.0 (8, 65)	49.0 (10, 65)	51.0 (8, 65)

Abbreviations: max = maximum; min = minimum.

Percentages are based on the number of participants in the Part 2 Safety Set,

Source: [Study mRNA-1273-P204 Table 14.1.5.2](#)

Data from ongoing trial as of 10 November 2021

Table 34: Participant Age and Gender by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg (N=380)	Elasomeran 100 µg (N=371)	Total (N=751)
Age, years			
Mean (SD)	8.6 (1.66)	8.6 (1.62)	8.6 (1.64)
Median	9.0	9.0	9.0
Min, max	6, 11	6, 11	6, 11
Sex, n (%)			
Male	195 (51.3)	172 (46.4)	367 (48.9)
Female	185 (48.7)	199 (53.6)	384 (51.1)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 10 November 2021.

Table 35: Participant Age and Gender in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg (N=3007)	Placebo (N=995)	Total (N=4002)
Age, years			
Mean (SD)	8.5 (1.65)	8.5 (1.64)	8.5 (1.65)
Median	8.0	9.0	9.0
Min, Max	6, 11	6, 11	6 ^a , 11
Sex, n (%)			
Male	1554 (51.7)	481 (48.3)	2035 (50.8)
Female	1453 (48.3)	514 (51.7)	1967 (49.2)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 10 November 2021.

Table 36: Participant Race by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg (N=380)	Elasomeran 100 µg (N=371)	Total (N=751)
Race, n (%)			
White	266 (70.0)	284 (76.5)	550 (73.2)
Black	34 (8.9)	13 (3.5)	47 (6.3)
Asian	28 (7.4)	25 (6.7)	53 (7.1)
American Indian or Alaska Native	0	2 (0.5)	2 (0.3)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	1 (0.1)
Multiracial	39 (10.3)	31 (8.4)	70 (9.3)
Other	3 (0.8)	10 (2.7)	13 (1.7)
Not reported	9 (2.4)	4 (1.1)	13 (1.7)
Unknown	0	2 (0.5)	2 (0.3)

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 10 November 2021.

Table 37: Participant Race in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg (N=3007)	Placebo (N=995)	Total (N=4002)
Race, n (%)			
White	1957 (65.1)	668 (67.1)	2625 (65.6)
Black	309 (10.3)	93 (9.3)	402 (10.0)
Asian	298 (9.9)	100 (10.1)	398 (9.9)
American Indian or Alaska Native	14 (0.5)	3 (0.3)	17 (0.4)
Native Hawaiian or other Pacific Islander	4 (0.1)	0	4 (< 0.1)
Multiracial	327 (10.9)	97 (9.7)	424 (10.6)
Other	62 (2.1)	22 (2.2)	84 (2.1)
Not reported	28 (0.8)	10 (1.0)	33 (0.8)
Unknown	9 (0.3)	1 (0.1)	10 (0.2)
Missing	4 (0.1)	1 (0.1)	5 (0.1)

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 10 November 2021.

Table 38: Participant Ethnicity by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg (N=380)	Elasomeran 100 µg (N=371)	Total (N=751)
Ethnicity, n (%)			
Hispanic or Latino	72 (18.9)	69 (18.6)	141 (18.8)
Not Hispanic or Latino	304 (80.0)	296 (79.8)	600 (79.9)

Characteristic	Elasomeran 50 µg (N=380)	Elasomeran 100 µg (N=371)	Total (N=751)
Not reported	3 (0.8)	3 (0.8)	6 (0.8)
Unknown	1 (0.3)	3 (0.8)	4 (0.5)

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 10 November 2021.

Table 39: Participant Ethnicity in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg (N=3007)	Placebo (N=995)	Total (N=4002)
Ethnicity, n (%)			
Hispanic or Latino	561 (18.7)	181 (18.2)	742 (18.5)
Not Hispanic or Latino	2417 (80.4)	805 (80.9)	3222 (80.5)
Not reported	22 (0.7)	5 (0.5)	27 (0.7)
Unknown	7 (0.2)	4 (0.4)	11 (0.3)

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 10 November 2021.

A total of 1294 children 6 years to < 12 years of age were administered a booster dose (elasomeran 25 µg) in the Booster Dose Phase of the study ([Table 40](#) to [Table 43](#)).

Table 40: Summary of Study Duration in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Duration of exposure, n (%)	Elasomeran 50 µg Primary Series - Booster (N=1294)
Received First Injection	1294 (100)
Received Second Injection	1294 (100)
< 168 Days Since Primary Series	3 (0.2)
≥ 168 and < 196 Days	48 (3.7)
≥ 196 and < 224 Days	566 (43.7)
≥ 224 and < 252 Days	480 (37.1)
≥ 252 and < 280 Days	21 (1.6)
≥ 280 and < 308 Days	72 (5.6)
≥ 308 and < 336 Days	66 (5.1)
≥ 336 and < 364 Days	26 (2.0)
≥ 364 Days	12 (0.9)
Time Since First Injection to Second Injection (Days)	
n	1294
Mean (SD)	30.9 (2.62)
Median	30.0
Q1, Q3	29.0, 32.0

	Elasomeran 50 µg Primary Series - Booster (N=1294)
Duration of exposure, n (%)	
Min, Max	27, 47
< 21 Days Since First Injection	0
≥ 21 and ≤ 42 Days Since First Injection	1284 (99.2)
> 42 Days and ≤ 56 Days Since First Injection	10 (0.8)
> 56 Days Since First Injection	0
Received Booster	1294 (100)
Time Since Primary Series Dose 2 to Booster (Days) [1]	
n	1294
Mean (SD)	235.0 (37.63)
Median	225.0
Q1, Q3	213.0, 239.0
Min, Max	124, 378
Follow-Up Time on Study After Booster (Days)	
n	1294
Mean (SD)	29.0 (13.68)
Median	29.0
Q1, Q3	18.0, 40.0
Min, Max	1, 57
< 28 Days	577 (44.6)
≥ 28 Days	717 (55.4)
≥ 28 and < 56 Days	694 (53.6)
≥ 56 Days	23 (1.8)
Person-years from Booster [2]	102.74
Time on Study from Dose 1 of mRNA-1273 (Days)	
n	1294
Mean (SD)	292.9 (35.95)
Median	280.5
Q1, Q3	277.0, 287.0
Min, Max	183, 434
Person-years from Dose 1 of mRNA-1273 [3]	1037.63

Percentages are based on the number of safety subjects in booster dose analysis.

[1] For subjects who received two doses of elasomeran in Primary Series, Time Since Primary Series is calculated as: Date of Booster — Date of Second Dose of elasomeran + 1.

[2] Person-years is defined as the total years from the booster dose date to the earlier date of study discontinuation or data cutoff.

[3] Person-years is defined as the total years from the first dose date of elasomeran to the earlier date of study discontinuation or data cutoff.

Source: [Study mRNA-1273-P204 Table 14.1.6.2](#) (23 May 2022).

Table 41: Participant Age Group and Gender by Dose Level in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg Primary Series - Booster (N=1294)
Age group (Years), n%	
≥ 6 and < 9	653 (50.5)
≥ 9 and < 12	641 (49.5)
Age (Years), n (%)	
6	194 (15.0)
7	204 (15.8)
8	255 (19.7)
9	235 (18.2)
10	235 (18.2)
11	171 (13.2)
Age (Years)	
n	1294
Mean (SD)	8.5 (1.62)
Median	8.0
Q1, Q3	7.0, 10.0
Min, Max	6, 11
Gender, n (%)	
Male	672 (51.9)
Female	622 (48.1)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.

Source: [mRNA-1273-P204 Table 14.1.3.13.2](#) (23 May 2022).

Table 42: Participant Race by Dose Level in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg Primary Series - Booster (N=1294)
Race, n (%)	
White	850 (65.7)
Black	142 (11.0)
Asian	101 (7.8)
American Indian or Alaska Native	6 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)
Multiracial	153 (11.8)
Other	24 (1.9)
Not reported	14 (1.1)
Unknown	3 (0.2)

Source: [mRNA-1273-P204 Table 14.1.3.13.2](#) (23 May 2022).

Table 43: Participant Ethnicity by Dose Level in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Years to < 12 Years)

Characteristic	Elasomeran 50 µg Primary Series - Booster (N=1294)
Ethnicity, n (%)	
Hispanic or Latino	202 (15.6)
Not Hispanic or Latino	1079 (83.4)
Not reported	10 (0.8)
Unknown	3 (0.2)

Source: [mRNA-1273-P204 Table 14.1.3.13.2](#) (23 May 2022).

In mRNA-1273-P204, a total of 224 children 2 years to < 6 years of age were treated in Part 1 (69 elasomeran 25 µg and 155 elasomeran 50 µg) and 4038 children 2 years to < 6 years of age were treated in Part 2 (3031 elasomeran 25 µg and 1007 placebo) ([Table 44](#) to [Table 51](#)).

Table 44: Summary of Study Duration by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

Duration of Exposure	Elasomeran 25 µg (N=69)	Elasomeran 50 µg (N=155)	Total (N=224)
≥ 7 days since first injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 35 days since first injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 56 days since first injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 7 days since second injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 56 days since second injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 140 days since second injection, n (%)	69 (100)	155 (100)	224 (100)
Study duration from dose 1, days			
Median (min, max)	236.0 (224, 238)	266.0 (204, 307)	263.0 (204, 307)
Study duration from dose 2, days			
Median (min, max)	207.0 (189, 210)	237.0 (173, 274)	231.0 (173, 274)

Abbreviations: max = maximum; min = minimum.

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.5.1](#)

Data from ongoing trial as of 21 February 2022.

Table 45: Summary of Blinded Study Duration in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

Duration of Exposure	Elasomeran 25 µg (N=3031)	Placebo (N=1007)	Total (N=4038)
Received first injection, n (%)	3031 (100)	1007 (100)	4038 (100)
Received second injection, n (%)	2960 (97.7)	970 (96.3)	3930 (97.3)
≥ 7 days since first injection, n (%)	3027 (99.9)	1004 (99.7)	4031 (99.8)
≥ 56 days since first injection, n (%)	2765 (91.2)	908 (90.2)	3673 (91.0)

	Elasomeran 25 µg (N=3031)	Placebo (N=1007)	Total (N=4038)
Duration of Exposure			
≥ 7 days since second injection, n (%)	2902 (95.7)	957 (95.0)	3859 (95.6)
≥ 28 days since second injection, n (%)	2713 (89.5)	892 (88.6)	3605 (89.3)
≥ 56 days since second injection, n (%)	2180 (71.9)	710 (70.5)	2890 (71.6)
≥ 84 days since second injection, n (%)	654 (21.6)	202 (20.1)	856 (21.2)
Study duration from dose 1, days			
Median (min, max)	103.0 (0, 127)	102.0 (1, 127)	103.0 (0, 127)
Study duration from dose 2, days			
Median (min, max)	71.0 (0, 99)	70.0 (0, 99)	71.0 (0, 99)

Abbreviations: max = maximum; min = minimum.

Percentages are based on the number of participants in the Part 2 Safety Set.

Participants received second injection after unblinding date are excluded. Study duration from second injection is 0 days for participants who received second injection with same unblinding date.

Source: [Study mRNA-1273-P204 Table 14.1.5.2](#)

Data from ongoing trial as of 21 February 2022.

Table 46: Participant Age Group and Gender by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

	Elasomeran 25 µg (N=69)	Elasomeran 50 µg (N=155)	Total (N=224)
Characteristic			
Age group, n (%)			
≥ 2 years and < 4 years	32 (46.4)	65 (41.9)	97 (43.3)
≥ 4 years and < 6 years	37 (53.6)	90 (58.1)	127 (56.7)
≥ 2 years and ≤ 36 months	9 (13.0)	26 (16.8)	35 (15.6)
> 36 months and < 6 years	60 (87.0)	129 (83.2)	189 (84.4)
Sex, n (%)			
Male	36 (52.2)	80 (51.6)	116 (51.8)
Female	33 (47.8)	75 (48.4)	108 (48.2)

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 21 February 2022.

Table 47: Participant Age Group and Gender in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

	Elasomeran 25 µg (N=3031)	Placebo (N=1007)	Total (N=4038)
Characteristic			
Age group, n (%)			
< 2 years ^a	24 (0.8)	12 (1.2)	36 (0.9)
≥ 2 years and < 4 years	2057 (67.9)	655 (65.0)	2712 (67.2)
≥ 4 years and < 6 years	950 (31.3)	340 (33.8)	1290 (31.9)
≥ 2 years and ≤ 36 months	999 (33.0)	345 (34.3)	1344 (33.3)
> 36 months and < 6 years	2032 (67.0)	662 (65.7)	2694 (66.7)
Sex, n (%)			
Male	1543 (50.9)	510 (50.6)	2053 (50.8)
Female	1488 (49.1)	497 (49.4)	1985 (49.2)

Abbreviations: IRT = interactive response technology.

Percentages are based on the number of participants in the Part 2 Safety Set.

*Some participants < 2 years were included in the ≥ 2 to 6 year subgroup, likely because of coincident enrollment of both age groups, entry errors at the time of randomization and other limitations of the IRT system.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 21 February 2022.

Table 48: Participant Race by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

Characteristic	Elasomeran 25 µg (N=69)	Elasomeran 50 µg (N=155)	Total (N=224)
Race, n (%)			
White	49 (71.0)	133 (85.8)	182 (81.3)
Black	3 (4.3)	7 (4.5)	10 (4.5)
Asian	8 (11.6)	3 (1.9)	11 (4.9)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	3 (4.3)	10 (6.5)	13 (5.8)
Other	6 (8.7)	2 (1.3)	8 (3.6)
Not reported	0	0	0
Unknown	0	0	0

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 21 February 2022.

Table 49: Participant Race in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

Characteristic	Elasomeran 25 µg (N=3031)	Placebo (N=1007)	Total (N=4038)
Race, n (%)			
White	2297 (75.8)	792 (78.6)	3089 (76.5)
Black	142 (4.7)	38 (3.8)	180 (4.5)
Asian	191 (6.3)	51 (5.1)	242 (6.0)
American Indian or Alaska Native	12 (0.4)	3 (0.3)	15 (0.4)
Native Hawaiian or other Pacific Islander	7 (0.2)	4 (0.4)	11 (0.3)
Multiracial	322 (10.6)	99 (9.8)	421 (10.4)
Other	43 (1.4)	16 (1.6)	59 (1.5)
Not reported	13 (0.4)	4 (0.4)	17 (0.4)
Unknown	4 (0.1)	0	4 (0.1)

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 21 February 2022.

Table 50: Participant Ethnicity by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

Characteristic	Elasomeran 25 µg (N=69)	Elasomeran 50 µg (N=155)	Total (N=224)
Ethnicity, n (%)			

Characteristic	Elasomeran 25 µg (N=69)	Elasomeran 50 µg (N=155)	Total (N=224)
Hispanic or Latino	18 (26.1)	23 (14.8)	41 (18.3)
Not Hispanic or Latino	51 (73.9)	129 (83.2)	180 (80.4)
Not reported	0	3 (1.9)	3 (1.3)
Unknown	0	0	0

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 21 February 2022.

Table 51: Participant Ethnicity in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (2 Years to < 6 Years)

Characteristic	Elasomeran 25 µg (N=3031)	Placebo (N=1007)	Total (N=4038)
Ethnicity, n (%)			
Hispanic or Latino	433 (14.3)	142 (14.1)	575 (14.2)
Not Hispanic or Latino	2579 (85.1)	856 (85.0)	3435 (85.1)
Not reported	14 (0.5)	8 (0.8)	22 (0.5)
Unknown	5 (0.2)	1 (0.1)	6 (0.1)

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 21 February 2022.

A total of 150 children 6 months to < 2 years of age were treated in Part 1 (elasomeran 25 µg) and 2350 children 6 months to < 2 years of age were treated in Part 2 (1761 elasomeran 25 µg and 589 placebo) ([Table 52](#) to [Table 59](#)).

Table 52: Summary of Study Duration by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Duration of Exposure	Elasomeran 25 µg (N=150)
≥ 7 days since first injection, n (%)	150 (100)
≥ 35 days since first injection, n (%)	150 (100)
≥ 56 days since first injection, n (%)	150 (100)
≥ 7 days since second injection, n (%)	150 (100)
≥ 28 days since second injection, n (%)	150 (100)
≥ 56 days since second injection, n (%)	150 (100)
≥ 140 days since second injection, n (%)	149 (99.3)
Study duration from dose 1, days	
Median (min, max)	263.0 (134, 278)
Study duration from dose 2, days	
Median (min, max)	233.5 (101, 249)

Abbreviations : max = maximum; min = minimum.

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.5.1](#)

Data from ongoing trial as of 21 February 2022.

Table 53: Summary of Blinded Study Duration in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Duration of Exposure	Elasomeran 25 µg (N=1761)	Placebo (N=589)	Total (N=2350)
Received first injection, n (%)	1761 (100)	589 (100)	2350 (100)
Received second injection, n (%)	1601 (90.9)	528 (89.6)	2129 (90.6)
≥ 7 days since first injection, n (%)	1729 (98.2)	581 (98.6)	2310 (98.3)
≥ 56 days since first injection, n (%)	1503 (85.3)	490 (83.2)	1993 (84.8)
≥ 7 days since second injection, n (%)	1578 (89.6)	515 (87.4)	2093 (89.1)
≥ 28 days since second injection, n (%)	1470 (83.5)	482 (81.8)	1952 (83.1)
≥ 56 days since second injection, n (%)	1138 (64.6)	368 (62.5)	1506 (64.1)
≥ 84 days since second injection, n (%)	276 (15.7)	91 (15.4)	367 (15.6)
Study duration from dose 1, days			
Median (min, max)	98.0 (1, 127)	97.0 (1, 127)	98.0 (1, 127)
Study duration from dose 2, days			
Median (min, max)	68.0 (0, 99)	68.0 (0, 99)	68.0 (0, 99)

Abbreviations: max = maximum; min = minimum.

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.5.2](#)

Data from ongoing trial as of 21 February 2022.

Table 54: Participant Age Group and Gender by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Characteristic	Elasomeran 25 µg (N=150)
Age group, n (%)	
≥ 6 months and < 1 year	37 (24.7)
≥ 1 year and < 2 years	113 (75.3)
Sex, n (%)	
Male	83 (55.3)
Female	67 (44.7)

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 21 February 2022.

Table 55: Participant Age Group and Gender in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Characteristic	Elasomeran 25 µg (N=1761)	Placebo (N=589)	Total (N=2350)
Age group, n (%)			
≥ 6 months and < 1 year	375 (21.3)	124 (21.1)	499 (21.2)
≥ 1 year and < 2 years	1373 (78.0)	462 (78.4)	1835 (78.1)
≥ 2 years ^a	13 (0.7)	3 (0.5)	16 (0.7)
Sex, n (%)			
Male	910 (51.7)	290 (49.2)	1200 (51.1)

Characteristic	Elasomeran 25 µg (N=1761)	Placebo (N=589)	Total (N=2350)
Female	851 (48.3)	299 (50.8)	1150 (48.9)

Abbreviations: IRT = interactive response technology.

Percentages are based on the number of participants in the Part 2 Safety Set.

^aDue to parallel enrollment of age groups, entry errors at the time of randomization and other limitations of the IRT system, some participants who were ≥ 2 years old were included in the 6 months to < 2 -years-old subgroup.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 21 February 2022.

Table 56: Participant Race by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Characteristic	Elasomeran 25 µg (N=150)
Race, n (%)	
White	125 (83.3)
Black	3 (2.0)
Asian	7 (4.7)
American Indian or Alaska Native	1 (0.7)
Native Hawaiian or other Pacific Islander	0
Multiracial	10 (6.7)
Other	3 (2.0)
Not reported	0
Unknown	1 (0.7)

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 21 February 2022.

Table 57: Participant Race in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Characteristic	Elasomeran 25 µg (N=1761)	Placebo (N=589)	Total (N=2350)
Race, n (%)			
White	1390 (78.9)	466 (79.1)	1856 (79.0)
Black	57 (3.2)	16 (2.7)	73 (3.1)
Asian	79 (4.5)	35 (5.9)	114 (4.9)
American Indian or Alaska Native	4 (0.2)	0	4 (0.2)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	186 (10.6)	64 (10.9)	250 (10.6)
Other	31 (1.8)	5 (0.8)	36 (1.5)
Not reported	9 (0.5)	2 (0.3)	11 (0.5)
Unknown	5 (0.3)	1 (0.2)	6 (0.3)

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 21 February 2022.

