EU Risk Management Plan for Spikevax (COVID-19mRNA vaccine)

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

RMP version number: 3.0

Data lock point for this RMP: 31 December 2021

Date of final sign off: 01 March 2022

Rationale for submitting an updated RMP:

- Update Spikevax indication to include individuals 6 years of age and older.
- Inclusion of mRNA-1273-P204 that evaluates the use of Spikevax in children 6 to < 12 years of age

Summary of significant changes in this RMP:

Compared to the previously approved COVID-19 Vaccine Moderna European Union (EU) RMP version 2.3, this RMP version 3.0 has been updated:

- To add paediatric information related to the new indication for individuals 6 years of age and older
- To update the Epidemiology of the Indication as of 31 December 2021
- To update the clinical trial exposure data for mRNA-1273-P204
- To add mRNA-1273-P204 as a Category 2 study in the Pharmacovigilance Plan
- To update the post-authorisation exposure data up to 31 December 2021
- To present the study protocols as previously approved protocols or final protocols not reviewed by the competent authority

RMP Module:		Significant Changes:
Part I Product Overview		Updated product details.
Part II Safety Specification		
1.	**Module SI Epidemiology of the indication(s) and target population(s)**	Details updated through 31 December 2021.
2.	**Module SII Non-clinical part of the safety specification**	No changes.
3.	**Module SIII Clinical trial exposure**	Updated mRNA-1273-P204 data.
4.	**Module SIV Populations not studied in clinical trials**	Updated paediatric information.

RMP Module:	Significant Changes:
5. Module SV Post-authorisation experience	Updated with cumulative data through 31 December 2021.
6. Module SVI Additional EU requirements for the safety specification	No changes.
7. Module SVII Identified and potential risks	Module SVII.2 updated to affirm no new safety concerns identified from mRNA-1273-P204.
8. Module SVIII Summary of the safety concerns	No changes.
Part III Pharmacovigilance plan	Included mRNA-1273-P204 as a Category 2 study.
Part IV Plans for post-authorisation efficacy studies	No changes.
Part V Risk minimisation measures	Added mRNA-1273-P204 as an additional PV activity for the relevant safety concerns.
Part VI Summary of the risk management plan	Added mRNA-1273-P204 as an additional PV activity for the relevant safety concerns and as another study in the post-authorisation development plan.
Part VII Annexes	Annex 2 – Included mRNA-1273-P204 as per Part III update. Annex 3 – Included mRNA-1273-P204 as per Part III update. Updated to present study protocols as previously approved protocols or final protocols not reviewed by the competent authority. Annex 7 – Removed references relating to deleted text in Module SVII sections SVII.1 and SVII.2. Annex 8 – Updated to reflect the changes made to the RMP.

Other RMP versions under evaluation:

Not Applicable

Details of the currently approved RMP:

Version number:	2.3
Approved with procedure:	EMEA/H/C/005791/II/0022 and EMEA/H/C005791/II/0028
Date of approval (opinion date):	10 February 2022

EU QPPV name[1] : 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 marketing authorisation applicant´s QPPV. The electronic signature is available on file.

Table of Contents

List of Figures

List of Tables

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
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
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
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicine 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
IM	Intramuscular(ly)
Ig	Immunoglobulin
IP	Investigational product
IR	Incidence rate
IRR	Incidence rate ratio
KPSC	Kaiser Permanente Southern California
LPLV	Last participant last visit
LNP	Lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS	Multisystem inflammatory syndrome
mRNA	Messenger ribonucleic acid
nAb	Neutralizing antibody(ies)
NHP	Nonhuman primate
NP	Nasopharyngeal
NPI	Nonpharmaceutical interventions
O/E	Observed to expected
PL	Patient leaflet
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
RMP	Risk management plan

RT-PCR	Reverse transcription polymerase chain reaction
SARS	Severe acute respiratory syndrome
SCRI	Self-controlled risk interval
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TESSy	The European Surveillance System
Th	T helper
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 COVID-19 mRNA vaccine and mRNA-1273 are used to identify the product.