Table 58: Participant Ethnicity by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Characteristic	Elasomeran 25 µg (N=150)
Ethnicity, n (%)	
Hispanic or Latino	15 (10.0)
Not Hispanic or Latino	134 (89.3)
Not reported	0
Unknown	1 (0.7)

Percentages are based on the number of participants in the Part 1 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.1.1](#)

Data from ongoing trial as of 21 February 2022.

Table 59: Participant Ethnicity in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 2 Years)

Characteristic	Elasomeran 25 µg (N=1761)	Placebo (N=589)	Total (N=2350)
Ethnicity, n (%)			
Hispanic or Latino	227 (12.9)	84 (14.3)	311 (13.2)
Not Hispanic or Latino	1517 (86.1)	498 (84.6)	2015 (85.7)
Not reported	15 (0.9)	6 (1.0)	21 (0.9)
Unknown	2 (0.1)	1 (0.2)	3 (0.1)

Percentages are based on the number of participants in the Part 2 Safety Set.

Source: [Study mRNA-1273-P204 Table 14.1.3.2](#)

Data from ongoing trial as of 21 February 2022.

A total of 145 children including 114 infants/toddlers 6 months to < 2 years of age and 31 children 2 to < 6 years of age were treated in Part 1 (elasomeran 25 µg) and received a BD (elasomeran 10 µg) in the Booster Dose Phase of the study ([Table 60](#) to [Table 63](#)).

Table 60: Summary of Study Duration in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 6 Years)

	Elasomeran 25 µg Primary Series - Booster 10 µg		
	6 Months to < 2 Years (N=114)	2 Years to < 6 Years (N=31)	Total (N=145)
Duration of exposure, n (%)			
Received First Injection	114 (100)	31 (100)	145 (100)
Received Second Injection	114 (100)	31 (100)	145 (100)
Time Since First Injection to Second Injection (Days)			
n	114	31	145
Mean (SD)	31.1 (2.60)	30.5 (2.23)	31.0 (2.53)
Median	30.0	30.0	30.0
Q1, Q3	29.0, 33.0	29.0, 30.0	29.0, 33.0

Min, Max	29, 42	29, 35	29, 42
< 21 Days Since First Injection	0	0	0
≥ 21 and ≤ 42 Days Since First Injection	114 (100)	31 (100)	145 (100)
> 42 Days and ≤ 56 Days Since First Injection	0	0	0
> 56 Days Since First Injection	0	0	0
Received Booster	114 (100)	31 (100)	145 (100)
Time Since Primary Series Dose 2 to Booster (Days) [1]			
n	114	31	145
Mean (SD)	323.3 (30.73)	287.1 (31.15)	315.5 (34.14)
Median	316.5	278.0	307.0
Q1, Q3	299.0, 349.0	270.0, 305.0	289.0, 342.0
Min, Max	267, 392	237, 375	237, 392
< 168 Days Since Primary Series	0	0	0
≥ 168 and < 196 Days	0	0	0
≥ 196 and < 224 Days	0	0	0
≥ 224 and < 252 Days	0	2 (6.5)	2 (1.4)
≥ 252 and < 280 Days	4 (3.5)	15 (48.4)	19 (13.1)
≥ 280 and < 308 Days	46 (40.4)	7 (22.6)	53 (36.6)
≥ 308 and < 336 Days	20 (17.5)	4 (12.9)	24 (16.6)
≥ 336 and < 364 Days	28 (24.6)	2 (6.5)	30 (20.7)
≥ 364 and < 392 Days	15 (13.2)	1 (3.2)	16 (11.0)
≥ 392 Days	1 (0.9)	0	1 (0.7)
Follow-Up Time on Study After Booster (Days)			
n	114	31	145
Mean (SD)	88.5 (30.37)	96.9 (31.76)	90.3 (30.76)
Median	94.0	107.0	99.0
Q1, Q3	64.0, 114.0	72.0, 114.0	67.0, 114.0
Min, Max	29, 137	11, 144	11, 144
< 28 Days	0	1 (3.2)	1 (0.7)
≥ 28 Days	114 (100)	30 (96.8)	144 (99.3)
≥ 28 and < 56 Days	20 (17.5)	3 (9.7)	23 (15.9)
≥ 56 Days	94 (82.5)	27 (87.1)	121 (83.4)
≥ 84 Days	64 (56.1)	23 (74.2)	87 (60.0)
≥ 112 Days	38 (33.3)	12 (38.7)	50 (34.5)
≥ 140 Days	0	1 (3.2)	1 (0.7)
Person-years from Booster [2]	27.62	8.22	35.85
Time on Study from Dose 1 of elasomeran (Days)			
n	114	31	145
Mean (SD)	440.9 (6.75)	412.5 (4.23)	434.8 (13.26)
Median	441.0	414.0	438.0
Q1, Q3	436.0, 444.0	413.0, 415.0	435.0, 443.0
Min, Max	404, 456	402, 416	402, 456
Person-years from Dose 1 of elasomeran [3]	137.60	35.01	172.61

Percentages are based on the number of safety subjects in booster dose analysis.

[1] For subjects who received two doses of elasomeran in Primary Series, Time Since Primary Series is calculated as: Date of Booster — Date of Second Dose of elasomeran + 1.

[2] Person-years is defined as the total years from the booster dose date to the earlier date of study discontinuation or data cutoff.

[3] Person-years is defined as the total years from the first dose date of elasomeran to the earlier date of study discontinuation or data cutoff.

Source: [Study mRNA-1273-P204 Table 14.1.6.1](#) (18 August 2022).

Table 61: Participant Age Group and Gender by Dose Level in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 6 Years)

Characteristic	Elasomeran 25 µg Primary Series - Booster 10 µg		
	6 Months to < 2 Years (N=114)	2 Years to < 6 Years (N=31)	Total (N=145)
Age (Years), n (%)			
< 1	28 (24.6)	0	28 (19.3)
1	86 (75.4)	0	86 (59.3)
2	0	8 (25.8)	8 (5.5)
3	0	8 (25.8)	8 (5.5)
4	0	14 (45.2)	14 (9.7)
5	0	1 (3.2)	1 (0.7)
Age (Years)			
n	114	31	145
Mean (SD)	0.94 (0.125)	3.26 (0.893)	1.43 (1.044)
Median	1.00	3.00	1.00
Q1, Q3	1.00, 1.00	2.00, 4.00	1.00, 1.00
Min, Max	0.5, 1.0	2.0, 5.0	0.5, 5.0
Age (Months) [1]			
n	114		
Mean (SD)	15.2 (4.92)		
Median	14.0		
Q1, Q3	11.0, 20.0		
Min, Max	6, 23		
Gender, n (%)			
Male	63 (55.3)	17 (54.8)	80 (55.2)
Female	51 (44.7)	14 (45.2)	65 (44.8)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.

[1] Age in months is summarised for ≥ 6 months and < 2 years group only.

Source: [mRNA-1273-P204 Table 14.1.3.13.1](#) (18 August 2022).

Table 62: Participant Race by Dose Level in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 6 Years)

Characteristic	Elasomeran 25 µg Primary Series - Booster 10 µg		
	6 Months to < 2 Years (N=114)	2 Years to < 6 Years (N=31)	Total (N=145)
Race, n (%)			
White	92 (80.7)	24 (77.4)	116 (80.0)
Black	3 (2.6)	1 (3.2)	4 (2.8)
Asian	6 (5.3)	3 (9.7)	9 (6.2)
American Indian or Alaska Native	1 (0.9)	0	1 (0.7)
Native Hawaiian or Other Pacific Islander	0	0	0

Multiracial	9 (7.9)	2 (6.5)	11 (7.6)
Other	3 (2.6)	1 (3.2)	4 (2.8)
Not reported	0	0	0
Unknown	0	0	0

Source: mRNA-1273-P204 Table 14.1.3.13.1 (18 August 2022).

Table 63: Participant Ethnicity by Dose Level in Part Booster Dose (Safety Set) in the Ongoing mRNA-1273-P204 Study (6 Months to < 6 Years)

Characteristic	Elasomeran 25 µg Primary Series - Booster 10 µg		
	6 Months to < 2 Years (N=114)	2 Years to < 6 Years (N=31)	Total (N=145)
Ethnicity, n (%)			
Hispanic or Latino	11 (9.6)	4 (12.9)	15 (10.3)
Not Hispanic or Latino	102 (89.5)	27 (87.1)	129 (89.0)
Not reported	1 (0.9)	0	1 (0.7)
Unknown	0	0	0

Source: mRNA-1273-P204 Table 14.1.3.13.1 (18 August 2022).

mRNA-1273-P304 study

This is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of elasomeran SARS-CoV-2 vaccine in SOT recipients and Healthy controls. Approximately 240 participants (220 adult kidney or liver transplant recipients and 20 healthy controls) who are least 18 years of age will be enrolled. All SOT recipients and healthy participants will receive 2 doses of 100 µg of elasomeran 28 days apart. The SOT recipients will be offered the opportunity to receive a third dose of elasomeran at Day 85. Study Endpoints included Safety and Reactogenicity and adverse events for 12 months after the last dose. Immunogenicity endpoints included neutralizing and binding antibody titres as surrogate endpoints to predict clinical benefit.

Table 64: Participants exposure by Age in mRNA-1273-P304 study

Age range	Participants (N)
≥18 and <65 years	114
≥65 and <75 years	22
≥75 and <85 years	2
Total	138

Data from ongoing trial as of 17 Dec 2021.

Table 65: Participant exposure by Gender in mRNA-1273-P304 study

Gender	Participants (N)
Male	69
Female	69

Total	138
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Data from ongoing trial as of 17 Dec 2021.

Table 66: Participant exposure by Racial group in mRNA-1273-P304 study

Race	Participants (N)
White	86
Black	28
Asian	8
American Indian or Alaska Native	2
Native Hawaiian or Other Pacific Islander	0
Other	9
Multiple	2
Not reported	1
Unknown	1
Missing	1
Total	138

Data from ongoing trial as of 17 Dec 2021.

Table 67: Participant exposure by Ethnicity in mRNA-1273-P304 study

Ethnicity	Participants (N)
Hispanic or Latino	11
Not Hispanic or Latino	127
Total	138

Data from ongoing trial as of 17 Dec 2021.

mRNA-1273-P301 (Phase 3)

The Phase 3 study (mRNA-1273-P301) is an ongoing pivotal two parts study. Part A is a randomized, stratified, observer-blind, placebo-controlled study to evaluate safety, efficacy, and immunogenicity of elasomeran in adults ≥ 18 years of age conducted in the US. This study enrolled 30,418 participants with no known history of SARS-CoV-2 infection, but whose location or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infection. Participants were randomly assigned to receive two injections of either 100 μ g of elasomeran vaccine or a placebo control given 28 days apart in a 1:1 ratio. The study enrolled adults at increased risk of complications from COVID-19 based on pre-existing medical co-morbidities. The study enrolled participants with underlying medical conditions at increased risk of severe COVID -19 such as chronic lung disease, significant cardiac disease, severe obesity diabetes, liver disease, and HIV infection. The Part B Open-Label Observational Phase of the study was prompted by the authorization of a COVID-19 vaccine under EUA. Transitioning the study to Part B permitted all ongoing study participants to be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and the option to offer all ongoing study participants who request unblinding, an opportunity to schedule a Participation Decision Visit to know their

original treatment assignment (placebo vs. elasomeran vaccine). The Part B Open-Label Observation Phase also provided the opportunity for EUA-eligible study participants who previously received placebo to actively request to receive 2 doses of elasomeran vaccine.

Table 68: Duration of Exposure in the Ongoing mRNA-1273-P301 Study (Part A)

Duration of Exposure	Elasomeran (N=15184)
Received First Injection	15184 (100)
Received Second Injection	14731 (97.0)
≥ 49 Days Since First Injection	15039 (99.0)
≥ 56 Days Since First Injection	15023 (98.9)
≥ 2 Months Since First Injection	14995 (98.8)
< 28 Days Since Second Injection	24 (0.2)
>= 28 and < 56 Days Since Second Injection	51 (0.3)
≥ 28 Days Since Second Injection	14707 (96.9)
≥ 56 Days Since Second Injection	14656 (96.5)
≥ 2 Months Since Second Injection	14645 (96.5)
>= 3 Months Since Second Injection	14595 (96.1)
>= 4 Months Since Second Injection	14485 (95.4)
>= 5 Months Since Second Injection	12861 (84.7)
>= 6 Months Since Second Injection	7499 (49.4)
Study Duration from First Injection (Days)	
Mean (Standard Deviation)	206.0 (31.02)
Median	213.0
Quartile 1, Quartile 3	197.0, 226.0
Minimum, Maximum	1, 243
Study Duration from Second Injection (Days)	
Mean (Standard Deviation)	173.7 (38.95)
Median	183.0
Quartile 1, Quartile 3	166.0, 194.0
Minimum, Maximum	0, 218

Table 69: Age Group and Gender in the Ongoing mRNA-1273-P301 Study (Part A)

Age Group	Elasomeran (N=15184)
Adults, 18-64 years	11415
Elderly, 65-74 years	3112
Elderly, 75-84 years	616
Elderly 85 + years	41
Gender	

Age Group	Elasomeran (N=15184)
Male	7918
Female	7266

Source: mRNA-1273-P301 Tables 14.1.6.2.2 and 14.1.6.2.4 (Data from ongoing trials as of 04 May 2021).

Table 70: Participant Race in the Ongoing mRNA-1273-P301 Study (Part A)

Race	Elasomeran (N=15184)
White	12034
Black or African American	1567
Asian	656
American Indian or Alaska Native	113
Native Hawaiian or Other Pacific Islander	36
Multiple	320
Other / Not reported / Unknown	458
Total	15184

Source: mRNA-1273-P301 Table 14.1.6.2.5 and Table 14.1.6.2.1 (Data extraction date: 04 May 2021).

Table 71: Participant Ethnicity in the Ongoing mRNA-1273-P301 Study (Part A)

Ethnicity	Elasomeran (N=15184)
Hispanic or Latino	3122
Not Hispanic or Latino	11920
Not Reported / Unknown	142
Total	15184

Source: mRNA-1273-P301 Table 14.1.6.2.6 and Table 14.1.6.2.1 (Data from ongoing trials as of 04 May 2021).

Table 72: Comorbidities in the Ongoing mRNA-1273-P301 Study (Part A)

Age and Risk Group: ≥ 18 and < 65 Years	Elasomeran (N=15184)
Number of Participants at Risk (N)	2320
Chronic lung disease	473
Significant cardiac disease	321
Severe obesity	896
Diabetes	919
Liver disease	84
HIV infection	77
Age and Risk Group: > 65 Years	
Number of Participants at Risk (N)	1128

Chronic lung disease	239
Significant cardiac disease	441
Severe obesity	174
Diabetes	541
Liver disease	20
HIV infection	17

Source: mRNA-1273-P301 Table 14.1.6.2.8 (Data extraction date: 04 May 2021).

Table 73: Risk Factors in the Ongoing mRNA-1273-P301 Phase 3 Study (Part A)

Age and Risk Group: ≥ 18 and < 65 Years	Elasomeran (N=15184)
At least one risk factor (N)	2320
One risk factor	1925
Two risk factors	351
Three risk factors	34
Four risk factors	9
Five risk factors	1
Six risk factors	0
Age and Risk Group: > 65 Years	
At least one risk factor (N)	1128
One risk factor	866
Two risk factors	223
Three risk factors	36
Four risk factors	3
Five risk factors	0
Six risk factors	0

source: mRNA-1273-P301 Table 14.1.6.2.9 (Data extraction date: 04 May 2021).

Table 74: Participants Age group in the Ongoing mRNA-1273-P301 Phase 3 Study (Part B)

	≥ 18 and < 65 Years			≥ 65 Years		
	Placebo- elasomeran (N=9,256)	Elasomeran (N=11,415)	Total (N=20671)	Placebo- elasomeran (N=3,392)	Elasomeran (N=3,769)	Total (N=7161)
≥ 18 and < 65 Years	9,256 (100)	11,415 (100)	20,671 (100)	0	0	0
≥ 65 and < 70 Years	0	0	0	1620 (47.8)	1,906 (50.6)	3,526 (49.2)

>=70 and <75 Years	0	0	0	1,092 (32.2)	1,206 (32.0)	2,298 (32.0)
>=75 and <80 Years	0	0	0	469 (13.8)	466 (12.4)	935 (13.0)
>=80 Years	0	0	0	211 (6.2)	191 (5.1)	402 (5.6)
Age Subgroup at Screening, n (%)						
>=18 and <65 Years	9,256 (100)	11,415 (100)	20,671 (100)	0	0	0
>=65 and <75 Years	0	0	0	2,712 (80.0)	3,112 (82.6)	5,824 (81.3)
>=75 and <85 Years	0	0	0	638 (18.8)	616 (16.3)	1,254 (17.5)
>=85 Years	0	0	0	42 (1.2)	41 (1.1)	83 (1.2)

Source: mRNA-1273-P301 Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021).

Table 75: Participants Risk Factors / Comorbidities in the Ongoing mRNA-1273-P301 Phase 3 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-elasomeran (N=9,256)	Elasomeran (N=11,415)	Total (N=20,671)	Placebo-elasomeran (N=3,392)	Elasomeran (N=3,769)	Total (N=7,161)
Age and Health Risk for Severe COVID-19, n (%)*						
>=18 and <65 Years and Not at Risk	7082 (76.5)	8890 (77.9)	15,972 (77.2)	2 (<0.1)	0	2 (<0.1)
>=18 and <65 Years and at Risk	2173 (23.5)	2524 (22.1)	4,697 (22.7)	3 (<0.1)	6 (0.2)	9 (0.1)
>=65 Years	1 (<0.1)	1 (<0.1)	2 (<0.1)	3387 (99.9)	3763 (99.8)	7150 (99.8)
Risk Factor for Severe COVID-19 at Screening, n (%)**						
Chronic Lung Disease	435 (4.7)	473 (4.1)	908 (4.4)	223 (6.6)	239 (6.3)	462 (6.4)
Significant Cardiac Disease	266 (2.9)	321 (2.8)	587 (2.8)	409 (12.1)	441 (11.7)	850 (11.8)

	>=18 and <65 Years			>=65 Years		
	Placebo-elasomeran (N=9,256)	Elasomeran (N=11,415)	Total (N=20,671)	Placebo-elasomeran (N=3,392)	Elasomeran (N=3,769)	Total (N=7,161)
Severe Obesity	786 (8.5)	896 (7.8)	1,682 (8.1)	139 (4.1)	174 (4.6)	313 (4.3)
Diabetes	780 (8.4)	919 (8.1)	1699 (8.2)	499 (14.7)	541 (14.4)	1040 (14.5)
Liver Disease	60 (0.6)	84 (0.7)	144 (0.7)	23 (0.7)	20 (0.5)	43 (0.6)
HIV Infection	67 (0.7)	77 (0.7)	144 (0.7)	14 (0.4)	17 (0.5)	31 (0.4)

Source: mRNA-1273-P301 Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021).

* Based on stratification factor from IRT, subjects who are < 65 years old are categorized as at risk for severe COVID-19 illness if they have at least 1 of the risk factors specified in the study protocol at Screening.

** Subjects could be under one or more categories, and are counted once at each category.

Table 76: Participants Gender in the Ongoing mRNA-1273-P301 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-elasomeran (N=9,256)	Elasomeran (N=11,415)	Total (N=20671)	Placebo-elasomeran (N=3,392)	Elasomeran (N=3,769)	Total (N=7161)
Sex, n (%)						
Male	4799 (51.8)	5841 (51.2)	10,640 (51.5)	1864 (55.0)	2077 (55.1)	3941 (55.0)
Female	4457 (48.2)	5574 (48.8)	10,031 (48.5)	1528 (45.0)	1692 (44.9)	3220 (44.9)

Source: mRNA-1273-P301 Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021).

Table 77: Participant Race in the Ongoing mRNA-1273-P301 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-elasomeran (N=9,256)	Elasomeran (N=11,415)	Total (N=20671)	Placebo-elasomeran (N=3,392)	Elasomeran (N=3,769)	Total (N=7161)
Race, n (%)						
White	7057 (76.2)	8654 (75.8)	15,711 (76.0)	3031 (89.4)	3380 (89.7)	6411 (89.5)
Black or African American	1075 (11.6)	1345 (11.8)	2420 (11.7)	204 (6.0)	222 (5.9)	426 (5.9)

	>=18 and <65 Years			>=65 Years		
	Placebo-elasomeran (N=9,256)	Elasomeran (N=11,415)	Total (N=20671)	Placebo-elasomeran (N=3,392)	Elasomeran (N=3,769)	Total (N=7161)
Asian	467 (5.0)	589 (5.2)	1056 (5.1)	59 (1.7)	67 (1.8)	126 (1.8)
American Indian or Alaska Native	76 (0.8)	92 (0.8)	168 (0.8)	24 (0.7)	21 (0.6)	45 (0.6)
Native Hawaiian or Other Pacific Islander	19 (0.2)	33 (0.3)	52 (0.3)	3 (<0.1)	3 (<0.1)	6 (<0.1)
Multiracial	250 (2.7)	288 (2.5)	538 (2.6)	27 (0.8)	32 (0.8)	59 (0.8)
Other	218 (2.4)	276 (2.4)	494 (2.4)	27 (0.8)	23 (0.6)	50 (0.7)
Not Reported	51 (0.6)	84 (0.7)	135 (0.7)	12 (0.4)	13 (0.3)	25 (0.3)
Unknown	43 (0.5)	54 (0.5)	97 (0.5)	5 (0.1)	8 (0.2)	13 (0.2)

Source: mRNA-1273-P301 Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021).

Table 78: Participant Ethnicity in the Ongoing mRNA-1273-P301 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-elasomeran (N=9256)	Elasomeran (N=11415)	Total (N=21671)	Placebo-elasomeran (N=3392)	Elasomeran (N=3769)	Total (N=7161)
Ethnicity, n (%)						
Hispanic or Latino	2222 (24.0)	2768 (24.2)	4990 (23.0)	275 (8.1)	354 (9.4)	629 (8.8)
Not Hispanic or Latino	6961 (75.2)	8549 (74.9)	15510 (71.5)	3079 (90.8)	3371 (89.4)	6450 (90.1)
Not Reported	43 (0.5)	72 (0.6)	115 (0.5)	25 (0.7)	33 (0.9)	58 (0.8)
Unknown	30 (0.3)	26 (0.2)	64 (0.3)	13 (0.4)	11 (0.3)	24 (0.3)

Source: mRNA-1273-P301 Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021).

mRNA-1273-P205 study

Study mRNA-1273-P205 is an ongoing, open-label, Phase 2/3 study that is evaluating the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS-CoV-2 variants including mRNA-1273.211, mRNA-1273 (Spikevax), mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA-1273-222 (Spikevax bivalent Original/Omicron BA.4-5).

The study consists of 7 parts: A, (1, 2), B, C, D, E, F, G, and H covering the following vaccines and doses:

Part A.1: 50 µg mRNA-1273.211 and 100 µg mRNA-1273.211

Part A.2: Second booster dose 50 µg mRNA-1273.214: Participants who received mRNA-1273.211 50 µg as a first booster dose in Part A.

Part B: 100 µg mRNA-1273

Part C: 50 µg mRNA-1273.617.2 and 100 µg mRNA-1273.617.2

Part D: 50 µg mRNA-1273.213 and 100 µg mRNA-1273.213

Part E: 100 µg mRNA-1273.213

Part F - Cohort 1- 50 µg mRNA-1273.529: Participants who previously received 100 µg mRNA 1273 primary series and have not received a mRNA-1273 booster dose previously.

Part F - Cohort 2, Second booster dose 50 µg mRNA-1273.529 or 50 µg mRNA-1273 dose: Participants who previously received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273

Part G – Second booster dose 50 µg mRNA-1273.214: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273

Part H - Second booster dose 50 µg mRNA-1273.222: Participants who received 100 µg mRNA-1273 primary series and a booster dose of 50 µg mRNA-1273

In total, 895 adults were treated with mRNA-1273.211 in Part A of the study including 300 adults treated with 50 µg mRNA-1273.211 and 595 adults treated with 100 µg mRNA-1273.211 up to 2 February 2022 ([Table 79](#) to [Table 82](#)).

A further 437 adults were treated with Spikevax bivalent (50 µg elasomeran/imelasomeran) in Part G of the study and 377 adults were treated with Spikevax (50 µg elasomeran) in Part F (Cohort 2), up to 27 April 2022 ([Table 83](#) to [Table 86](#)). In Part H enrolment is currently ongoing.

Table 79: Duration of Exposure in the Ongoing mRNA-1273-P205 Study (Part A)

	mRNA-1273.211 50 µg (N=300)	mRNA-1273.211 100 µg (N=595)	Total mRNA-1273.211 (N=895)
Number of Subjects, n (%)			
Received Injection	300 (100)	595 (100)	895 (100)
≥ 28 Days Since Injection	299 (99.7)	593 (99.7)	892 (99.7)
≥ 2 Months Since Injection	299 (99.7)	586 (98.5)	885 (98.9)
≥ 3 Months Since Injection	299 (99.7)	586 (98.5)	885 (98.9)

≥ 4 Months Since Injection	299 (99.7)	585 (98.3)	884 (98.8)
≥ 6 Months Since Injection	297 (99.0)	583 (98.0)	880 (98.3)
≥ 8 Months Since Injection	290 (96.7)	0	290 (32.4)
≥ 10 Months Since Injection	0	0	0
Study Duration from Injection (Days)			
Mean (SD)	243.7 (16.11)	208.1 (22.47)	220.0 (26.55)
Median	245.0	210.0	216.0
Q1, Q3	245.0, 246.0	206.0, 216.0	209.0, 245.0
Min, Max	13, 251	16, 218	13, 251

Abbreviations: max = maximum; min = minimum.

1 Month= 30.4375 Days

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part A subjects (mRNA-1273.211) immunogenicity data up to Day 181 visit. The data cutoff date for safety and SARS-CoV-2 infection is 02Feb2022.

Source: [Study P205 Table 14.1.6.1](#)

Table 80: Age Group and Gender in the Ongoing mRNA-1273-P205 Study (Part A)

	mRNA-1273.211 50 µg (N=300)	mRNA-1273.211 100 µg (N=595)	Total mRNA-1273.211 (N=895)
Age group, n (%)			
≥ 18 years and < 65 years	238 (79.3)	449 (75.5)	687 (76.8)
≥ 65 years	62 (20.7)	146 (24.5)	208 (23.2)
Gender, n (%)			
Male	133 (44.3)	264 (44.4)	397 (44.4)
Female	167 (55.7)	331 (55.6)	498 (55.6)

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part A subjects (mRNA-1273.211) immunogenicity data up to Day 181 visit. The data cutoff date for safety and SARS-CoV-2 infection is 02Feb2022.

Source: [Study P205 Table 14.1.3.1](#)

Table 81: Participant Race in the Ongoing mRNA-1273-P205 Study (Part A)

	mRNA-1273.211 50 µg (N=300)	mRNA-1273.211 100 µg (N=595)	Total mRNA-1273.211 (N=895)
Race, n (%)			
White	257 (85.7)	520 (87.4)	777 (86.8)
Black or African American	19 (6.3)	34 (5.7)	53 (5.9)
Asian	9 (3.0)	18 (3.0)	27 (3.0)
American Indian or Alaska Native	1 (0.3)	5 (0.8)	6 (0.7)
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	1 (0.1)
Multiracial	7 (2.3)	7 (1.2)	14 (1.6)
Other	4 (1.3)	6 (1.0)	10 (1.1)
Not Reported	3 (1.0)	3 (0.5)	6 (0.7)
Unknown	0	1 (0.2)	1 (0.1)

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part A subjects (mRNA-1273.211) immunogenicity data up to Day 181 visit. The data cutoff date for safety and SARS-CoV-2 infection is 02Feb2022.

Source: [Study P205 Table 14.1.3.1](#)

Table 82: Participant Ethnicity in the Ongoing mRNA-1273-P205 Study (Part A)

	mRNA-1273.211 50 µg (N=300)	mRNA-1273.211 100 µg (N=595)	Total mRNA-1273.211 (N=895)
Ethnicity, n (%)			
Hispanic or Latino	38 (12.7)	52 (8.7)	90 (10.1)
Not Hispanic or Latino	262 (87.3)	539 (90.6)	801 (89.5)
Not Reported	0	4 (0.7)	4 (0.4)
Unknown	0	0	0

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part A subjects (mRNA-1273.211) immunogenicity data up to Day 181 visit. The data cutoff date for safety and SARS-CoV-2 infection is 02Feb2022.

Source: [Study P205 Table 14.1.3.1](#)

Table 83: Duration of Exposure in the Ongoing mRNA-1273-P205 Study (Part G/ Part F Cohort 2)

	Part G Elasomeran/Imelasomeran 50 µg (N=437)	Part F Cohort 2 Elasomeran 50 µg (N=377)
Number of subjects, n (%)		
Received Injection	437 (100)	377 (100)
≥ 28 Days Since Injection	436 (99.8)	377 (100)
≥ 56 Days Since Injection	0	285 (75.6)
≥ 2 Months Since Injection	0	114 (30.2)
≥ 3 Months Since Injection	0	0
Follow up Time from Injection (Days)		
Mean (SD)	43.1 (4.13)	57.9 (4.08)
Median	43.0	57.0
Q1, Q3	41.0, 45.0	56.0, 62.0
Min, Max	22, 51	51, 66

Abbreviations: max = maximum; min = minimum.

1 Month= 30.4375 Days

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part F Cohort 2 (elasomeran) and Part G subjects (elasomeran/imelasomeran) immunogenicity data up to Day 29 visit. The data cutoff date for safety and SARS-CoV-2 infection is 27Apr2022.

Source: [Study P205 Table 14.1.6.1.8](#)

Table 84: Age Group and Gender in the Ongoing mRNA-1273-P205 Study (Part G/ Part F Cohort 2)

	Part G Elasomeran/Imelasomeran 50 µg (N=437)	Part F Cohort 2 Elasomeran 50 µg (N=377)
Age group, n (%)		
≥ 18 years and < 65 years	263 (60.2)	227 (60.2)
≥ 65 years	174 (39.8)	150 (39.8)
Gender, n (%)		
Male	179 (41.0)	186 (49.3)
Female	258 (59.0)	191 (50.7)

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part F Cohort 2 (elasomeran) and Part G subjects (elasomeran/imelasomeran) immunogenicity data up to Day 29 visit. The data cutoff date for safety and SARS-CoV-2 infection is 27Apr2022.

Source: [Study P205 Table 14.1.3.1.8](#)

Table 85: Participant Race in the Ongoing mRNA-1273-P205 Study (Part G/Part F Cohort 2)

	Part G Elasomeran/Imelasomeran 50 µg (N=437)	Part F Cohort 2 Elasomeran 50 µg (N=377)
Race, n (%)		
White	381 (87.2)	322 (85.4)
Black or African American	31 (7.1)	29 (7.7)
Asian	14 (3.2)	16 (4.2)
American Indian or Alaska Native	0	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)
Multiracial	7 (1.6)	2 (0.5)
Other	3 (0.7)	2 (0.5)
Not Reported	1 (0.2)	3 (0.8)
Unknown	0	1 (0.3)

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part F Cohort 2 (elasomeran) and Part G subjects (elasomeran/imelasomeran) immunogenicity data up to Day 29 visit. The data cutoff date for safety and SARS-CoV-2 infection is 27Apr2022.

Source: [Study P205 Table 14.1.3.1.8](#)

Table 86: Participant Ethnicity in the Ongoing mRNA-1273-P205 Study (Part G/Part F Cohort 2)

	Part G Elasomeran/Imelasomeran 50 µg (N=437)	Part F Cohort 2 Elasomeran 50 µg (N=377)
Ethnicity, n (%)		
Hispanic or Latino	46 (10.5)	37 (9.8)
Not Hispanic or Latino	390 (89.2)	340 (90.2)
Not Reported	1 (0.2)	0
Unknown	0	0

Percentages are based on the number of subjects in the Safety Set.

This interim analysis includes Part F Cohort 2 (elasomeran) and Part G subjects (elasomeran/imelasomeran) immunogenicity data up to Day 29 visit. The data cutoff date for safety and SARS-CoV-2 infection is 27Apr2022.

Source: [Study P205 Table 14.1.3.1.8](#)

mRNA-1273-P306 study

Study mRNA-1273-P306 is an ongoing open-label, Phase 3 study to evaluate the safety and immunogenicity of the mRNA-1273.214 vaccine (Spikevax bivalent Original/Omicron BA.1), for SARS-CoV-2 variants of concern in participants aged 6 months to < 6 years. The study consists of 2 parts:

Part 1 enrolled participants aged 6 months to <6 years who have not been previously vaccinated against SARS-CoV-2. Participants receive 2 doses of the mRNA-1273.214 vaccine (Spikevax bivalent Original/Omicron BA.1) and will be followed for approximately 12 months after the

second dose for safety and additional immunogenicity follow-up. Participants who have not been previously vaccinated against SARS-CoV-2, will receive 2 IM injections of 25 µg mRNA-1273.214 on Day 1 and Day 29.

Part 2 enrolled participants aged 6 months to <6 years who have previously been vaccinated with a mRNA-1273 (Spikevax) primary series in Study mRNA-1273-P204. Participants received a single booster dose of the mRNA-1273.214 vaccine (Spikevax bivalent Original/Omicron BA.1), at least 4 months after completion of the mRNA-1273 (Spikevax) primary series and will be followed for approximately 6 months after the booster dose for safety and immunogenicity. Participants who have previously been vaccinated with a mRNA-1273 primary series, will receive a single IM booster dose (BD) of 10 µg mRNA-1273.214 at least 4 months after the last dose on BD Day 1.

Table 87: Duration of Exposure in the Ongoing mRNA-1273-P306 Study (Part 1)

Duration of exposure	mRNA-1273.214 50 µg ≥6 months and <2 years (N=48)	mRNA-1273.214 50 µg ≥2 years and <6 years (N=131)	Total mRNA-1273.214 50 µg (N=179)
Number of subjects, n (%)			
Received first injection	48 (100)	131 (100)	179 (100)
Received second injection	36 (75.0)	106 (80.9)	142 (79.3)
≥ 7 days since first injection	47 (97.9)	123 (93.9)	170 (95.0)
≥ 35 days since first injection	38 (79.2)	108 (82.4)	146 (81.6)
≥ 56 days since first injection	30 (62.5)	86 (65.6)	116 (64.8)
≥ 7 days since second injection	33 (68.8)	100 (76.3)	133 (74.3)
≥ 21 days since second injection	28 (58.3)	88 (67.2)	116 (64.8)
≥ 28 days since second injection	28 (58.3)	80 (61.1)	108 (60.3)
≥ 28 days and < 56 days since second injection	6 (12.5)	18 (13.7)	24 (13.4)
≥ 56 days since second injection	22 (45.8)	62 (47.3)	84 (46.9)
≥ 84 days since second injection	9 (18.8)	33 (25.2)	42 (23.5)
≥ 112 days since second injection	2 (4.2)	14 (10.7)	16 (8.9)
≥ 140 days since second injection	0	0	0
Study duration from first injection (days)			
n	48	131	179
Mean (SD)	76.8 (39.72)	83.4 (45.68)	81.6 (44.15)
Median	75.5	85.0	85.0
Q1, Q3	41.5, 107.5	46.0, 118.0	43.0, 113.0
Min, Max	6, 165	1, 168	1, 168
Person-years from first injection [1]	10.09	29.91	40.00
Study duration from second injection (days) [2]			
n	48	131	179
Mean (SD)	45.3 (40.54)	52.7 (42.50)	50.7 (42.00)
Median	41.0	49.0	49.0
Q1, Q3	0.5, 78.5	13.0, 85.0	6.0, 82.0

Duration of exposure	mRNA-1273.214 50 µg ≥6 months and <2 years (N=48)	mRNA-1273.214 50 µg ≥2 years and <6 years (N=131)	Total mRNA-1273.214 50 µg (N=179)
Min, Max	0, 137	0, 138	0, 138
Study duration from second injection in participants who received second injection (days)			
n	36	106	142
Mean (SD)	60.3 (35.66)	65.2 (37.65)	64.0 (37.09)
Median	67.0	72.0	68.0
Q1, Q3	31.0, 85.5	34.0, 97.0	34.0, 90.0
Min, Max	1, 137	1, 138	1, 138

Abbreviations: max = maximum; min = minimum; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.

Percentages are based on the number of subjects in Safety Set.

[1] Person-years is defined as the total years from the first dose date to the earlier date of study discontinuation or data cut-off.

[2] Study duration from second injection is 0 day for subjects who did not receive second injection.

Source: [Study mRNA-1273-P306 Table 14.1.5.1](#) (05 December 2022).

Table 88: Participant Age Group and Gender in the Ongoing mRNA-1273-P306 Study (Part 1)

Characteristic	mRNA-1273.214 50 µg ≥6 months and <2 years (N=48)	mRNA-1273.214 50 µg ≥2 years and <6 years (N=131)	Total mRNA-1273.214 50 µg (N=179)
Age (years), n (%)			
<1	21 (43.8)	0	21 (11.7)
1	27 (56.3)	0	27 (15.1)
2	0	41 (31.3)	41 (22.9)
3	0	46 (35.1)	46 (25.7)
4	0	23 (17.6)	23 (12.8)
5	0	21 (16.0)	21 (11.7)
Age (years)			
n	48	131	179
Mean (SD)	0.82 (0.227)	3.18 (1.051)	2.55 (1.387)
Median	1.00	3.00	3.00
Q1, Q3	0.50, 1.00	2.00, 4.00	1.00, 3.00
Min, Max	0.5, 1.0	2.0, 5.0	0.5, 5.0
Age (months) [1]			
n	48		
Mean (SD)	13.2 (6.20)		
Median	13.5		
Q1, Q3	6.0, 18.5		
Min, Max	6, 23		
Gender, n (%)			
Male	22 (45.8)	76 (58.0)	98 (54.7)
Female	26 (54.2)	55 (42.0)	81 (45.3)

Abbreviations: max = maximum; min = minimum; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.

Percentages are based on the number of subjects in Safety Set.

[1] Age in months is summarised for ≥6 months and <2 years group only.

Source: [Study mRNA-1273-P306 Table 14.1.3.2.1](#) (05 December 2022).

Table 89: Participant Race in the Ongoing mRNA-1273-P306 Study (Part 1)

Characteristic	mRNA-1273.214 50 µg ≥6 months and <2 years (N=48)	mRNA-1273.214 50 µg ≥2 years and <6 years (N=131)	Total mRNA-1273.214 50 µg (N=179)
Race, n (%)			
White	31 (64.6)	86 (65.6)	117 (65.4)
Black	11 (22.9)	35 (26.7)	46 (25.7)
Asian	4 (8.3)	1 (0.8)	5 (2.8)
American Indian or Alaska Native	0	1 (0.8)	1 (0.6)
Native Hawaiian or Other Pacific Islander	0	0	0
Multiracial	1 (2.1)	7 (5.3)	8 (4.5)
Other	1 (2.1)	1 (0.8)	2 (1.1)
Unknown	0	0	0
Not reported	0	0	0

Percentages are based on the number of subjects in Safety Set.

Source: [Study mRNA-1273-P306 Table 14.1.3.2.1](#) (05 December 2022).

Table 90: Participant Ethnicity in the Ongoing mRNA-1273-P306 Study (Part 1)

Characteristic	mRNA-1273.214 50 µg ≥6 months and <2 years (N=48)	mRNA-1273.214 50 µg ≥2 years and <6 years (N=131)	Total mRNA-1273.214 50 µg (N=179)
Ethnicity, n (%)			
Hispanic or Latino	4 (8.3)	17 (13.0)	21 (11.7)
Not Hispanic or Latino	44 (91.7)	114 (87.0)	158 (88.3)
Not reported	0	0	0
Unknown	0	0	0

Percentages are based on the number of subjects in Safety Set.

Source: [Study mRNA-1273-P306 Table 14.1.3.2.1](#) (05 December 2022).