Part I: Products Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	COVID-19 mRNA vaccine (nucleoside modified)
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Vaccine, COVID-19 Vaccines (J07BX03)
Marketing Authorisation Holder	MODERNA BIOTECH SPAIN, S.L. Calle Monte Esquinza 30 28010 Madrid Spain
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area	Spikevax
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** 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 mRNA-1273 Drug Substance in place of the normal uridine base to minimise the indiscriminate recognition of the mRNA-1273 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). **Structure of mRNA**  Abbreviations: mRNA, messenger RNA; PolyA, polyadenylated; UTR, untranslated region. **Summary of mode of action** 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). The spike glycoprotein is membrane bound, mimicking the presentation of natural infection.

	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. **Important information about its composition** The active substance is 0.10 mg mRNA encoding the pre fusion stabilized spike glycoprotein of SARS-CoV-2 (embedded in SM-102 lipid nanoparticles) The other ingredients are lipidSM-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.
Hyperlink to the Product Information	Module 1
Indication(s) in the EEA	Current: Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older.
Dosage in the EEA	Current: ***Primary series*** *Individuals 12 years of age and older* Spikevax is administered as a course of 2 (two) 100 microgram doses (0.5 mL each). *Children 6 through 11 years of age* Spikevax is administered as a course of 2 (two) 50 microgram doses (0.25 mL each, containing 50 micrograms mRNA, which is half of the primary dose for individuals 12 years and older). It is recommended to administer the second dose 28 days after the first dose. *Severely immunocompromised aged 6 years and older* A third dose may be given at least 28 days after the second dose to individuals 12 years of age and older (0.5 mL, 100 micrograms) and children 6 through 11 years (0.25 mL, 50 micrograms) who are severely immunocompromised (see section 4.4). ***Booster dose*** *Individuals 18 years of age and older* A booster dose of Spikevax (0.25 mL, containing 50 micrograms mRNA, which is half of the primary dose) should be given intramuscularly to adults at least 3 months after completion of the primary series. Spikevax may be used to boost adults who have received a primary series with Spikevax or a primary series comprised of another mRNA vaccine or adenoviral vector vaccine.

Pharmaceutical form(s) and strengths	Current: Spikevax is a dispersion for injection. It is supplied as a multidose vial that contains 10 doses of 0.5 mL each or a maximum of 20 doses of 0.25 mL each. One dose (0.5 mL) contains 100 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles). One dose (0.25 mL) contains 50 micrograms of elasomeran, a COVID-19 mRNA Vaccine (embedded in SM-102 lipid nanoparticles).
Vaccine construct and the formulation	It is 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. The other ingredients are Lipid 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.
Is/will the product be subject to additional monitoring in the EU?	Yes.

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 years 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 COVID-19 infection prevention and control living guideline: mask use in community settings, 22 December 2021 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 27 December 2021, approximately 290,469,670 confirmed cases and 5,442,452 deaths have been attributed to the COVID-19 pandemic globally (WHO 2021a). Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions (WHO 2020a and WHO COVID-19 infection prevention and control living guideline: mask use in community settings, 22 December 2021 2020b).

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 27 December 2021, 30.8% of global mortality from SARS-CoV-2 was from the European Region (WHO 2019).

Data collected by the European Centre for Disease Prevention and Control (ECDC) from 30 countries indicated that the 14-day case notification rate for the European Union/European Economic Area (EU/EEA) the end of week 52 of 2021 (31 December 2021) was 1384.3 per 100,000 population . It was highest in Ireland (3470.9/100,000), Cyprus (3084.6/100,000), Iceland (2793.5/100,000) and Spain (2641.3/100,000). It was lowest in Romania (71.3/100,000), Bulgaria (343.0/100,000), Hungary (346.8/100,000), Austria (424.3/100,000) and Poland (435.8/100, 000) (ECDC 2021a).

At the same date (week ending 31 December 2021), the 14-day number of COVID-19 deaths per 1,000,000 persons was 51.3/1,000,000. It was highest in Poland (160.8/1,000,000), Croatia (154.7/1,000,000), Hungary (149.9/1,000,000), Bulgaria (134.6/1,000,000) and Slovakia (123.1/1,000,000). The lowest 14-day number of COVID-19 deaths per 1,000,000 was in Iceland (2.7/1,000,000), Malta (5.8/1,000,000), Sweden (10.6/1,000,000), Ireland (15.5/1,000,000), and Romania (18.3/1,000,000) (ECDC 2021a).