Table 91: Duration of Exposure in the Ongoing mRNA-1273-P306 Study (Part 2)

Duration of exposure	mRNA-1273.214 10 µg ≥6 months and <2 years (N=114)	mRNA-1273.214 10 µg ≥2 years and <6 years (N=425)	Total mRNA-1273.214 10 µg (N=539)
Number of subjects, n (%)			
Received booster injection	114 (100)	425 (100)	539 (100)
≥ 7 days since booster injection	114 (100)	425 (100)	539 (100)
≥ 21 days since booster injection	114 (100)	425 (100)	539 (100)
≥ 28 days since booster injection	113 (99.1)	425 (100)	538 (99.8)

	mRNA-1273.214 10 µg ≥6 months and <2 years (N=114)	mRNA-1273.214 10 µg ≥2 years and <6 years (N=425)	Total mRNA-1273.214 10 µg (N=539)
Duration of exposure			
≥ 28 days and < 56 days since booster injection	0	5 (1.2)	5 (0.9)
≥ 56 days since booster injection	113 (99.1)	420 (98.8)	533 (98.9)
≥ 84 days since booster injection	109 (95.6)	417 (98.1)	526 (97.6)
≥ 112 days since booster injection	72 (63.2)	294 (69.2)	366 (67.9)
≥ 140 days since booster injection	14 (12.3)	37 (8.7)	51 (9.5)
Study duration from booster injection (days)			
Mean (SD)	117.6 (19.68)	118.9 (16.82)	118.6 (17.45)
Median	114.5	117.0	117.0
Q1, Q3	110.0, 127.0	109.0, 130.0	109.0, 130.0
Min, Max	25, 166	34, 167	25, 167
Person-years from booster injection [1]	36.71	138.33	175.04

Abbreviations: max = maximum; min = minimum; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.

Percentages are based on the number of subjects in Safety Set.

[1] Person-years is defined as the total years from the booster dose date to the earlier date of study discontinuation or data cutoff.

Source: [Study mRNA-1273-P306 Table 14.1.5.2](#) (05 December 2022).

Table 92: Participant Age Group and Gender in the Ongoing mRNA-1273-P306 Study (Part 2)

	mRNA-1273.214 10 µg ≥6 months and <2 years (N=114)	mRNA-1273.214 10 µg ≥2 years and <6 years (N=425)	Total mRNA-1273.214 10 µg (N=539)
Characteristic			
Age (years), n (%)			
<1	2 (1.8)	0	2 (0.4)
1	112 (98.2)	0	112 (20.8)
2	0	138 (32.5)	138 (25.6)
3	0	113 (26.6)	113 (21.0)
4	0	125 (29.4)	125 (23.2)
5	0	49 (11.5)	49 (9.1)
Age (years)			
n	114	425	539
Mean (SD)	1.00 (0.013)	3.20 (1.021)	2.73 (1.277)
Median	1.00	3.00	3.00
Q1, Q3	1.00, 1.00	2.00, 4.00	2.00, 4.00
Min, Max	0.9, 1.0	2.0, 5.0	0.9, 5.0
Age (months) [1]			
n	114		
Mean (SD)	19.1 (3.04)		
Median	20.0		

Characteristic	mRNA-1273.214 10 µg ≥6 months and <2 years (N=114)	mRNA-1273.214 10 µg ≥2 years and <6 years (N=425)	Total mRNA-1273.214 10 µg (N=539)
Q1, Q3	17.0, 22.0		
Min, Max	11, 23		
Gender, n (%)			
Male	52 (45.6)	224 (52.7)	276 (51.2)
Female	62 (54.4)	201 (47.3)	263 (48.8)

Abbreviations: max = maximum; min = minimum; Q1 = quartile 1; Q3 = quartile 3; SD = standard deviation.

Percentages are based on the number of subjects in Safety Set.

[1] Age in months is summarised for ≥6 months and <2 years group only.

Source: [Study mRNA-1273-P306 Table 14.1.3.2.2](#) (05 December 2022).

Table 93: Participant Race in the Ongoing mRNA-1273-P306 Study (Part 2)

Characteristic	mRNA-1273.214 10 µg ≥6 months and <2 years (N=114)	mRNA-1273.214 10 µg ≥2 years and <6 years (N=425)	Total mRNA-1273.214 10 µg (N=539)
Race, n (%)			
White	91 (79.8)	346 (81.4)	437 (81.1)
Black	1 (0.9)	16 (3.8)	17 (3.2)
Asian	6 (5.3)	20 (4.7)	26 (4.8)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	2 (0.5)	2 (0.4)
Multiracial	15 (13.2)	37 (8.7)	52 (9.6)
Other	0	0	0
Unknown	0	1 (0.2)	1 (0.2)
Not Reported	1 (0.9)	3 (0.7)	4 (0.7)

Percentages are based on the number of subjects in Safety Set.

Source: [Study mRNA-1273-P306 Table 14.1.3.2.2](#) (05 December 2022).

Table 94: Participant Ethnicity in the Ongoing mRNA-1273-P306 Study (Part 2)

Characteristic	mRNA-1273.214 10 µg ≥6 months and <2 years (N=114)	mRNA-1273.214 10 µg ≥2 years and <6 years (N=425)	Total mRNA-1273.214 10 µg (N=539)
Ethnicity, n (%)			
Hispanic or Latino	7 (6.1)	52 (12.2)	59 (10.9)
Not Hispanic or Latino	105 (92.1)	371 (87.3)	476 (88.3)
Not reported	1 (0.9)	1 (0.2)	2 (0.4)
Unknown	1 (0.9)	1 (0.2)	2 (0.4)

Percentages are based on the number of subjects in Safety Set.

Source: [Study mRNA-1273-P306 Table 14.1.3.2.2](#) (05 December 2022).

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Participants were excluded from the studies according to the general criteria listed below. Detailed descriptions of all exclusion criteria are provided in the individual protocols.

Table 95: Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
Paediatric participants.	Clinical development programs generally investigate first the benefit-risk in adults. In adults, the risk of symptomatic and severe COVID-19 disease is higher.	No	A paediatric investigation plan was agreed upon by the Agency. Respective studies are ongoing in paediatric patient groups ages 6 months to < 12 years and 12 years to < 18 years.
Pregnant/Lactating women.	Clinical development generally first demonstrates safety and efficacy in non-pregnant and lactating women.	Yes*	Not applicable.
Acutely ill/febrile (temperature >38°C/100.4°F) prior to screening visit.	Allowance of these conditions would confound assessment of safety and these febrile participants might already be infected with SARS-CoV-2.	No	It is common medical practice to not administer vaccines in febrile participants. Febrile participants with minor illnesses could be enrolled at the discretion of the investigator. This is managed with the product prescribing information.
Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients.	Participants with medical history significant for allergic reactions following the vaccine or its excipients are at increased risk for hypersensitivity reactions when receiving another vaccine.	No	It is common medical practice to not administer a new vaccine in participants who have history of significant allergic reactions to the vaccine or its excipients.
Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy.	Participants have a potential risk of hematoma due to the puncture of the deep tissues. Allowance of these conditions would confound assessment of safety.	No	It is common medical practice to not administer a product by the intramuscular route in participants with coagulopathy or bleeding disorders although the use of a needle with proper gauge can decreased the risk.

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
Known history of SARS-CoV-2 infection Of note, in Phase 3 mRNA-1273-P301 study seropositive participants are not excluded from enrolment, although they are excluded from the Per-Protocol cohort.	Allowance of this condition would confound assessment of safety and efficacy.	No	Baseline SARS-CoV-2 status was negative for most participants in Study mRNA-1273-P301. Testing occurred on the day of vaccination with Dose 1, and results were available subsequently. In the Safety Set, 347 participants in the elasomeran group had positive baseline SARS-CoV-2 status (Source Table 14.1.3.2.2).
Has received or plans to receive a non-study vaccine within 28 days prior to or after any dose of IP (except for seasonal influenza vaccine which is not permitted within 14 days before or after any dose of vaccine).	Allowance of this condition would confound assessment of safety and efficacy.	Yes*	Not applicable.
Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections (HIV positive participants with CD4+ T-cell count ≥ 350 cells/mm ³ and an undetectable HIV viral load within the past year [low level variations from 50-500 viral copies which do not lead to changes in antiretroviral therapy are permitted]).	Allowance of these conditions would confound assessment of efficacy.	Yes*	Participants with stable HIV infection were enrolled in Study mRNA-1273-P301 (n=176). The small number of participants precludes complete assessment of risk.
Has received systemic immunosuppressants or immune-modifying drugs for	Allowance of these conditions would confound assessment of efficacy.	Yes*	Not applicable.

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
> 14 days in total within 6 months prior to Screening (for corticosteroids \geq 20 mg/day of prednisone equivalent).			
Has received systemic immunoglobulins or blood products within 3 months prior to the day of screening.	Allowance of these conditions would confound assessment of efficacy.	Yes*	Not applicable.
Has donated \geq 450 mL of blood products within 28 days prior to Screening.	Allowance of these conditions would confound assessment of safety.	No	It is common practice to not give blood prior to entry in a clinical trial. There is no suspected biological reason to expect the safety or efficacy of elasomeran in these participants would be different from the rest of the population receiving elasomeran.

* No longer safety concerns in the RMP.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

Rare Adverse Drug Reactions

The vaccine exposed population of the Phase 3 mRNA-1273-P301 study allowed the detection of rare events with a frequency of 1/10,000 persons or 0.01%. Most rare AEs of special interest (AESIs) for post-marketing safety surveillance have incidence rates lower than the 2/10,000 persons or 0.02%.

Adverse Drug Reactions of Long Latency

The current vaccination regimen for the elasomeran vaccine consists of two doses administered 28 days apart. There is no prolonged exposure to elasomeran. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently, with a rapid degradation of the mRNA as demonstrated in the nonclinical biodistribution study; thus, no long-term sequelae due to vaccine exposure are expected.

In both the elasomeran injection group and the placebo group in the Phase 3 mRNA-1273-P301 study, the median follow-up time after randomization for the entire period up to the data cut-off for database lock (including Part A and Part B) was 212 days (range: 1 to 243 days). The median duration of follow-up from randomization to the PDV/unblinding (i.e., Part A) before the data cut-

off date was 148 days (range: 30 to 241 days). For participants who received both injections, the median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183 days (range: 1 to 218 days), or approximately 6 months. Therefore, with additional follow up time there has been more opportunity to observe potential adverse drug reactions (ADRs) that might occur with more prolonged latency.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Program

Table 96: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Paediatric participants	<p>Studies are ongoing in paediatric patient groups ages 6 months to < 12 years and 12 years to < 18 years. Clinical trial data from Study mRNA-1273-P203 that includes 12 years to \leq 18 years participants are presented in this RMP. On 23 Jul 2021, EMA (CHMP) has recommended granting an extension of indication for the COVID-19 vaccine Spikevax (previously COVID-19 Vaccine Moderna) to include use in children aged 12 to 17 years. In ongoing Study mRNA-1273-P204, 751 children 6 to < 12 years of age have been exposed to elasomeran (380 elasomeran 50 µg and 371 elasomeran 100 µg) in Part 1 (Table 14.1.5.1) and 4002 children 6 to < 12 years of age (3007 elasomeran 50 µg and 995 placebo) in Part 2 (Table 14.1.5.2 (Data extraction date: 10 November 2021)). A total of 1294 children 6 to < 12 years of age were administered a booster dose (elasomeran 25 µg) in the Booster Dose Phase of the study (Table 14.1.6.2 (Data extraction 23 May 2022)). On 02 March 2022, EMA (CHMP) recommended granting an extension of indication for the COVID-19 vaccine Spikevax to include use in children aged 6 to 11 years.</p> <p>In Study mRNA-1273-P204, a total of 224 children 2 to < 6 years of age were exposed to elasomeran (69 elasomeran 25 µg and 155 elasomeran 50 µg) in Part 1 (Table 14.1.5.1) and 4038 children 2 to < 6 years of age were treated in Part 2 (3031 elasomeran 25 µg and 1007 placebo) (Table 14.1.5.2 (Data extraction date: 21 February 2022)). Furthermore, 150 children 6 months to < 2 years of age were exposed to elasomeran 25 µg in Part 1 (Table 14.1.5.1) and 2350 children 6 months to < 2 years of age were treated in Part 2 (1761 elasomeran 25 µg and 589 placebo) (Table 14.1.5.2 (Data extraction date: 21 February 2022)). A total of 145 children including 114 infants/toddlers 6 months to < 2 years of age and 31 children 2 to < 6 years of age treated in Part 1 (elasomeran 25 µg) were administered a booster dose (elasomeran 10 µg) in the Booster Dose Phase of the study (Table 14.1.6.1 (Data extraction date: 18 August 2022)).</p> <p>Cumulatively, as of 17 December 2022, a total of 10,080 cases (1,224 serious and 37 fatal cases) with 21,597 events 2,920 serious events) reported in children <18 years of age. Of these total cases, 8,153 cases were medically confirmed. When gender was known more cases were reported in females (51.7%; 5,213 cases) compared to males (42.8%; 4,315), with small proportion of cases (5.5%; 552 cases) having no gender reported. The mean age was 13.8 years (SD: 4.6) and median age was 16.0 years (min: -1.0/max: 17.0). Majority of these cases were</p>

Type of Special Population	Exposure
	received from regulatory authorities (73.5%; 7,404 cases), with highest number of cases reported in United States (50.0%; 5,041 cases), EEA (22.6%; 2,282 cases), Asia (11.4%; 1,153 cases) followed by Latin America (7.0%; 708 cases) and Australia (5.7%; 570 cases). Use of Spikevax monovalent and Spikevax bivalent vaccines in paediatric population is approved (see Part I).
Pregnant women	<p>Pregnant women were excluded from the clinical trials, although a small number of pregnancies were reported in the elasomeran clinical program. In mRNA-1273-P301 Part A, 16 pregnancies were reported in the elasomeran group and 11 pregnancies were reported in the placebo group. Of the outcomes known as of 04 May 2021, 1 participant in the placebo group experienced a live birth. The participant was induced due to polyhydramnios and gestational diabetes and the child was noted as having congenital anomalies. Five participants (2 in the elasomeran group and 3 in the placebo group) experienced spontaneous abortion/miscarriage. In Part B, pregnancy was reported for 18 participants who received elasomeran in Part A and 19 participants who received placebo in Part A and elasomeran in Part B. Among the few known outcomes, spontaneous abortion/miscarriage was reported for 1 participant in the elasomeran group and 3 participants in the placebo–elasomeran group; elective termination was reported for 1 participant in the placebo–elasomeran group. A developmental and reproductive study with elasomeran in female Sprague-Dawley rats was completed in December 2020 with no adverse findings. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development.</p> <p>Cumulatively up to 17 December 2022, Moderna has received 5,131 pregnancy cases with 16,817 events (pregnancy and non-pregnancy specific), of which 5,467 events were serious, after receipt of Spikevax. Of the 5,131 pregnancy cases, 2,463 cases were medically confirmed, 1,817 (35.4%) cases were serious, and 32 had fatal outcomes. There are 53 reports classified as stillbirth but there is insufficient evidence to support a causal relationship between Spikevax and stillbirth. Cumulatively, there have been 140 reports of congenital anomalies. Upon medical review, 64 pregnancy reports (some contain parent-child duplicates) occurred in fetuses and neonates and the other 76 reports of congenital anomalies occurred in non-pregnancy cases. Review of the congenital anomalies indicates that the anomalies are varied in type, aetiology, and critical gestational age at exposure; indicating that the anomalies have occurred as part of the background incidence rather than as a result of vaccine exposure.</p> <p>Published literature has not identified any evidence of an increased risk of pregnancy, foetal or neonatal complications related to Spikevax maternal immunisation. Furthermore, published literature supports the favourable benefit/risk profile of maternal Spikevax immunisation as there is transfer of maternal antibodies to the foetus and early evidence that infants benefit from passive protection from SARS-CoV-2 infection and severe disease following maternal COVID-19 vaccination. Use of Spikevax in pregnancy is now embedded in clinical practice and included in relevant health guidelines and the SmPC states that Spikevax can be used during pregnancy.</p>

Type of Special Population	Exposure
Breastfeeding women	<p>Lactating women were excluded from clinical trials. There have been no reports of women taking elasomeran while breastfeeding in the elasomeran clinical program. Cumulatively up to 17 December 2022, Moderna has received 2,036 lactation cases (6,922 events) of which 527 were serious cases (2,026 serious events); no cases reported a fatal outcome. There were 508 cases medically confirmed. These cases and cases from the literature of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhoea, and pyrexia are consistent with the safety profile of Spikevax or what is expected in the general population (ACOG 2007; UpToDate 2021; UpToDate 2022). No safety concerns related to Spikevax vaccination during lactation have been identified.</p> <p>Vaccination can induce cytokines which can be passed via breast milk but vaccination while breast-feeding has not been linked to adverse events in infants (Sachs 2013). In fact, women with fever and illness are encouraged to continue breast-feeding given the positive impact of the transfer of antibodies, which has also been reported for COVID-19 vaccines, as well as to support infant nutritional needs (UpToDate 2021). Use of Spikevax while breast-feeding is now embedded in clinical practice and included in relevant health guidelines and the SmPC states that Spikevax can be used during breast-feeding.</p>
Participants with relevant comorbidities [#]	
Participants with hepatic impairment ¹	<p>In the clinical trial mRNA-1273-P301 (Part A), 104 (0.7%) participants with hepatic disease have been exposed to elasomeran (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 83 (0.7%) in placebo+elasomeran vaccine group and 104 (0.7%) in mRNA vaccine group participants with hepatic disease have been exposed (Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021)).</p>
Participants with renal impairment	<p>A Phase 3b open-label safety and immunogenicity study (elasomeran - Study mRNA-1273-P304) in target population of approximately 220 adult solid organ transplant recipients is ongoing.</p> <p>Cumulatively, as of 17 December 2022, a total of 54,153 cases (246,375 events) were reported in frail individuals, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these 54,153 cases, 1496 individuals had a medical history of chronic kidney disease.</p> <p>Use of Spikevax in frail individuals with unstable health conditions and co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines.</p>
Participants with cardiovascular impairment ²	<p>In the Study mRNA-1273-P301 (Part A), 762 (5.0%) participants with significant cardiac diseases have been exposed to elasomeran (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 675 (5.3%) in placebo+elasomeran vaccine group and 762 (5.0%) in mRNA vaccine group participants with significant cardiac diseases have been exposed (Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021)).</p> <p>Cumulatively, as of 17 December 2022, a total of 54,153 cases (246,375 events) were reported in frail individuals, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these 54,153 cases, 2214 individuals had a medical history of coronary artery disease and 4011 individuals a medical history of atrial fibrillation.</p> <p>Use of Spikevax in frail individuals with unstable health conditions and</p>

Type of Special Population	Exposure
	co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines.
Immunocompromised participants	<p>In the clinical development program, participants with immunosuppression were generally excluded. In Study mRNA-1273-P301 (Part A), participants with HIV who did not meet the exclusion criteria were enrolled. A total of 94 (0.6%) participants with HIV were exposed to elasomeran (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 81 (0.6%) in placebo+ elasomeran vaccine group and 94 (0.6%) in mRNA vaccine group participants with HIV were exposed (Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021)). A Phase 3b open-label safety and immunogenicity study (elasomeran -Study mRNA-1273-P304) in target population of approximately 220 adult solid organ transplant recipients is ongoing.</p> <p>Cumulatively, as of 17 December 2022, there were 7,559 cases (31,444 events) in immunocompromised individuals, of which 2,936 were serious cases (11,514 serious events); there were 199 cases reporting a fatal outcome; 3,829 cases were medically confirmed. There was a higher number of cases reported cumulatively in females (4,785; 63.3%) when compared to males (2,567; 34.0%), with 207 cases (2.7%) missing gender information. Among the reported cases, the median age was 60.0 years with a range of 0.3 year to 101.0 years (571 cases had missing age information). Cumulatively, most of the events reported a resolved/ resolving outcome (13,482; 42.9%), with 8,482 events (30.2%) reported as not resolved. Review of the safety information has not identified any patterns/trends or specific safety concerns in the immunocompromised population. Serious events and fatal reports are heavily confounded by underlying medical conditions. The general pattern of commonly reported adverse events in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population.</p> <p>In general, public health and professional groups recommend COVID-19 vaccination for immunocompromised patients. These recommendations highlight the likely potential benefits of COVID-19 vaccines in this population with the potential risk of more severe COVID-19 infections, sequelae, and impact on underlying immune-mediated diseases (Botwin 2021; Briggs 2021; Izmirly 2022; Tang 2021). Use of Spikevax in immunocompromised individuals is now embedded in clinical practice and included in relevant health guidelines and in the SmPC.</p>
Participants with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	While most participants enrolled in clinical trials were White, participants from other races or ethnicities were also enrolled. In the Phase 3 mRNA-1273-P301 study (Part A), 12034 (79.3%) participants were White, 1567 (10.3%) were Black or African American; 3122 (20.6%) were Hispanic or Latino, and 656 (4.3%) were Asian (mRNA-1273-P301 study Table 14.1.6.2.5 and Table 14.1.6.2.6). In the Phase 2/3 Study mRNA-1273-P203, 2084 (83.8%) participants were White, 83 (3.3%) were Black, 142 (5.7%) were Asian, 118 (4.7%) were