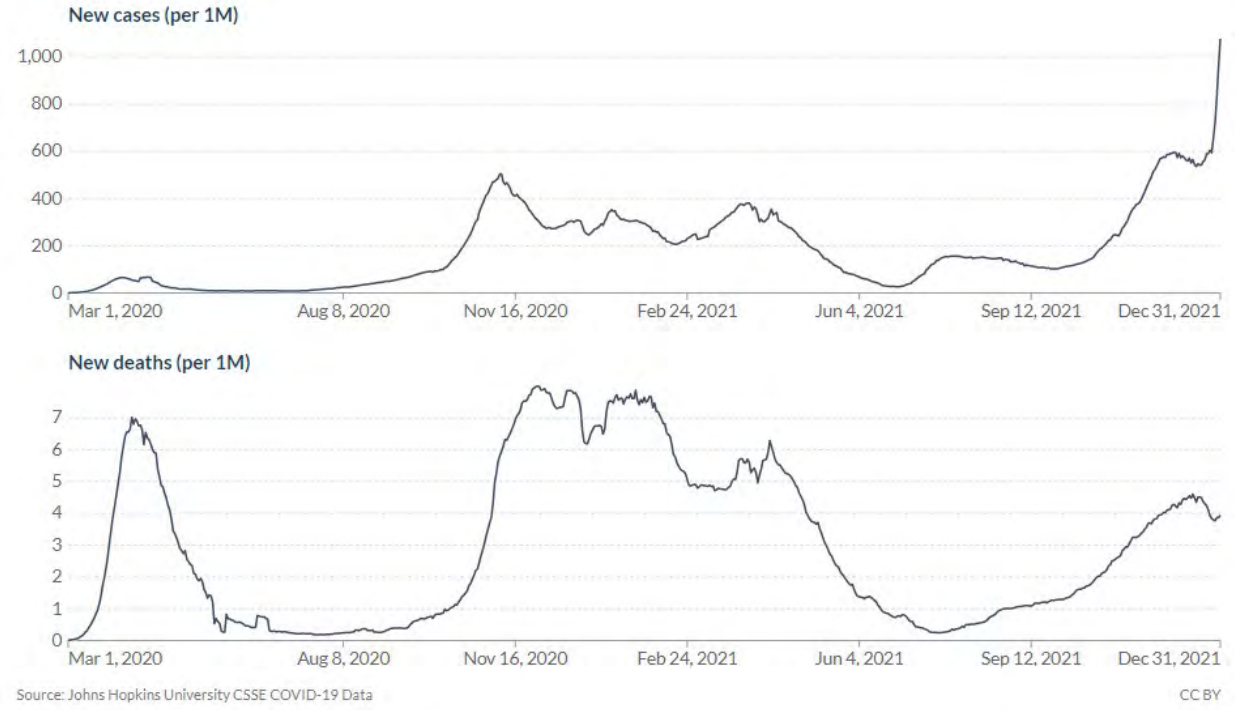
The below table presents key epidemiology indicators per country.

Table 2: 14-Day Case and Death Notification Rates in the EU/EEA (Week ending 31 December 2021)

Country	Case Rate (14-day notification per 100,000 inhabitants)	Death Rate (14-day notification per 100,000,000 inhabitants)
EU/EEA (total)	1384.3	51.3
Austria	424.3	22.6
Belgium	1067.5	32.4
Bulgaria	343.0	134.6
Croatia	1123.4	154.7
Cyprus	3084.6	28.2
Czechia	715.6	87.9
Denmark	2623.0	21.5
Estonia	807.8	39.1
Finland	1174.5	28.6
France	2476.8	37.4
Germany	484.1	41.4
Greece	2315.1	96.0
Hungary	346.8	149.9
Iceland	2793.5	2.7
Ireland	3470.9	15.5
Italy	1852.6	33.6
Latvia	518.0	73.4
Liechtenstein	1450.4	25.8
Lithuania	773.8	63.3
Luxembourg	1362.5	22.4
Malta	2443.4	5.8
Netherlands	1067.8	18.3
Norway	921.3	18.8
Poland	435.8	160.8
Portugal	2007.7	20.0
Romania	71.3	18.3
Slovakia	731.1	123.1
Slovenia	877.6	59.2
Spain	2641.3	20.1
Sweden	847.6	10.6

Figure 1 displays the cases and deaths in the EU from March 2020 to 31 Dec 2021 (ECDC 2021a).

Figure 1: COVID-19 Cases and Deaths in the EU per Million People, 7-Day Rolling Average



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 2021b).

Among the 15 EU/EEA countries with an acceptable sequencing volume in the period from 14 June to 31 December 2021 (the most recent data available in week 52 (week ending on 31 December), the median (range) of the VOC reported in all samples sequenced was 0.0% (0.0-0.1%) for B.1.351 (Beta), 25.7% (0.5-98%) for B.1.617.2 (Delta), 0.1% (0.1-0.1%) for P.1 (Gamma), and 67.9% (1.8-99.5%) for B.1.1.529 (Omicron) (ECDC 2021a).

Age specific Case Notification rates

The case notification rate was significantly higher among elderly populations during the first 3 months of the pandemic. However, this has shifted during the past several months, with younger age groups (<15 years and 15-24 years old) now 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 NPIs as older population groups achieve vaccination including booster doses (ECDC 2021b).

Incidence Among Adolescents in the EU/EEA

Country level and pooled case-based data reported to The European Surveillance System (TESSy) by 16 countries in the EU/EEA indicate that case notification rates among adolescents are among the highest since the start of the pandemic (01 Jun 2021) (ECDC 2021b).

Data on the 14-day age-specific notification rate of new COVID-19 cases available as of week 52 (i.e., week ending 31 December 2021) is available per age group and country at TESSy (ECDC 2021c). For children and adolescents < 15 years-old rates, notification rate was highest in Denmark (3043.4/100,000), Iceland (2691.3/100,000), Spain (2397.2/100,000), Cyprus (2178.6/100,000) and Italy (1812.9/100,000). Among people aged 15-24 years the 14-day notification rate per 100,000 persons is currently highest in Cyprus (6560.8/100,000), Greece (6346.2/100,000), Denmark (5335.5/100,000), Iceland (4690.4/100,000) and Malta (4327.6/100,000).

Incidence of COVID-19 in the US

As of January 5, 2022, the current 7-day moving average of daily new cases (586,391) increased 85.7% compared with the previous 7-day moving average (315,851). A total of 57,898,239 COVID-19 cases have been reported in the United States as of January 5, 2022.

As observed with the EU/EEA data, there has been a shift in case notification rate towards younger age groups. This has not been reflected in an increased mortality in this age group due to increase in the vaccination of the younger age groups and they remain less vulnerable to severe manifestations of the disease.

Figure 2 below presents the trends in cases per 100,000 population by age group since 01 March 2020 to 31 December 2021 (CDC 2021a).

Figure 2: Cases by age group (per 100,000) from 01 March 2020 to 31 December 2021 in the US (CDC)