Type of Special Population	Exposure
	<p>multiracial and 280 (11.3%) were Hispanic or Latino (study mRNA-1273-P203 Table 14.1.3.13.1).</p> <p>Spikevax has been administered extensively worldwide in populations of different ethnic origin (>800 million individuals vaccinated with at least one dose). No safety concerns related to ethnic origin have been identified.</p>
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Others	
1. Participants ≥ 75 years of age	<p>In the Phase 3 mRNA-1273-P301 study (Part A), a total of 616 (4.1%) participants were 75 to 84 years of age and 41 (0.3%) were ≥ 85 years of age (Table 14.1.6.2.4). In study P201 (Part A), a total of 11 (2.75) participants were 75 to 84 years of age and 3 (0.8%) were ≥ 85 years of age.</p> <p>Cumulatively, as of 17 December 2022, a total of 54,153 cases (246,375 events) were reported in frail individuals, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these, 37,792 cases (69.8%) were medically confirmed, 19,708 (36.4%) were serious, and 2,457 cases (4.5%) had a fatal outcome. The median age of frail individuals was 61.0 years (range: less than 1 year – 121.0 years); 1,161 reports were missing age information. A total of 52,174 cases were reported in individuals ≥ 75 years of age (7.9% of the total number of cases reported), including 33,373 cases in females (5.1%), 17,824 cases in males (2.7%), and 977 cases where the gender was not specified (0.1%).</p> <p>Use of Spikevax in frail individuals with unstable health conditions and co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines.</p>
2. Diabetes (Type 1, Type 2)	<p>In the Phase 3 mRNA-1273-P301 study (Part A), 1460 (9.6%) participants with diabetes have been exposed to elasomeran (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 1279 (10.1%) in placebo+elasomeran vaccine group and 1460 (9.6%) in mRNA vaccine group participants with diabetes have been exposed (Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021)).</p> <p>Cumulatively, as of 17 December 2022, a total of 54,153 cases (246,375 events) were reported in frail individuals, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these 54,153 cases, 10,819 individuals had a medical history of diabetes mellitus and 5274 individuals a medical history of Type 2 diabetes mellitus.</p> <p>Use of Spikevax in frail individuals with unstable health conditions and co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines.</p>
3. Chronic lung disease ³	<p>In the Phase 3 mRNA-1273-P301 study (Part A), 712 (4.7%) participants with chronic lung disease have been exposed to elasomeran (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 658 (5.2%) in placebo+elasomeran vaccine group and 712 (4.7%) in mRNA vaccine group participants with chronic lung disease have been exposed (Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021)).</p> <p>Cumulatively, as of 17 December 2022, a total of 54,153 cases (246,375</p>

Type of Special Population	Exposure
	<p>events) were reported in frail individuals, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these 54,153 cases, 17,470 individuals had a medical history of asthma and 4188 individuals had a medical history of COPD.</p> <p>Use of Spikevax in frail individuals with unstable health conditions and co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines.</p>
4. Severe obesity (BMI > 40 kg/m ²)	<p>In the Phase 3 mRNA-1273-P301 study (Part A), 1070 (7.1%) participants with severe obesity have been exposed to elasomeran (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 925 (7.3%) in placebo+elasomeran vaccine group and 1070 (7.1%) in mRNA vaccine group participants with severe obesity have been exposed (Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021)).</p> <p>Cumulatively, as of 17 December 2022, a total of 54,153 cases (246,375 events) were reported in frail individuals, which represents 8.2% of all cases reported in all populations (658,759 cases). Of these 54,153 cases, 2411 individuals had a medical history of obesity.</p> <p>Use of Spikevax in frail individuals with unstable health conditions and co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines.</p>
5. HIV infection	<p>In the Phase 3 mRNA-1273-P301 study (Part A), participants with HIV who did not meet the exclusion criteria have been enrolled. A total of 94 (0.6%) participants with HIV have been exposed to elasomeran (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 81 (0.6%) in placebo+elasomeran vaccine group and 94 (0.6%) in mRNA vaccine group participants with HIV have been exposed (Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021)).</p> <p>Cumulatively, as of 17 December 2022, there were 7,559 cases (31,444 events) in immunocompromised individuals, of which 2,936 were serious cases (11,514 serious events); there were 199 cases reporting a fatal outcome; 3,829 cases were medically confirmed.</p> <p>Use of Spikevax in immunocompromised individuals is now embedded in clinical practice and included in relevant health guidelines and in the SmPC.</p>

In the Phase 3 mRNA-1273-P301 study, comorbidities are defined as follows:

¹Hepatic disease including cirrhosis;

²Significant cardiac disease such as heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension;

³Chronic lung disease such as emphysema and chronic bronchitis, idiopathic pulmonary fibrosis and cystic fibrosis, or moderate to severe asthma.

Part II: Module SV – Post-Authorisation Experience

SV.1.1. Method Used to Calculate Exposure

Moderna supply chain estimates are used to define the number of doses Spikevax distributed by country; however, administration data are tracked by health officials within countries receiving the vaccine. Therefore, Moderna estimates administration of Spikevax based on information retrieved through the US Centers for Disease Control and Prevention (<https://covid.cdc.gov/covid-data->

[tracker/#vaccinations](https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab)), the European Centres for Disease Control (<https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab>), Health Canada (<https://health-infobase.canada.ca/covid-19/vaccination-coverage/>), the Swiss Federal Office of Public Health (<https://www.covid19.admin.ch/en/epidemiologic/vacc-doses>), and Our World in Data (<https://ourworldindata.org/covid-vaccinations>).

SV.1.2. Exposure

Cumulatively, as of 17 January 2023, a total of 1,315,850,356 doses of Spikevax (Original) had been delivered to 91 countries and an estimated total of 773,062,084 doses had been administered. North America, Europe, and Asia accounted for approximately 90% of Spikevax doses distributed and approximately 84% of Spikevax doses administered. Low- and middle-income countries ([The World Bank 2022](#)) are estimated to account for approximately 13% of the doses distributed globally and approximately 13% of doses administered.

Cumulatively, as of the end of the reporting period, 128,902,523 booster doses of Spikevax Bivalent .214 (Spikevax bivalent Original/Omicron BA.1) had been delivered to 41 countries and an estimated total of 70,896,388 doses had been administered. Europe, Asia, and Canada accounted for approximately 96% of doses distributed and approximately 96% of doses administered. A total of 149,722,244 booster doses of Bivalent .222 (Spikevax bivalent Original/Omicron BA.4-5) had been delivered to 31 countries and an estimated total of 82,347,234 doses had been administered. The US, Canada, Europe, and Asia accounted for >98% of all doses delivered and administered.

Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 421,938,298 individuals received a first dose, 278,631,565 received a second dose, 169,254,388 received a third dose, and 66,929,884 received a fourth dose, with third and fourth doses including both original Spikevax (Original) and Spikevax bivalent booster dose formulations. Because of variation in the timing of use of Spikevax bivalent boosters and limited available global data, extrapolation from the US to estimate the use of bivalent boosters was not deemed appropriate.

Information on distribution by sex, age, or receipt of Spikevax was not identifiable based on information published by ECDC at the time that the data were accessed (<https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab>).

Part II: Module SVI – Additional EU Requirements for the Safety Specification

Not relevant for COVID-19 vaccines.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Important identified risks	Anaphylaxis
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. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Removal of vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) as an important potential risk

Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) was included as an important potential risk in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021).

The MAH has closely monitored VAED including VAERD and presented cumulative reviews in Monthly Safety Summary Reports (MSSRs) as well as in Periodic Safety Update Reports (PSURs) since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of VAED including VAERD as an important potential risk. A summary of the data is presented below.

Vaccine-associated enhanced disease was raised as a safety concern for COVID-19 vaccines early in the pandemic, but current evidence does not suggest that this hypothetical construct presents a

confirmed risk. More than 772 million Spikevax doses are estimated to have been administered since the first EUA up to 17 December 2022, and it is likely that VAED would have been observed and reported if it were both confirmed and more than a very rare event. Motivation to monitor COVID-19 vaccine recipients for possible VAED arose from sources such as animal models in which pathogenesis suggested a common potential mechanism producing VAED related to respiratory syncytial virus (RSV) vaccines in MERS and SARS-CoV-1 ([Lambert 2020](#)). To date, no pathognomonic presentation of VAED has been recognised following immunisation of >902 million individuals with Spikevax vaccines. Furthermore, analysis of the immune profile of Spikevax in a mouse model shows elicitation of a protective immune profile that is not associated with vaccine-enhanced disease upon SARS-CoV-2 challenge ([DiPiazza 2021](#)).

There is currently no widely accepted case definition for VAED; however, a recent publication by the Brighton Collaboration provides some guidance for assessment of potential VAED in COVID-19 ([Munoz 2021](#)). In this guidance, it is suggested that VAED may be identified first as a vaccine failure (i.e., VAED requires exposure to and infection by SARS-CoV-2 in a person who has been fully immunised). The authors acknowledge that there is presently no pathognomonic set of clinical findings to characterise VAED. Furthermore, case classifications that can be readily applied to individual-level data from spontaneous reporting are not defined. The Brighton Collaboration working group states that a definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. Probable cases must show an increase in severity or rates of atypical findings when compared to a non-vaccinated control group, however this criterion must be considered at a population or group level rather than an individual level. Given that there have been numerous epidemiologic studies evaluating effectiveness of mRNA vaccines in millions of vaccinees and that there have not been findings showing an increased risk of COVID-19 disease in vaccinees (or a subgroup of vaccinees) compared to those not vaccinated, real world evidence for occurrence of VAED is lacking. Moreover, there is an absence of medical literature supporting the existence of VAED due to Spikevax or mRNA vaccines against COVID-19.

The removal of VAED including VAERD as an important potential risk is supported by the following considerations:

- The MAH has monitored VAED in each PSUR since EUA (18 Dec 2020) at the request of the EMA and other health authorities. Over the years of analysis and given the amount of safety data accumulated given the unprecedented use of these vaccines, the MAH has found no evidence to support the hypothesis that this phenomenon exists or that there is a causal relationship to the vaccine.
- Despite the large number of doses of Spikevax that has been administered worldwide, no cases of VAED have been reported to the MAH's global safety database.
- As of 17 December 2022, SARS-CoV-2 vaccines have not been associated with VAED in preclinical studies or clinical use. Even with the emergence of multiple new variants/serotypes of SARS-CoV-2, with their potential to provoke sub-neutralising antibodies in individuals who have encountered similar (but poorly cross reactive) epitopes, as was the case for SARS-CoV-2 variant Omicron, no enhancement of disease has been reported.
- Despite widespread use of the Spikevax vaccines (>800 million individuals vaccinated

with at least one dose) there is no convincing evidence to support the hypothesis that VAED exists or that it has a causal relationship to the vaccine.

- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to VAED.

In conclusion, the MAH considers there is sufficient justification for removing VAED including VAERD as an important potential risk from the RMP and proposes to continue monitoring VAED including VAERD through routine surveillance and ongoing post-authorisation safety studies as applicable.

Removal of Use in immunocompromised subjects as missing information

Use in immunocompromised subjects was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021) as immunocompromised and/or immunosuppressed people were excluded from the pivotal clinical trials ([Table 95](#)).

The MAH has closely monitored use in immunocompromised subjects and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of use in immunocompromised subjects as missing information. A summary of the data is presented below.

Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/effectiveness of the vaccine in immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date.

Epidemiological studies have not indicated any significantly increased risk of side-effects in immunocompromised individuals after vaccination with Spikevax, and they have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving Spikevax ([Sáez-Peñataro 2022](#); [Napuri 2022](#)). Analyses have found a higher risk of hospitalisation or death from COVID-19 in those with a variety of immunocompromising conditions, including rheumatic diseases, haematological malignancies, solid organ transplants, and HIV ([Vijenthira 2020](#); [Ao 2021](#)). Factors that increase the risk of severe COVID-19 in the general population, such as older age, chronic kidney disease, cardiovascular disease, and other co-morbidities, are significant drivers of risk in immunocompromised individuals. Moreover, some immunodeficiencies seem to increase the risk above and beyond traditional risk factors.

Cumulative review of post-marketing safety data has not identified any patterns/trends or specific safety concerns in the immunocompromised population. Serious events and fatal reports are heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported adverse events in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population.

In general, public health and professional groups recommend COVID-19 vaccination for immunocompromised patients. These recommendations highlight the likely potential benefits of COVID-19 vaccines in this population with the potential risk of more severe COVID-19 infections, sequelae, and impact on underlying immune-mediated diseases ([Botwin 2021](#); [Briggs 2021](#); [Izmirly 2022](#); [Tang 2021](#)).

Currently, some countries have approved/authorised/recommend a third dose in the primary series as well as a fourth “booster” dose and fifth “second booster” in severely immunocompromised individuals, as well as a third booster dose in mildly immunosuppressed individuals (and the general population) due to waning of immunity and the emergence of new variants. A higher percentage of reports for Dose 3 and Dose 4 during the review period of PSUR #4 (19 Jun 2022 to 17 Dec 2022) compared to the cumulative period (18 Dec 2020 to 17 Dec 2022) likely reflects increased booster vaccination uptake and reporting of booster cases in the immunocompromised subpopulation during this period.

After careful review of all new safety data for the safety topic of use in immunocompromised individuals, and given that this population is at an increased risk for severe COVID-19 infection, the benefit-risk profile for Spikevax remains favourable. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data in immunocompromised subjects reported in the global safety database indicates that the general pattern of commonly reported adverse events in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications is comparable to the general population, rather than as a result of vaccine exposure.
- The MAH continues to evaluate use in immunocompromised subjects in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- Throughout the world all the EUA received for Spikevax includes recommendations for additional doses for immunocompromised subjects
- Use of Spikevax in immunocompromised subjects is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.
- Data from study mRNA-1273-P304, 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 showed that the 3-dose primary series and BD of mRNA-1273 were well tolerated with an acceptable safety profile in immunocompromised post-transplant population.
- Data from study mRNA-1273-P904 showed that all AESI that met threshold for SCRI analysis in the IC population also met the threshold in the general population, and no new risks specific to immunocompromised persons were identified.
- A comprehensive review of the published literature did not identify any elasmomeres immunization safety concerns for the immunocompromised (IC) population. The literature search yielded 579 articles. The articles were medically/scientifically reviewed to identify

articles relevant to the safety and benefit/risk profile of Spikevax/Elasomeran in the context of the IC population. There were 402 articles that discussed COVID-19 disease or its impact on IC individuals, effect of the pandemic on the IC, therapeutic approaches for treatment of IC individuals, case reports/series, review articles and studies that did not include SPIKEVAX /Elasomeran and/or mRNA vaccines. The remaining 177 articles contained information regarding mRNA vaccine administration in the IC population. Most of these articles discussed information in the context of IC individuals with the possibility of lower immune response to the COVID-19 vaccine, the need for booster doses due to the waning immune response over time and the emergence of variants (Omicron) and subvariants, the effectiveness of the vaccine and risk factors for breakthrough COVID-19 and severe COVID-19 disease. The literature demonstrates that for IC individuals, the risk of COVID-19 infection is related to significant morbidity and mortality. This most recent assessment of the literature concerning the use of Spikevax and mRNA vaccines is associated with significantly less severe outcomes in COVID-19 infections.

- Overall, the published data reviewed through this literature search support a positive benefit-risk of the use of elasomeran for the IC subpopulation and support the understanding of the use of the vaccine in this subpopulation.

The removal of use in immunocompromised subjects as missing information is supported by the following considerations:

- Extended use of the Spikevax vaccines in immunocompromised individuals has provided extensive safety information in this sub-population group to no longer be considered missing information.
- Use of Spikevax in immunocompromised individuals is already included in the SmPC and embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to use in immunocompromised subjects as long-term safety is being maintained as missing information.

In conclusion, the MAH considers there is sufficient justification for removing use in immunocompromised subjects as missing information from the RMP and proposes to continue monitoring use in immunocompromised subjects through routine surveillance and ongoing post-authorisation safety studies as applicable.

Removal of Interactions with other vaccines as missing information

Interactions with other vaccines was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021).

The MAH has closely monitored interactions with other vaccines and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June

2022 to 17 December 2022, presents detailed data supporting the removal of interactions with other vaccines as missing information. A summary of the data is presented below.

The safety profile of Spikevax when co-administered with non-COVID-19 vaccines is being monitored, including their use with the new Spikevax bivalent vaccines. As COVID-19 vaccines become available to children who are also being vaccinated against childhood infectious diseases, the safety and efficacy of coadministration is being evaluated with routine surveillance activities.

Overall, cumulatively up to 17 December 2022, adverse events reported for individuals receiving non-COVID-19 vaccines concomitantly with Spikevax, were generally comparable to those seen in the general population after vaccination with non-COVID-19 vaccines and were related to reactogenicity events commonly seen after vaccination with Spikevax. A review of the data showed that events reported in individuals receiving concurrent vaccines with Spikevax continue to primarily occur in individuals >50 years of age, with a higher number of reports involving females, as it is seen in the general population, with a time to onset (TTO) of less than 7 days. Reports in the paediatric population comprised mainly product administration errors. The highest reported events were seen with coadministration with the influenza vaccine.

Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show increased adverse events. Therefore, WHO considers that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

The cumulative review of the safety information did not identify any patterns/trends or specific safety concerns in individuals receiving concurrent vaccines with Spikevax. Serious events and fatal reports were heavily confounded by underlying medical conditions. Otherwise, the general pattern of commonly reported adverse events in those individuals receiving concurrent vaccines with Spikevax was comparable to the general population. No interactions between Spikevax and other non-COVID-19 vaccines have been observed.

After careful review of all new safety data received for the safety topic of interaction with other vaccines, the benefit-risk profile for Spikevax remains favourable. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data on individuals receiving concurrent vaccines with Spikevax reported in the global safety database indicates that the general pattern of commonly reported adverse events are consistent with expected reactogenicity events and are comparable to events observed in the general population receiving other widely used vaccines.
- Available evidence on COVID-19 vaccine coadministration with influenza vaccine does not show an increase in reporting of adverse events. Health authorities consider that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.
- Use of Spikevax with other vaccines, including childhood immunisation vaccines is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.

The removal of interaction with other vaccines as missing information is supported by the following considerations:

- Extended use of the Spikevax vaccines in conjunction with other vaccines has provided extensive safety information for interactions with other vaccines to no longer be considered missing information.
- Concomitant use of other vaccines with Spikevax is included in the SmPC: High dose quadrivalent influenza vaccine can be concomitantly administered with Spikevax.
- The MAH continues to evaluate interaction with other vaccines in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- Concomitant use of the vaccine with the influenza vaccine is already included in the product's labelling, and the use of Spikevax with other vaccines is embedded in clinical practice and included in relevant health guidelines and no longer constitute missing information in the safety profile of Spikevax.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to interaction with other vaccines as long-term safety is being maintained as missing information.

In conclusion, the MAH considers there is sufficient justification for removing interactions with other vaccines as missing information from the RMP, and proposes to continue monitoring interactions with other vaccines through routine surveillance and ongoing post-authorisation safety studies as applicable.

Removal of use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) as missing information

Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021).

The MAH has closely monitored use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as missing information. A summary of the data is presented below.

Frail patients are considered at higher risk of complications due to COVID-19 infection including hospitalisations and deaths; and for this reason, are prioritised candidates for vaccination. Since frail subjects with unstable health conditions and co-morbidities were excluded from the

registration trials, ModernaTx, Inc is characterising safety through post-marketing routine monitoring of adverse events in this special subpopulation. Frailty refers to a state of vulnerability to stressors characterised by a decreased physiological reserve, resulting in poor health outcomes compared to individuals of the same chronological age ([Rockwood 2018](#)).

There is growing evidence to supporting the safety profile of the COVID-19 vaccine in immunocompromised patients, such as HIV-infected patients, diabetics, and patients with cardiopulmonary diseases, is similar to that in the general population. Presently, the US Centers for Disease Control and Prevention, British Society for Immunology, and various other governmental and professional societies and organisations endorse COVID-19 vaccination in the immunocompromised population. Overall, recommendations for use in patients with immunocompromising medical conditions and immunosuppressing medications on the efficacy of the vaccine may support the extrapolation into the frail subpopulation indicating potential benefits to outweigh theoretical risks. The frail population was the first sub-population group vaccinated with Spikevax and other COVID-19 vaccines given that this population was recognised to have the potential for more severe complications due to COVID-19 infection. This same recommendation is still in place for vaccination against SARS-CoV2 and its variants.

Overall, the general pattern of commonly reported adverse events in the frail subpopulation is consistent with expected Spikevax reactogenicity and comparable to those events observed in the general population and in patients with these underlying conditions, especially the elderly. This is to be expected, as the elderly comprise 30.2% of the frail subpopulation in the reporting period of PSUR #4.

As expected with the time course of reactogenicity events observed in the general population, event clustering in the frail subpopulation was observed in the three-day window after vaccination, irrespective of dose number. Notably, reports of event term COVID-19 were much less prevalent in serious cases in the frail subpopulation (1.3%) compared to the general population (2.0%). This is likely due to the preferential roll out of boosters to this frail subpopulation in many countries. The most frequently reported event terms in serious cases in the frail subpopulation closely match those seen both in the elderly population and in the general population as a whole. Fatal cases in the frail subpopulation in the reporting period (2.0%) were strongly confounded by multiple co-morbidities and the advanced age in the elderly, which comprise a little less than a third of the frail subgroup.

Case reports across all available vaccines after doses 3 and above have increased as expected with uptake of booster doses administered in many countries in the period of PSUR #4. With this increase in booster dosing, more events were reported after dose 3 than any other dose in this reporting period. The adverse event profile observed after booster doses in the frail subpopulation is similar to that seen in the general population, notably as reactogenicity events with similar time to onset for dose 3 as after dose 1 and dose 2.

The few cases reported in frail children and adolescent subpopulations did not reveal any new or unusual pattern of events.

With the scale in distribution of Spikevax bivalent vaccines to frail and vulnerable groups globally, the accumulated safety data have not revealed any safety concerns or significant novel events in the frail subpopulation or key differences among the various types of vaccines, compared to the general population.

The MAH has monitored use in frail subjects with unstable health conditions and co-morbidities in each MSSR as well as PSURs since EUA (18 Dec 2020) at the request of the EMA and other health authorities. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data in frail subjects with unstable health conditions and co-morbidities reported in the global safety database indicates that the general pattern of commonly reported adverse events in those frail subjects with unstable health conditions and co-morbidities is comparable to the general population, rather than as a result of vaccine exposure.
- The MAH continues to evaluate use in frail subjects with unstable health conditions and co-morbidities in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- Use of Spikevax in frail subjects with unstable health conditions and co-morbidities has become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines and no longer constitutes missing information in the safety profile of Spikevax.

The removal of use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as missing information is supported by the following considerations:

- Extensive use of the Spikevax vaccines (>800 million individuals vaccinated with at least one dose), including in frail subjects with unstable health conditions and co-morbidities, has provided extensive safety information in this sub-population group to no longer be considered missing information.
- The MAH continues to evaluate use in frail subjects with unstable health conditions and co-morbidities in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of Spikevax with respect to use in frail subjects with unstable health conditions and co-morbidities as long-term safety is being maintained as missing information.

In conclusion, the MAH considers there is sufficient justification for removing use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders) as missing information from the RMP, and proposes to continue monitoring use in frail individuals with unstable health conditions and co-morbidities through routine surveillance and ongoing post-authorisation safety studies as applicable.

Removal of use in subjects with autoimmune or inflammatory disorders as missing information

Use in subjects with autoimmune or inflammatory disorders was included as missing information in the RMP at the time of initial conditional marketing authorisation for Spikevax in the EU (06 January 2021).

The MAH has closely monitored use in subjects with autoimmune or inflammatory disorders and presented cumulative reviews in MSSRs as well as in PSURs since the EUA (18 December 2020) at the request of the EMA and other health authorities. The most recent PSUR, PSUR #4 covering the period 19 June 2022 to 17 December 2022, presents detailed data supporting the removal of use in subjects with autoimmune or inflammatory disorders as missing information. A summary of the data is presented below.

Ongoing review of the literature finds articles that primarily discuss the decreased immunogenicity/effectiveness of the vaccine in the immunocompromised population, the waning effectiveness of the vaccine over time, the potential benefit of boosters, including bivalent boosters in the context of the Omicron variant and subvariants, and recommendations for immunosuppressant regime management in the context of vaccination. No significant safety concerns have been identified in the literature to date.

In general, public health and professional groups recommend COVID-19 vaccination for patients with autoimmune or inflammatory disorders (AI/ID). These recommendations highlight the likely potential benefits of COVID-19 vaccines in this population with the potential risk of more severe COVID-19 infections, sequelae, and impact on underlying immune-mediated diseases ([Botwin 2021](#); [Briggs 2021](#); [Izmirlly 2022](#); [Tang 2021](#)).

Of note, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine and may be a risk factor for more severe COVID-19 disease ([Duly 2022](#); [Tallantyre 2022](#)).

Exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID-19 vaccines ([Torres-Aguilar 2019](#); [Watad 2021](#); [Ishay 2021](#)). While decreased immunogenicity for those on immunosuppressive therapies and the hypothetical risk of disease exacerbation have been recognised by professional and public health organisations, given the risk of more severe COVID-19 and sequelae, vaccination is generally recommended with monitoring and management of any potential flare or exacerbation after vaccination.

Thus far, there have been no specific safety concerns identified for individuals with AI/ID. Epidemiological studies have not indicated any significantly increased risk of side-effects in individuals with AI/ID after vaccination with Spikevax. Epidemiological studies have indicated that the safety/tolerability profile in those individuals studied is consistent with that observed in general populations receiving Spikevax ([Giannoccaro 2022](#); [Machado 2021](#); [Sattui 2021](#); [Lupo-Stanghellini 2022](#)).

In the review period for PSUR #4 and cumulatively, the most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea, and arthralgia) among medical history of autoimmune and/or inflammatory disease (MedHx AI/ID) cases receiving Spikevax (both Original and Bivalents) represent expected reactogenicity. The types and distribution of the most frequently reported events is comparable to those observed with Spikevax (Original) in MedHx AI/ID cases and those receiving Spikevax Bivalent .214 (Original/BA.1) or SPIKEVAX Bivalent.222 (Original/BA.4/5).

During the reporting period for PSUR #4, the potential cases of exacerbation of underlying autoimmune and inflammatory disorders reported after vaccination with Spikevax (Original and

bivalent vaccines) may have limited information and lack a description of the baseline disease status or historic pattern of flares, the clinical course, diagnostics/labs/imaging, treatment, outcome, clear time to onset and/or dose number. Those reports also include signs and symptoms of reactogenicity that could mimic signs and symptoms of autoimmune disease (such as fever, myalgia, fatigue, arthralgia, headache), and thus it may be difficult to fully differentiate transient reactogenicity from AI/ID reactivation/flare. Given the natural waxing and waning course of AI/ID, and that there are no reliable reference data of the background rates of respective flares, the cases do not represent a safety concern at this time.

The MAH has monitored use in individuals with AI/ID in each MSSR as well as PSURs since EUA (18 Dec 2020) at the request of the EMA and other health authorities. Over the years of analysis and the large scale of use of Spikevax (and other COVID-19) vaccines and boosters, the MAH has found:

- Review of the safety data individuals with AI/ID reported in the global safety database indicates that the general pattern of commonly reported adverse events in those with a medical history of autoimmune/inflammatory disorder is comparable to the general population, rather than as a result of vaccine exposure.
- Exacerbation of autoimmune conditions can be related to inflammation caused by infections and thus it is hypothetically possible that such exacerbations could be related to the immune response to vaccines, including mRNA COVID-19 vaccines. This has been recognised by professional and public health organisations; yet, given the risk of the potential consequences of COVID-19 infection, some are recommending vaccination with monitoring and management of any potential flare or exacerbation occurring after vaccination. In addition, those individuals with AI/ID may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine, and/or make them more susceptible to infections.
- Use of Spikevax in individuals with AI/ID is embedded in clinical practice and included in the SmPC and relevant health guidelines.
- The MAH continues to evaluate use in individuals with autoimmune and inflammatory disorders (AI/ID) in reports of Spikevax (Original and Bivalent Boosters) via routine pharmacovigilance activities as well as through post-authorisation safety studies.

The removal of use in individuals with autoimmune and inflammatory disorders as missing information is supported by the following considerations:

- Extended use of the Spikevax vaccines (>800 million individuals vaccinated with at least one dose) has provided extensive safety information including individuals with autoimmune and inflammatory disorders (AI/ID) to support the removal of this population as missing information.
- There is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterise the safety profile of the product with respect to individuals with autoimmune and inflammatory disorders.

In conclusion, the MAH considers there is sufficient justification for removing use in subjects with autoimmune or inflammatory disorders as missing information from the RMP, and proposes to

continue monitoring use in individuals with autoimmune or inflammatory disorders through routine surveillance and ongoing post-authorisation safety studies as applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Table 97: Presentation of Important Identified Risks

Important Identified Risk	Myocarditis
Potential mechanisms	<p>Myocarditis is an under-diagnosed cardiac disease resulting from any one of a broad range of infectious, immune, and toxic causes. Most cases of myocarditis are caused by infectious agents, toxic substances, drugs or autoimmune disorders. Hence, it is increasingly recognized that myocarditis is an inflammatory condition of the myocardium triggered by various factors rather than a distinct cardiovascular disease. Infectious causes include viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa. Noninfectious triggers have been identified such as toxins, auto immune 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 flu-like symptoms and fever and developed cardiac involvement between 4 and 7 days after the onset of influenza symptoms (Onitsuka 2001).</p> <p>Evaluation of the post-authorization safety data suggest a very rare risk of myocarditis following COVID-19 vaccination, the mechanisms involved in such vaccine-related myocarditis are not clear based on the data currently available.</p>
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from clinical trials and the post-authorisation safety.
Characterization of risk	<p>In Study mRNA-1273-P301 (Part A), there were 15,184 participants exposed to the elasomeran vaccine, and 15,166 participants in the placebo arm. There were no reported TEAEs of Myocarditis follow-up period after vaccination. No cases have been reported in Part B of the study (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B])).</p> <p>Using post authorization safety data, an evaluation of all the cases identified as cases of Myocarditis, utilizing the WHO-UMC causality assessment and the newly developed DRAFT Myocarditis Brighton Collaboration case definition (30 May 2021) was conducted. A total of 77 cases were identified. Analysis of the 77 cases that reported events of myocarditis using the WHO-UMC standardized case causality assessment revealed that there were 20 reports (8% of the Myocarditis cases) classified as “Possible” events, 11 reports were classified as “Conditional”, 17 reports were classified as “Unlikely”, and 29 were classified as “Unassessable”. Of the “Possible” 20 cases, there were 18 males and 2 females. Their ages were between 18 and 52 years of age. The reported TTO was between 0 days and 10 days (Median= 3 days). The 20 reports that were classified as “Possible” according to the WHO-UMC causality assessment, were evaluated according to the Myocarditis Brighton Collaboration case definition. Out of the 20 possible reports, there were 2 classified as Level 1 (Definitive case); 12 classified as Level 2 (Probable case); and 6 were classified as Level 4 (a</p>

	<p>reported event of myocarditis with insufficient evidence to meet level 1,2 or 3 of the case definition).</p> <p>As of DLP of this RMP, there were 362 cases of Myocarditis reported. The corresponding reporting rate of myocarditis was 3.45 per 100,000 person – years based on a 21-day risk window following each dose of vaccine administered.</p>
Risk factors and risk groups	<p>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.</p> <p>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 (Golpour 2021). 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.</p> <p>The spontaneous reports included in the global safety database included 4 cases that reported previous COVID-19 infection (5.9%) with these reports in the 18 to 39 years of age group. There were 5 reports of previous Myocarditis/ Pericarditis medical history (5.9%), 14 reports of cardiovascular conditions (16.5%), 5 with Thyroid conditions (5.9%), and 12 (14.1%) had previous medical histories of allergy-type conditions including history of anaphylaxis.</p>
Preventability	<p>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 (Blauwet 2009).</p> <p>Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.</p> <p>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.</p> <p>Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.</p> <p>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 (Wallace 2021).</p> <p>Current SmPC and PIL adequately covers the information on this risk awareness to the health care professionals, caregivers and vaccinees.</p>
Impact on the benefit-risk balance of the product	<p>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 Spikevax and myocarditis is considered of at least a reasonable possibility. The majority of the cases</p>

	have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended (Gargano 2021).
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 mechanisms	Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterized by chest pain, pericardial friction rub, changes in the electrocardiogram (ECG) and occasionally, a pericardial effusion. Generally, the diagnosis requires 2 of these 4 features. Epidemiologic data on the incidence of acute pericarditis are lacking, likely because this condition is frequently inapparent clinically, despite its presence in numerous disorders (Imazio 2015). 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 emergency department for chest pain unrelated to acute myocardial infarction (MI). Although acute pericarditis occurs in all age groups and in men and women, it presents most often in men 20 to 50 years of age. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases. Other common causes include infection, renal failure, myocardial infarction (MI), post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from the clinical trials and post-authorisation safety data.
Characterization of risk	In study mRNA-1273-P301 (Part A), in the safety set, there were 15,184 participants exposed to the elasomeran vaccine, and 15,166 participants in the placebo arm. There were four TEAE of “Pericarditis” in P301: Two TEAEs in the Placebo arm, and two in the Vaccine arm of the safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the >18 to <65 years of age. The events in the vaccination arm were reported in a male in his 60s’ and a female in her 50s’. In Part B, one case of acute pericarditis (verbatim: “acute infective pericarditis”) was reported in a male in his 60s’ in the placebo group; the event occurred 24 days after a COVID-19 diagnosis. In addition, one case of pericardial effusion was reported as an SAE (resolving) in a 20s’ years old male in the placebo–elasomeran group. No participant in the elasomeran group experienced pericarditis (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B])).

Important identified risk	Pericarditis
	<p>A review of the spontaneous reports from the company's global safety identified 68 case reports with the PTs of Pericarditis. All of the aforementioned reports were considered serious reports. As a difference with the Myocarditis reports, most of the Pericarditis reports (64.7%) involved persons >50 years of age. There was not an important difference between the reported genders, with 51% Males, and 47% females. There was not an important difference in the TTO for the pericarditis cases with 16% reporting a TTO less than 1 day, 18 % for each 2 to 3 days and 4 to 7 days. The majority of the reports reported a TTO of more than 8 days following last vaccination. Occurrence following dose 1 was very similar (37% of reports) to the one seeing following dose 2 (41%). Dose number was not reported in 22% of the cases.</p> <p>Evaluation of all the 68 cases identified as cases of Pericarditis, utilizing the WHO-UMC causality assessment, there were 18 reports that were classified as "Possible" according to the WHO-UMC causality assessment. Of these "Possible" 18 cases, there were 9 males and 9 females. Their ages were between 28 and 82 years of age (Median= 51.5). 8 reports were after the 1st dose, 9 after the 2nd dose of the elasomeran vaccine, and 1 did not provided dose information. The reported TTO was between 1 days and 23 days (Mean 11.3 days). The rest of the 68 cases that reported Pericarditis, 11 cases (16.2%) were classified as "Conditional"; 21 cases (30.8%) were classified as "Unassessable/ Unclassifiable"; and 18 (26.5%) were classified as "Unlikely".</p> <p>The post-marketing reporting rate for pericarditis (without myocarditis) was 2.16 per 100,000 person-years based on a 21-day risk window following each dose of vaccine administered.</p>
Risk factors and risk groups	<p>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 (Sharif 2013).</p> <p>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.</p> <p>A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years (Imazio 2008). 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 (Kytö 2014).</p> <p>Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.</p>
Preventability	<p>Pericarditis may be caused by many disorders (e.g., infection, myocardial infarction, 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</p>

Important identified risk	Pericarditis
	<p>friction rub, electrocardiographic changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram (Hoit 2020).</p> <p>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.</p> <p>Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.</p> <p>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.</p> <p>Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.</p> <p>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 (Wallace 2021).</p>
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.

Table 98: Presentation of Missing Information

Missing Information	Use in Pregnancy and While Breast-Feeding
Evidence source	As pregnancy was an exclusion criterion for the mRNA clinical trials, there is limited data from the use of elasomeran in pregnant women from the clinical trials. A developmental and reproductive study with elasomeran in female Sprague-Dawley rats was completed in December 2020 with no adverse findings. In post authorization, preliminary analysis of the v-Safe pregnancy registry conducted by the US CDC did not identify safety signals (Shimabukuro 2021).
Anticipated risk/consequence of the	Targeted populations of the indication will include women of childbearing

missing information	potential, thus, the use of elasomeran in pregnant and breastfeeding women may happen. Pregnancy outcome data will be collected in enhanced pharmacovigilance. An observational cohort pregnancy study will inform on the risk of adverse outcome in women who were exposed to elasomeran during pregnancy.
Missing Information	Long-Term Safety
Evidence source	Per protocols, the clinical development program has a safety follow up period of 12 months in the ongoing Phase 1 study 20-0003, Phase 2a Study mRNA-1273-P201 and, 24 months in the Phase 3 study mRNA-1273-P301. In the Phase 3 Study mRNA-1273-P301 the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183°days (range: 1 to 218 days), or approximately 6 months. The follow up time is through Day 209 for the Phase 1 study DMID 20-0003 and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.
Anticipated risk/consequence of the missing information	The long-term safety profile remains to be characterised. The long-term safety profile is to be characterised through continued trial follow-up, active surveillance for safety, a European post-authorisation safety study, and routine pharmacovigilance.

Part II: Module SVIII – Summary of the Safety Concerns

Table 99: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Myocarditis Pericarditis
Important potential risks	None
Missing information	Use in pregnancy and while breast-feeding Long-term safety

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

The MAH has an established signal management process including signal detection, validation and evaluation of spontaneous reports from all sources. During signal detection data sources are screened for new safety information related to Spikevax. Following initial review of the available data, a determination is made on the basis of the nature and the quality of the new information whether further investigation is warranted, at which point those topics referred for further investigation are considered “validated signals”. Potential signal detection data sources include safety data from MAH-sponsored clinical trials and clinical as well as non-interventional studies, spontaneous AE reports, published literature, and communications from external sources, including regulatory agencies, and (if applicable) business partners. Moderna’s PV system relies primarily on AEs contained in its global PV database (Argus platform) that captures suspected AE reports and in addition, signal from regulatory databases (eg Eudravigilance, VAERS). Routine PV also includes a periodic review of the literature that involves targeted keyword searches in widely recognised databases (i.e., MEDLINE, EMBASE). Moderna performs a weekly aggregate quantitative signal detection review of the global safety database in order to identify possible adverse reactions. Moderna also conducts monthly safety reports that are shared with regulatory agencies worldwide.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific adverse reaction follow-up questionnaires for Spikevax

Myocarditis / Pericarditis Questionnaire

The questionnaire is intended to collect structured information on cases of myocarditis and pericarditis. It is intended to assist with capturing information that can support case classification using the Myocarditis Brighton Collaboration case definition ([Brighton Collaboration 2021](#)) as well as the CDC working case definitions on Acute Myocarditis ([Gargano 2021](#)) and Acute Pericarditis ([Gargano 2021](#)).

Signal Detection

The Moderna signal management process for Spikevax includes signal detection, validation, prioritization, evaluation, and recommendation for actions as well as documentation and tracking of signals. It follows the principles of the Good Pharmacovigilance Practices Module IX for Signal Management (refer to <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices>).

Moderna signal detection strategy for Spikevax is described in the product safety strategy form. It describes the data sources, type and frequency of the signal detection analyses summarised in [Table 100](#).

As available, standard case definitions from the Brighton Collaboration will be used to classify AESIs by level of diagnostic certainty.

Table 100: Spikevax Signal Data Sources and Frequency of Evaluations

Data Source	Frequency of Safety Evaluations
Company global safety database	Ongoing monitoring of Individual Cases Safety Reports (ICSRs) from all sources, safety concerns, and Adverse Events (AE) of Special Interest. Weekly aggregated review of ICSRs for trend analyses. Review of disproportionate reporting of preferred terms (PT) during a time interval as compared to all data prior to the RP for Spikevax. Review of endpoints of interest (ie, case counts, demographics, country of origin, time to onset, seriousness, batch numbers, fatalities, AE from the product surveillance list of safety topics and based on MedDRA system organ class and high-level term, and identification of potential clusters of ICSRs.
Literature	Weekly literature review. Any literature abstract or article signal detection run will be reviewed.
EudraVigilance	Continuous monitoring. Biweekly critical review of the EudraVigilance data analysis system using available reports (i.e, Electronic Reaction Monitoring Reports [e-RMRs] and active substance groupings, ICSR line listings and ICSR forms).
VAERS	Frequency of review will depend on public availability of redacted VAERS extracts. Current estimates based on public communication as well as processing time indicate this frequency will range between every two to four weeks. Generation of disproportionality scores using Empirical Bayesian Geometrical Mean and its 90% confidence intervals after new uploads of Vaccine Adverse Event Reporting System extracts in Empirica Signal.
Health Authorities websites	Ongoing review of data published on the Safety Web Portals of selected major regulatory agencies to identify required actions regarding the product and similar products.

Product surveillance to identify safety signals will occur for any reported AEs including reactogenicity. Safety surveillance prioritization is for the safety concerns of the RMP, AESIs, or those AEs that may be serious or known to be often medicine related.

If any cluster of events is detected which points towards an unexpected event/syndrome, Moderna will perform appropriate signal evaluation and will provide this information to the appropriate regulatory agencies.

Table 101: Product Surveillance List of Spikevax Signalling Strategy By Category

Category	Safety Topics (Updates may be Needed if New Adverse Events Emerge)
Safety concerns	Myocarditis Pericarditis Use in pregnancy and while breast-feeding Long-term safety

Category	Safety Topics (Updates may be Needed if New Adverse Events Emerge)
Adverse events of special interest (AESI)	List of AESI (AESIs will be updated at least quarterly and as new information arises): Brighton Collaboration (Safety Platform for Emergency vACCines) ACCESS protocol US Centers for Disease Control and Prevention (preliminary list of AESI for VAERS surveillance) Medicines and Healthcare products Regulatory Agency (unpublished guideline).
Standard safety topics	Off-label Use Overdose Vaccination Administration Errors Product Quality Issues Drug-Drug Interactions Death Paediatric Use Geriatric Use Designated Medical Events (EMA/326038/2020)

As enhanced pharmacovigilance activities and to further support signal detection, observed rates of AEs will be compared with the expected rates which will be available from the scientific literature or other sources including those reported by the EMA-funded COVID-19 vaccine monitoring ACCESS program (Dodd 2020). Specifically, Moderna will use the AESIs agreed with the EMA to compare their observed reporting rates during the time period of the vaccination with Spikevax to the published expected incidence rates resulting from the ACCESS retrospective multi-database dynamic cohort study, conducted during the years 2017 to 2020, including the period of SARS-CoV-2 circulation in Europe.

During the evaluation of validated signals, Moderna will have access to a large US population of de-identified patient level information in healthcare claims databases to conduct additional Observed to Expected (O/E) analyses in defined cohorts as well as to potentially launch inferential epidemiologic studies to evaluate these safety signals in a rapid manner. This database, used in support of US PASS protocol mRNA-1273-P903, became available for signal assessment Q32021.

Reporting to EMA

Valid ICSRs that fulfil the local regulatory requirements for submission to the EudraVigilance database will be submitted within the 15- or 90-day time frame. This includes any COVID-19 cases requiring hospitalisation, vaccination administration errors, and MIS that may have been reported to occur in vaccinees.

Per consideration on core requirements for RMPs of COVID19 vaccine, coreRMP19 guidance EMA/PRAC/709308/2022, from the start of the distribution of Spikevax, Moderna regularly prepares a Summary Safety Report (SSR) (Table 102) for submission to health authorities in complement to the submission of routine periodic reports (Periodic Benefit-Risk Evaluation Reports). The need and frequency of submission of SSRs are re-evaluated based on the available evidence from post-marketing. SSRs and Periodic Safety Update Reports include results of the O/E analyses for AESIs as appropriate.

Table 102: Spikevax Summary Safety Reports

Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately)
Interval and cumulative number of reports, overall and by age groups and in special populations (e.g., pregnant women)
Interval and cumulative number of reports per HLT and SOC
Summary of designated medical events
Reports per EU country
Exposure data (lot distribution data total and per country)
Changes to reference safety information in the interval, and current CCDS
Ongoing and closed signals in the interval
AESI and RMP safety concerns: reports – numbers and relevant cases, including O/E analyses
Fatal reports -numbers and relevant cases, including O/E analyses
Risk/benefit considerations

Subsequent SSR content requirements will be defined by previous SSR assessment(s).

Potential Medication Errors

Large scale mass vaccination may potentially introduce the risk of medication errors related to storage, handling, dosing, and administration errors associated with a multidose vial, and confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC.

Traceability

The SmPC includes instructions for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability.

The vaccine carton labelling also contains a scannable 2D barcode that provides the batch/lot number and expiry date. In addition, Moderna 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.

III.2 Additional Pharmacovigilance Activities

In addition to actions targeted at identified and potential risks described in the safety specifications, the MAH intends to address general safety through continued clinical trial follow-up, a European Post Authorisation Safety Study, an observational study of Spikevax using routinely collected health data in 5 European countries, which monitors safety of Spikevax in pregnancy, a US Post Authorization safety study, and an observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy, collecting data in the US.

The immunogenicity and safety of mRNA vaccine boosters for SARS-CoV-2 variants, including Spikevax bivalent Original/Omicron BA.1 and Spikevax bivalent Original/Omicron BA.4-5, are

being evaluated in an open-label Phase 2/3 study. Some other study protocols will be updated to include these bivalent vaccines.

Study key detailed information is provided in text below and milestones in [Table 103](#).

Table 103: Additional Pharmacovigilance Activities

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
mRNA-1273- P203 <i>US</i> <i>Part 3 – US and Ex-US</i>	A Phase 2/3, Randomized, Observer-Blind, Placebo- Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age Interventional <i>Ongoing</i>	Evaluate the safety, reactogenicity, and effectiveness of Spikevax Assess safety and immunogenicity of mRNA-1273.222.	Randomized, observer- blind, placebo- controlled study	Healthy adolescents 12 to < 18 years of age	LPLV: 09 Jun 2025 Interim long- term safety CSR for Part A & B: 31 Oct 2022 Final CSR: 15 Jul 2025
mRNA-1273- P204 <i>US, Canada</i>	Phase 2/3, two- part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo- controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of elasomeran administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	Two-part, open-label, dose- escalation, age de- escalation and subsequent randomized, observer- blind, placebo- controlled expansion study	The study population includes healthy children of 3 age groups (6 years to < 12 years, 2 years to < 6 years, and 6 months to < 2 years) No participants in Part 1 participate in Part 2 of the study	Study start: 15 Mar 2021 Final CSR: 31 Mar 2024

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
	Interventional <i>Ongoing</i>				
mRNA-1273-P301 <i>US</i>	Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older <i>Ongoing</i>	Long-term safety data and durability of vaccine effectiveness (VE)	Randomized, stratified, observer-blind, placebo-controlled study	Males and females (≥ 18 years of age), who are at risk of SARS-CoV-2 infection with no known history of SARS-CoV-2 infection, including participants at increased risk of complications from COVID-19. Participants ≥ 65 years of age were eligible for enrolment with or without underlying medical conditions that might further increasing their risk of severe COVID-19.	LPLV: 30 Sep 2022 Interim CSR: 15 Oct 2021 Long-term follow-up Part B & C Interim CSR: 31 Dec 2022 Final CSR: 19 Dec 2023
Study mRNA-1273-P304 <i>US</i>	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. <i>Ongoing</i>	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of elasomeran. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.	Open label single treatment arm study in solid organ transplant recipients and healthy controls	Approximately 240 adult (≥ 18 years of age) male and female participants (220 kidney or liver transplant recipients, and 20 healthy adults) will be enrolled	Protocol submission: 05 Feb 2021 Interim Report: 31 Mar 2023 Final CSR: 31 May 2024
mRNA-1273-P903 <i>US</i>	Post-Authorization Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated	Secondary database analysis using retrospective analyses of pre-vaccination data as well as	A sample of pediatric, adolescent and adult individuals enrolled in health plans contributing data to HealthVerity will be used for	Protocol submission: 31 Jan 2021 Interim updates: 30 Apr 2021, 31 Jul 2021, 31 Oct 2021, 31 Jan 2022,

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
	Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity. Non-interventional Ongoing	safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	prospectively updating data during the vaccination period. It will include estimation of background rates of observed versus expected rates, and self-controlled risk interval analyses.	calculation of background rates. Patients from this dataset as well as additional patients with evidence of SARS-CoV-2 vaccination will be included as vaccine uptake increases.	30 Apr 2022, 31 Jul 2022, 31 Oct 2022, 31 Jan 2023 Final study report: 30 Jun 2023.
mRNA-1273-P904 Denmark, Norway, Italy, Spain, United Kingdom	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU. Non-interventional Study protocol will be adapted to stratify the result by Spikevax and Spikevax bivalents (both Original/Omicron BA.1 and BA.4-5), and to report on the progress and eventual updates in the submissions of the interim results	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: - To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group.	Secondary database analysis of observational data to estimate incidence rates of safety events of interest and other clinically significant events in cohorts of COVID-19 vaccine recipients in the EU.	Pediatric, adolescent, and adult individuals within the catchment area of participating data partners from the VAC4EU network	Feasibility assessment: 31 Jan 2021 Protocol submission: 30 Jun 2021 Interim updates: 30 Sep 2021, 31 Mar 2022, 30 Sep 2022, 31 Mar 2023 Final study report: 31 Dec 2023

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
	<i>Ongoing</i>	Secondary objective: - To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders			
mRNA-1273-P905 <i>Denmark, Norway, Italy, Spain, United Kingdom</i>	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries. Non-interventional Study protocol will be adapted to stratify the result by Spikevax and	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax? Primary objectives: - To determine whether exposure to the Moderna	Secondary database analysis comparing birth prevalence of study outcomes for pregnancies with and without COVID-19 Vaccine Moderna exposure.	The study population will encompass all pregnancies, identifiable in the databases, ending in a live or still birth; a spontaneous abortion; or an induced abortion, or an ectopic pregnancy, as identifiable in the participating databases	Feasibility assessment: 31 Jan 2021; Protocol submission: 30 Jun 2021; Interim updates: 31 Mar 2022, 30 Sep 2022, 31 Mar 2023; Final study report: 31 Dec 2023

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
	Spikevax bivalents (both Original/Omicron BA.1 and BA.4-5), and to report on the progress and eventual updates in the submissions of the interim results Planned	COVID-19 vaccine during pregnancy is associated with an increased risk of: a. Pregnancy complications b. Adverse pregnancy outcomes c. Major congenital malformations in the offspring (overall and organ-specific if feasible) d. Adverse neonatal outcomes Secondary objectives: - To describe utilization of COVID-19 Vaccine Moderna in pregnancy			
mRNA-1273-P901 US	Real-world study of the effectiveness of the Moderna COVID-19 Vaccine Non-interventional <i>Ongoing</i>	Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) in a large integrated healthcare system in the United States Primary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing	Prospective cohort study using electronic healthcare data from the Kaiser Permanente Southern California Integrated healthcare system	Individuals ≥ 6 months of age	Protocol submission: 01 Mar 2021 Interim updates: 14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 30 Jun 2022; 31 Jul 2022; 14 Dec 2022; 30 Jun 2023; 20 Dec 2023 Final study report: 14 Apr 2025

Study Number <i>Country(ies)</i>	Study Title <i>Study Type</i> <i>Study Status</i>	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
		<p>SARS-CoV-2 infection</p> <p>2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease</p> <p>Secondary Objectives</p> <p>1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-COV-2 infection by age and by sex</p> <p>2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection by race/ethnicity groups</p> <p>3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals with chronic diseases (e.g., chronic kidney disease, lung disease including chronic obstructive pulmonary disease [COPD] and asthma, diabetes)</p> <p>4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine</p>			

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
		<p>in preventing SARS-CoV-2 infection in individuals who are immunocompromised (e.g., HIV, cancer, transplant, immunosuppressive medications)</p> <p>5. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals with autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus)</p> <p>6. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in frail individuals</p> <p>7. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine administered during pregnancy in preventing SARS-CoV-2 infection in pregnant women</p> <p>8. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing</p>			

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
		<p>SARS-CoV-2 infection among individuals with a history of SARS-CoV-2 infection</p> <p>9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection when given concomitantly with another vaccine</p> <p>10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic SARS-CoV-2 infection</p> <p>11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic SARS-CoV-2 infection</p> <p>12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection</p> <p>13. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease</p> <p>14. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing</p>			

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
		<p>SARS-CoV-2 infection</p> <p>15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease.</p> <p>16. To assess the effectiveness of two doses of Moderna COVID-19 vaccine against SARS-CoV-2 variants (test-negative design)</p> <p>17. To assess the effectiveness of one dose of Moderna COVID-19 vaccine against SARS-CoV-2 variants (test-negative design)</p> <p>18. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection and severe COVID-19 disease in non-immunocompromised individuals</p> <p>19. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection and severe COVID-19 disease in immunocompromised individuals</p>			

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
mRNA-1273-P910 <i>Denmark, Norway, Spain, United Kingdom</i>	Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2 <i>Planned</i>	Describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.	Observational cohort study	Spikevax recipients and individuals diagnosed with myocarditis of all ages	Protocol submission: 26 Apr 2022 Interim report: 30 Aug 2022 31 Jan 2023 30 Jun 2023 31 Jan 2024 30 Jun 2024 31 Jan 2025 Final study report: 30 Jun 2025
mRNA-1273-P911 <i>US</i>	Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) <i>Ongoing</i>	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasomeran (SPIKEVAX) and Moderna COVID 19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).	Observational cohort study	Individuals diagnosed with myocarditis of all ages	Protocol submission: 30 Apr 2022 Interim report: 31 Oct 2022 31 Oct 2023 31 Oct 2024 31 Oct 2025 31 Oct 2026 31 Oct 2027 Final study report: 31 Oct 2028
mRNA-1273-P205 <i>US</i>	A Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants Initial development Ongoing	To evaluate the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS-CoV-2 variants including mRNA-1273.211, Spikevax, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA-	Open-label Phase 2/3 study consisting of 7 parts: A, (1, 2), B, C, D, E, F, G, and H.	Men and nonpregnant women, at least 18 years of age who previously received 2 doses of Spikevax (with other criteria depending on the Part of the study)	Study Start: 28 May 2021 Protocol Submission: 30 Jun 2022 Interim report: 30 Jun 2022 LSLV: 30 Apr 2023 Final CSR: 30 April 2024

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
		1273.222 (Spikevax bivalent Original/Omicron BA.4-5).			
mRNA-1273- P919 US	An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy Non- interventional Planned	This observational post-marketing safety study will evaluate the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to Spikevax during pregnancy.	Observational cohort study	An administrative claims data source in the US will be selected that includes capture of longitudinal data on diagnoses, procedures, medications, and vaccines used across all applicable healthcare settings (inpatient, emergency, and outpatient care). Mothers and infants will be linked via a common identifier and date of birth event. Mothers will be included in the study if they have adequate database enrollment to capture all pregnancy and pre-pregnancy baseline data with no prenatal exposure to major teratogenic infections or medications.	Protocol submission: 28 Oct 2022 Study completion: 30 Sep 2023 Final study report: 31 Mar 2024
mRNA-1273- P920 US	Post-marketing safety of Moderna Omicron- containing bivalent SARS- CoV-2 mRNA- 1273 booster vaccines in the United States	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	Observational cohort study with signal refinement through self- controlled risk interval analyses.	Pediatric, adolescent and adult individuals enrolled in health plans contributing data to HealthVerity.	Protocol submission: 01 Nov 2022 Interim report: 15 Sep 2023 Final study report:

Study Number Country(ies)	Study Title Study Type Study Status	Rationale and Study Objectives	Study Design	Study Population(s)	Milestones
	<i>Planned</i>	clinical practice.			15 Sep 2024
mRNA-1273- P306 US	An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years <i>Ongoing</i>	Evaluate the safety and reactogenicity of 25 µg of the mRNA-1273.214 vaccine administered as a 2-dose primary series 28 days apart in participants aged 6 months to < 6 years Evaluate the safety and reactogenicity of 10 µg of the mRNA-1273.214 vaccine administered as a single booster dose (BD) at least 4 months post-Dose 2 in participants aged 6 months to < 6 years, who have previously received mRNA-1273 as a primary series	Two parts open label double treatment arm study for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years	Individuals 6 Months to < 6 Years that are unvaccinated against SARS-CoV-2 or	Protocol submission: 27 May 2022 Study completion: 31 May 2024 Final study report: 31 Jan 2025

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 104: Ongoing and Planned Additional Pharmacovigilance Activities

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances				
None				
Category 3 – Required pharmacovigilance activities				
Study mRNA-1273-P301	Evaluate long-term safety data and durability of vaccine effectiveness (VE)	Vaccine-associated enhanced	Interim CSR	15 Oct 2021
			Long-term follow-up	31 Dec 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Study Status: Ongoing		disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Myocarditis Pericarditis Long-term safety	Part B & C Interim CSR	
			Final CSR	19 Dec 2023
Study mRNA-1273-P203 A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age Study Status: Ongoing	Evaluate the safety, reactogenicity, and effectiveness of Spikevax. Assess safety and immunogenicity of mRNA-1273.222	Myocarditis Pericarditis Long-term safety	Interim long-term safety CSR for Part A & B	31 Oct 2022
			Final CSR	15 Jul 2025
Study mRNA-1273-P204 Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age Study status: Ongoing	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of elasomeran administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Long-term safety	Study start	15 Mar 2021
			Final CSR	31 Mar 2024

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study mRNA-1273-P205 Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants Study status: Ongoing	Evaluate the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS CoV-2 variants including mRNA-1273.211, Spikevax, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA-1273.222 (Spikevax bivalent Original/Omicron BA.4-5).	Long-term safety	Study start	28 May 2021
			Interim report:	30 Jun 2022
			Final CSR	30 Apr 2024
Study mRNA-1273-P304 A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls Study status: Ongoing	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of elasomeran. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.	Myocarditis Pericarditis Use in immunocompromised subjects* AESI	Protocol submission	05 Feb 2021
			Interim report	31 Mar 2023
			Final CSR	31 May 2024
Study mRNA-1273-P903 Post-Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity Study status: Ongoing	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Long-term safety AESI and emerging validated safety signals	Protocol submission	31 Jan 2021
			Interim updates	30 Apr 2021, 31 Jul 2021, 31 Oct 2021, 31 Jan 2022, 30 Apr 2022, 31 Jul 2022, 31 Oct 2022, 31 Jan 2023
			Final study report	30 Jun 2023
Study mRNA-1273-P904 Post-Authorization Active Surveillance	The overarching research question of this study: Is the occurrence of each adverse event of special interest	Myocarditis Pericarditis Vaccine-associated	Protocol submission	30 Jun 2021

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Study status: Ongoing	(AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: - To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group. Secondary objective: - To assess whether vaccination with Spikevax is associated with increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders	enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)* Long-term safety Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)* Use in subjects with autoimmune or inflammatory disorders*	Interim Updates	30 Sep 2021, 31 Mar 2022, 30 Sep 2022, 31 Mar 2023,
			Final study report	31 Dec 2023
Study mRNA-1273-P905 Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries Study status: Ongoing	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax? Primary objectives: - To determine whether exposure to the Moderna	Use in pregnancy	Protocol submission	30 Jun 2021
			Interim updates	31 Mar 2022, 30 Sep 2022, 31 Mar 2023
			Final study report	31 Dec 2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	<p>COVID-19 vaccine during pregnancy is associated with an increased risk of:</p> <ul style="list-style-type: none"> a. Pregnancy complications b. Adverse pregnancy outcomes c. Major congenital malformations in the offspring (overall and organ-specific if feasible) d. Adverse neonatal outcomes <p>Secondary objectives:</p> <ul style="list-style-type: none"> - To describe utilization of COVID-19 Vaccine Moderna in pregnancy 			
<p>Study mRNA-1273-P901</p> <p>Real-world study of the effectiveness of the Moderna COVID-19 Vaccine</p> <p>Study Status: Ongoing</p>	<p>Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) in a large integrated healthcare system in the United States</p> <p>Primary Objectives</p> <ol style="list-style-type: none"> 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease <p>Secondary Objectives</p> <ol style="list-style-type: none"> 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection by age and by sex 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection by race/ethnicity groups 	<p>Use in immunocompromised subjects*</p> <p>Interaction with other vaccines, as possible*</p> <p>Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disorders)*</p> <p>Use in subjects with autoimmune or inflammatory disorders*</p>	Protocol submission	01 Mar 2021
			Interim updates	14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 30 Jun 2022; 31 Jul 2022; 14 Dec 2022; 30 Jun 2023; 20 Dec 2023
			Final study report	14 Apr 2025

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	<p>3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals with chronic diseases (e.g., chronic kidney disease, lung disease including chronic obstructive pulmonary disease [COPD] and asthma, diabetes)</p> <p>4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals who are immunocompromised (e.g., HIV, cancer, transplant, immunosuppressive medications)</p> <p>5. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in individuals with autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus)</p> <p>6. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection in frail individuals</p> <p>7. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine administered during pregnancy in preventing SARS-CoV-2 infection in pregnant women</p> <p>8. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection among individuals with a history of SARS-CoV-2 infection</p>			

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	<p>9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection when given concomitantly with another vaccine</p> <p>10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic SARS-CoV-2 infection</p> <p>11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic SARS-CoV-2 infection</p> <p>12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection</p> <p>13. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease</p> <p>14. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection</p> <p>15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease.</p> <p>16. To assess the effectiveness of two doses of Moderna COVID-19 vaccine against SARS-CoV-2 variants (test-negative design)</p> <p>17. To assess the effectiveness of one dose of Moderna COVID-19 vaccine against SARS-CoV-2 variants (test-negative design)</p> <p>18. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in</p>			

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	preventing SARS-CoV-2 infection and severe COVID-19 disease in non-immunocompromised individuals 19. To assess the effectiveness of a booster dose of Moderna COVID-19 vaccine in preventing SARS-CoV-2 infection and severe COVID-19 disease in immunocompromised individuals			
mRNA-1273-P910 Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2 Study status: Planned	Describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.	Myocarditis, Pericarditis	Protocol submission	26 Apr 2022
			Interim report	30 Aug 2022 31 Jan 2023 30 Jun 2023 31 Jan 2024 30 Jun 2024 31 Jan 2025
			Final study report	30 Jun 2025
mRNA-1273-P911 Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) Study status: Ongoing	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasomeran (SPIKEVAX) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).	Myocarditis	Protocol submission	30 Apr 2022
			Interim report	31 Oct 2022 31 Oct 2023 31 Oct 2024 31 Oct 2025 31 Oct 2026 31 Oct 2027
			Final study report	31 Oct 2028
mRNA-1273-P919 An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy Study status: Planned	This observational post-marketing safety study will evaluate the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections following maternal exposure to Spikevax during pregnancy.	Use in pregnancy	Protocol submission	28 Oct 2022
			Study completion	30 Sep 2023
			Final study report	31 Mar 2024
mRNA-1273-P920	The overarching aim of this study is to characterize the	Anaphylaxis* Myocarditis	Protocol submission	01 Nov 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States Study status: Planned	safety of the Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccine as used in routine clinical practice.	Pericarditis Use in immunocompromised subjects* AESI and emerging validated safety signals	Interim report	15 Sep 2023
			Final study report	15 Sep 2024
mRNA-1273-P306 An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years Study status: Ongoing	Evaluate the safety and reactogenicity of 25 µg of the mRNA-1273.214 vaccine administered as a 2-dose primary series 28 days apart in participants aged 6 months to < 6 years Evaluate the safety and reactogenicity of 10 µg of the mRNA-1273.214 vaccine administered as a single booster dose (BD) at least 4 months post-Dose 2 in participants aged 6 months to < 6 years, who have previously received mRNA-1273 as a primary series	Anaphylaxis* Myocarditis Pericarditis Long-term safety	Protocol submission	27 May 2022
			Study completion:	31 May 2024
			Final study report:	31 Jan 2025

* No longer safety concerns in the RMP.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 105: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Myocarditis	<p><u>Routine risk communication:</u> SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC Section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2).</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>
Pericarditis	<p><u>Routine risk communication:</u> SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. (SmPC Section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2).</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>
Use in pregnancy and while breast-feeding	<p><u>Routine risk communication:</u> SmPC, Section 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data; PL: 2. What you need to know before you are given Spikevax?</p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u> None.</p>

Safety Concern	Routine Risk Minimisation Activities
Long-term safety	<u>Routine risk communication:</u> None. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> None. <u>Other routine risk minimisation measures beyond the Product Information:</u> None.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety of Spikevax.

V.3 Summary of Risk Minimisation Measures

Table 106: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC Sections 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects PL Section 2 and 4</p> <p>Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC section 4.4).</p> <p>Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2).</p> <p><u>Additional risk minimisation measures:</u></p> <p>None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>Targeted follow up questionnaire to collect structured clinical details of myocarditis or myopericarditis in individuals who have received Spikevax (see Section III.1).</p> <p><u>Additional pharmacovigilance activities (final CSR due date):</u></p> <p>Study mRNA-1273-P903 (final CSR: 30 Jun 2023) Study mRNA-1273-P904 (final CSR: 31 Dec 2023) Study mRNA-1273-P204 (final CSR; 31 Mar 2024) Study mRNA-1273-P301 (final CSR: 19 Dec 2023) Study mRNA-1273-P304 (final CSR: 31 May 2024) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P306 (final CSR: 31 Jan 2025) Study mRNA-1273-P910 (final CSR: 28 Feb 2025) Study mRNA-1273-P911 (final CSR: 31 Oct 2028) Study mRNA-1273-P920 (final CSR: 15 Sep 2024)</p>

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pericarditis	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 Special Warnings and Precautions for Use; 4.8 Undesirable effects; PL Section 2 and 4. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). <u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> Targeted follow up questionnaire to collect structured clinical details of pericarditis in individuals who have received Spikevax (see Section III.1). <u>Additional pharmacovigilance activities (final CSR due date):</u> Study mRNA-1273-P903 (final CSR: 30 Jun 2023) Study mRNA-1273-P904 (final CSR: 31 Dec 2023) Study mRNA-1273-P204 (final CSR; 31 Mar 2024) Study mRNA-1273-P301 (final CSR: 19 Dec 2023) Study mRNA-1273-P304 (final CSR: 31 May 2024) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P306 (final CSR: 31 Jan 2025) Study mRNA-1273-P920 (final CSR: 15 Sep 2024) Study mRNA-1273-P910 (final CSR: 28 Feb 2025)</p>
Use in pregnancy and while breast-feeding	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.6 Fertility, pregnancy and lactation; 5.3 Preclinical safety data; PL Section 2. <u>Additional risk minimisation measures:</u> None.</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None. <u>Additional pharmacovigilance activities (final CSR due date):</u> Study mRNA-1273-P905 (final CSR: 31 Dec 2023) Study mRNA-1273-P919 (final CSR: 31 Mar 2024)</p>
Long-term safety	<p><u>Routine risk minimisation measures:</u> None. <u>Additional risk minimisation measures:</u> None.</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None. <u>Additional pharmacovigilance activities (final CSR due date):</u> Study mRNA-1273-P903 (final CSR: 30 Jun 2023) Study mRNA-1273-P904 (final CSR: 31 Dec 2023) Study mRNA-1273-P204 (final</p>

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		CSR; 31 Mar 2024) Study mRNA-1273-P301 (final CSR: 19 Dec 2023) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P205 (final CSR: 30 Apr 2024) Study mRNA-1273-P306 (final CSR: 31 Jan 2025)

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Spikevax (Elasomeran), Spikevax bivalent Original/Omicron BA.1 (Elasomeran/Imelasomeran), and Spikevax bivalent Original/Omicron BA.4-5 (Elasomeran/Davesomeran)

This is a summary of the risk management plan (RMP) for Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5. The RMP details important risks of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5, how these risks can be minimised, and how more information will be obtained about Spikevax's, Spikevax bivalent Original/Omicron BA.1's, and Spikevax bivalent Original/Omicron BA.4-5's risks and uncertainties (missing information).

Spikevax's, Spikevax bivalent Original/Omicron BA.1's, and Spikevax bivalent Original/Omicron BA.4-5's summaries of product characteristics (SmPCs) and their package leaflets give essential information to healthcare professionals and patients on how Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 should be used.

This summary of the RMP for Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the Spikevax's, Spikevax bivalent Original/Omicron BA.1's, and Spikevax bivalent Original/Omicron BA.4-5's RMP.

I The Medicine and What it is Used for

Spikevax is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months of age and older. Spikevax bivalent Original/Omicron BA.1 is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19. Spikevax bivalent Original/Omicron BA.4-5 is authorised for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 6 months of age and older.

The active substance in Spikevax is mRNA encoding the SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and it is given by intramuscular route. The active substances in Spikevax bivalent Original/Omicron BA.1 are mRNA encoding the original SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and mRNA encoding the SARS-CoV-2 Spike protein of the Omicron variant embedded in lipid nanoparticles (imelasomeran) and it is given by intramuscular route. The active substances in Spikevax bivalent Original/Omicron BA.4-5 are mRNA encoding the original SARS-CoV-2 Spike protein embedded in lipid nanoparticles (elasomeran) and mRNA encoding the SARS-CoV-2 Spike protein of the Omicron variant embedded in lipid nanoparticles (davesomeran) and it is given by intramuscular route.

Further information about the evaluation of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 benefits can be found in the Spikevax EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA)

website, under the medicine's webpage:
www.ema.europa.eu/en/medicines/human/EPAR/spikevax

II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5, together with measures to minimise such risks and the proposed studies for learning more about Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about Adverse Reactions (ARs) is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 is not yet available, it is listed under “missing information” below.

In the case of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5, these measures are supplemented with additional pharmacovigilance activities mentioned under the relevant important risks below.

II.A List of Important Risks and Missing Information

Important risks of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5 are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Spikevax, Spikevax bivalent Original/Omicron BA.1, and Spikevax bivalent Original/Omicron BA.4-5. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 107: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Myocarditis Pericarditis
Important potential risks	None
Missing information	Use in pregnancy and while breast-feeding Long-term safety

II.B Summary of Important Risks

Table 108: Important Identified Risk: Myocarditis

Important Identified Risk: Myocarditis	
Evidence for linking the risk to the medicine	Data to evaluate the safety concern were derived from clinical trials and the post-authorisation safety.
Risk factors and risk groups	<p>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.</p> <p>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. 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.</p> <p>The spontaneous reports included in the global safety database included 4 cases that reported previous COVID-19 infection (5.9%) with these reports in the 18 to 39 years of age group. There were 5 reports of previous Myocarditis/ Pericarditis medical history (5.9%), 14 reports of cardiovascular conditions (16.5%), 5 with Thyroid conditions (5.9%), and 12 (14.1%) had previous medical histories of allergy-type conditions including history of anaphylaxis.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects</p> <p>Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC Section 4.4).</p> <p>Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2).</p> <p><u>Additional risk minimisation measures:</u></p> <p>None</p>

Important Identified Risk: Myocarditis	
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P910 Study mRNA-1273-P911 Study mRNA-1273-P301 Study mRNA-1273-P304 Study mRNA-1273-P203 Study mRNA-1273-P306 Study mRNA-1273-P920 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 109: Important Identified Risk: Pericarditis

Important Identified Risk: Pericarditis	
Evidence for linking the risk to the medicine	Data to evaluate the safety concern were derived from the clinical trials and post-authorisation safety data.
Risk factors and risk groups	<p>In most cases, the cause of pericarditis is idiopathic or is assumed to be due to a viral infection. 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.</p> <p>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.</p> <p>A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years. 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.</p> <p>Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.</p>

Important Identified Risk: Pericarditis	
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. (SmPC Section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). <u>Additional risk minimisation measures:</u> None.</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u> Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P301 Study mRNA-1273-P304 Study mRNA-1273-P203 Study mRNA-1273-P910 Study mRNA-1273-P306 Study mRNA-1273-P920 See Section II.C of this summary for an overview of the post-authorisation development plan.</p>

Table 110: Missing information: Use in Pregnancy and While Breast-Feeding

Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data PL Section 2 <u>Additional risk minimisation measures:</u> None</p>
Additional pharmacovigilance activities	<p><u>Additional pharmacovigilance activities:</u> Study mRNA-1273-P905 Study mRNA-1273-P919 See section II.C of this summary for an overview of the post-authorisation development plan.</p>

Table 111: Missing information: Long-Term Safety

Risk minimisation measures	<u>Routine risk minimisation measures:</u> None <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P301 Study mRNA-1273-P203 Study mRNA-1273-P205 Study mRNA-1273-P306 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of Spikevax, Spikevax bivalent Original/Omicron BA.1, or Spikevax bivalent Original/Omicron BA.4-5.

II.C.2 Other Studies in Post-Authorisation Development Plan

The following studies are considered ongoing and/or planned additional pharmacovigilance activities:

Study Title and Number	Purpose of the Study
Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older (mRNA-1273-P301)	Long-term safety data and durability of vaccine effectiveness (VE).
A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age (mRNA-1273-P203)	Evaluate the safety, reactogenicity, and effectiveness of Spikevax. Assess safety and immunogenicity of mRNA-1273.222.
Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age (mRNA-1273-P204)	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of elasomeran administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age

Study Title and Number	Purpose of the Study
Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants (mRNA-1273-P205)	Evaluate the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS CoV-2 variants including mRNA-1273.211, Spikevax, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA-1273.222 (Spikevax bivalent Original/Omicron BA.4-5)
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 (mRNA-1273-P304)	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of SARS-CoV-2 elasmomeran vaccine. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.
Post-Authorisation 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 (mRNA-1273-P903)	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria.
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (mRNA-1273-P904)	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax?
Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries (mRNA-1273-P905)	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax?
Real-world study of the effectiveness of the Moderna COVID-19 vaccine (mRNA-1273-P901)	Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) in a large integrated healthcare system in the United States.
Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2 (mRNA-1273-P910)	Describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.
Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) (mRNA-1273-P911)	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasmomeran (SPIKEVAX) and Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5).
An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy	This observational post-marketing safety study will evaluate the risk of adverse pregnancy outcomes, birth outcomes, infant outcomes, or early life infections

Study Title and Number	Purpose of the Study
(mRNA-1273-P919)	following maternal exposure to Spikevax during pregnancy
Post-marketing safety of Moderna Omicron-containing bivalent SARS-CoV-2 mRNA-1273 booster vaccines in the United States (mRNA-1273-P920)	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.
An Open-Label, Phase 3 Study to Evaluate the Safety and Immunogenicity of the mRNA-1273.214 Vaccine for SARS-CoV-2 Variants of Concern in Participants Aged 6 Months to < 6 Years (mRNA-1273-P306)	Evaluate the safety and reactogenicity of 25 µg of the mRNA-1273.214 vaccine administered as 2-dose primary series 28 days apart in participants aged 6 months to < 6 years. Evaluate the safety and reactogenicity of 10 µg of the mRNA-1273.214 vaccine administered as a single booster dose (BD) at least 4 months post-Dose 2 in participants aged 6 months to < 6 years, who have previously received mRNA-1273 as a primary series

Part VII: Annexes

Annex 1 - EudraVigilance Interface

Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

[Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms](#)

Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV

Annex 6 – Details of Proposed Additional Risk Minimisation Activities

Annex 7 – Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan Over Time

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Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Follow-Up Forms

Myocarditis / Pericarditis Questionnaire

Supplemental Follow-up Questions for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna's COVID-19 vaccine (mRNA-1273)

Patient Initials/Gender:

Patient DOB/Age:

Reported Event(s):

Please provide the following additional information to the best of your knowledge and return with the general vaccine adverse event report form. When providing a date as part of your response, please be as accurate as possible. You may attach additional pages and notes, as needed.

Please indicate below whether the patient currently has, or has had in the past, any of the following cardiovascular conditions. If any apply, please provide the additional details requested.

Condition		Start date(s)	Stop date(s)	Details of illness, including treatment with start and stop dates (medications, surgeries, and other procedures)
Myocarditis	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	
Pericarditis	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	
Hypertension	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	
Thrombosis (blood clots) – e.g. pulmonary embolism, deep vein thrombosis (DVT), etc.	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	
Cardiac arrhythmia (e.g. atrial fibrillation (afib), supraventricular tachycardia (SVT), etc.)	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	
Myocardial infarction (heart attack)	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	
Coronary artery disease	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	
Other heart or vascular condition -specify: _____	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk		<input type="checkbox"/> Ongoing	

Supplemental Follow-up Questions for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna's COVID-19 vaccine (mRNA-1273)

Patient Initials/Gender:

Patient DOB/Age:

Reported Event(s):

Does the patient have a history of any of the following conditions?

Condition		If yes, please specify:
Bacterial Infections in the last 6 months (e.g. Streptococcal (Strep) or Staphylococcal (Staph) infections)	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Diagnosis: Treatment with dates: Date recovered:
Viral Infections in the last 6 months (COVID-19, Influenza (Flu), Parvovirus, Enterovirus (Cocksackie virus), etc.)	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Diagnosis: Treatment with dates: Date recovered:
Fungal Infections in the last 6 months (e.g. yeast infections (Candida), Aspergillus, Histoplasma, etc.)	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Diagnosis: Treatment with dates: Date recovered:
Tick-borne disease (Lyme disease, Ehrlichiosis, Babesiosis, etc.)	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Diagnosis: Treatment with dates:
Autoimmune disorders (e.g. systemic lupus erythematosus (SLE), Sjogren's syndrome, giant cell arteritis, rheumatoid arthritis, mixed connective tissue disease, rheumatic fever, etc.)	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Diagnosis: Treatment with dates:
HIV	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Treatment with dates: Current status of disease:
Use of Immunosuppressant medications	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Medication: Condition treated: Stop date:

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Supplemental Follow-up Questions for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna's COVID-19 vaccine (mRNA-1273)

Patient Initials/Gender:

Patient DOB/Age:

Reported Event(s):

Condition		If yes, please specify:
Cancer	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Diagnosis: Treatments with dates: Current status of disease:
Radiation and/or Chemotherapy treatment	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unk	Start date: Type of treatment & how often: Condition treated: Stop date:

Please describe the patient's participation in sports or other strenuous physical activities (include type of activity, how often, and when they last participated): ☐ Unknown ☐ No sports/strenuous activities

Please check all symptoms experienced surrounding the events, provide onset dates, and how long each lasted/duration. If still ongoing, please note "ongoing" for the duration.

<input type="checkbox"/> New onset chest pain/pressure	<input type="checkbox"/> Cough	<input type="checkbox"/> Abnormal tiredness	<input type="checkbox"/> Abdominal pain
Start date:	Start date:	Start date:	Start date:

Duration:	Duration:	Duration:	Duration:
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<input type="checkbox"/> Shortness of breath	<input type="checkbox"/> Weakness	<input type="checkbox"/> Swelling in feet/ankles	<input type="checkbox"/> Dizziness/Fainting
Start date:	Start date:	Start date:	Start date:

Duration:	Duration:	Duration:	Duration:
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<input type="checkbox"/> Sudden, excessive sweating	<input type="checkbox"/> Nausea, vomiting, or diarrhea	<input type="checkbox"/> Shoulder/upper back pain	<input type="checkbox"/> Palpitations/Irregular heart beats
Start date:	Start date:	Start date:	Start date:

Duration:	Duration:	Duration:	Duration:
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MCN:

Supplemental Follow-up Questions for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna's COVID-19 vaccine (mRNA-1273)

Patient Initials/Gender:

Patient DOB/Age:

Reported Event(s):

Please provide details of any treatment for the potential/confirmed myocarditis/pericarditis diagnosis:

Treatment	Dose/ Frequency	Route	Start Date	Stop Date

* * * *

Please provide details for the following physical and diagnostic exams:

Exam	Completed?	If yes, date collected with results including units and reference ranges (records may be attached, if needed):
Physical Exam	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Pulsus Paradoxus: <input type="checkbox"/> No <input type="checkbox"/> Yes – If yes: Expiratory SBP_____; Inspiratory SBP_____ Pericardial friction rub: <input type="checkbox"/> Yes <input type="checkbox"/> No Other abnormal findings:
Troponin T	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date(s): Results with units: Normal range:
Troponin I	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date(s): Results with units: Normal range:
CK-MB	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date(s): Results with units: Normal range:
C-reactive protein (CRP)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date(s): Results with units: Normal range:
D-dimer	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date(s): Results with units: Normal range:
Erythrocyte sedimentation rate (sed rate, ESR, Westergren sed rate)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date(s): Results with units: Normal range:

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Supplemental Follow-up Questions for Reports of Potential/Confirmed Myocarditis/Pericarditis with the use of Moderna's COVID-19 vaccine (mRNA-1273)

Patient Initials/Gender:

Patient DOB/Age:

Reported Event(s):

Exam	Completed?	If yes, date collected with results including units and reference ranges (records may be attached, if needed):	
Chest X-ray	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date:	Interpretation/results:
Electrocardiogram (EKG)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date:	Interpretation/results:
Echocardiogram	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date:	Interpretation/results:
Magnetic Resonance Imaging (MRI)/Cardiac MRI	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date:	Interpretation/results:
Computed Tomography/CT scan	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date:	Interpretation/results:
Pericardial/Endomyocardial biopsy	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Date: Results:	