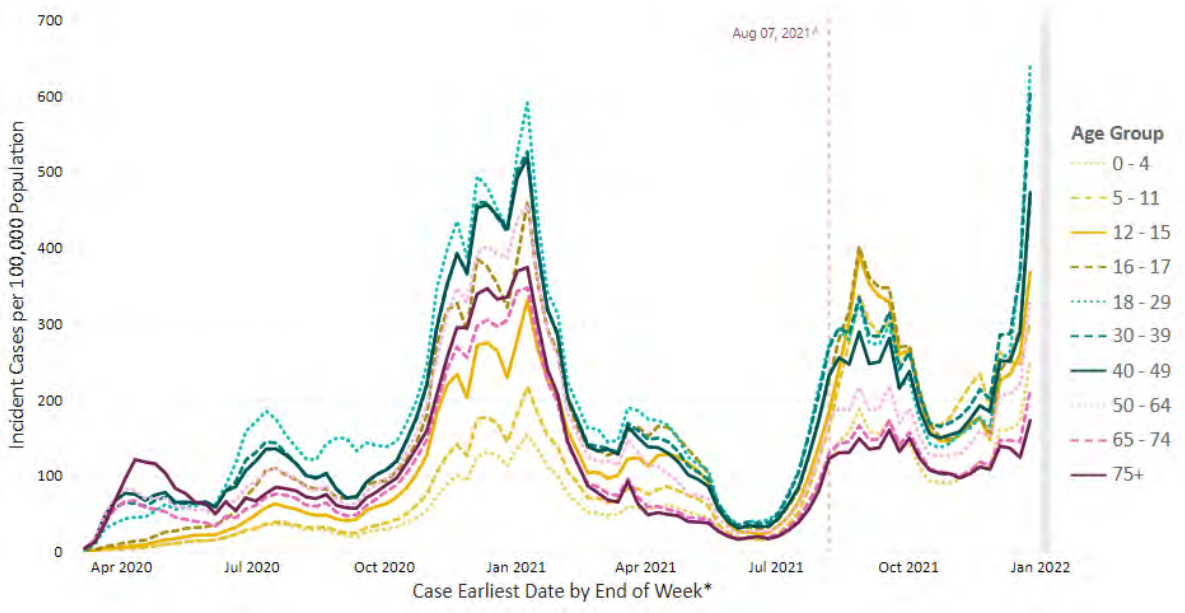
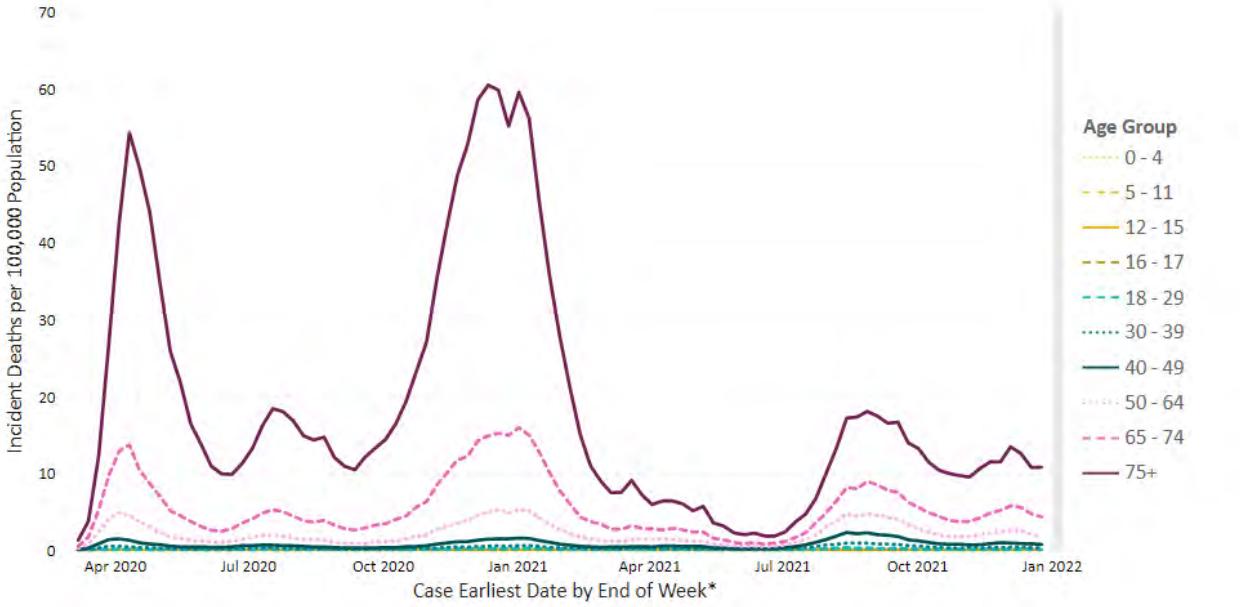


Figure 3 below presents the trends in deaths per 100,000 population by age group from 01 March 2020 to 31 December 2021. The death rates are still higher in the elderly age groups compared to the younger age groups.

Figure 3: Deaths by age group (per 100,000) from 01 March 2020 to 31 December 2021 in the US (CDC)



The estimated weekly proportions (% total with 95% confidence intervals [CI]) of the most common SARS-CoV-2 lineages circulating in the US (from 26 December 2021 to 01 January 2022) were 89.2% (95% CI: 87.5-90.8%) for B.1.1.529 (Omicron), 9.7% (95% CI: 0.2-11.4%) for B.1.617.2 (Delta) and 1.1% (95% CI: 0.7-1.6%) for others ("Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed). To note, variant proportions are adjusted using statistical weighting to correct for the non-random sampling of sequencing data over time and across states and to provide more representative national estimates. As of 10 February 2022, in the US, no SARS-CoV-2 variants are designated as VOI.

Risk Factors for severe COVID-19 outcomes

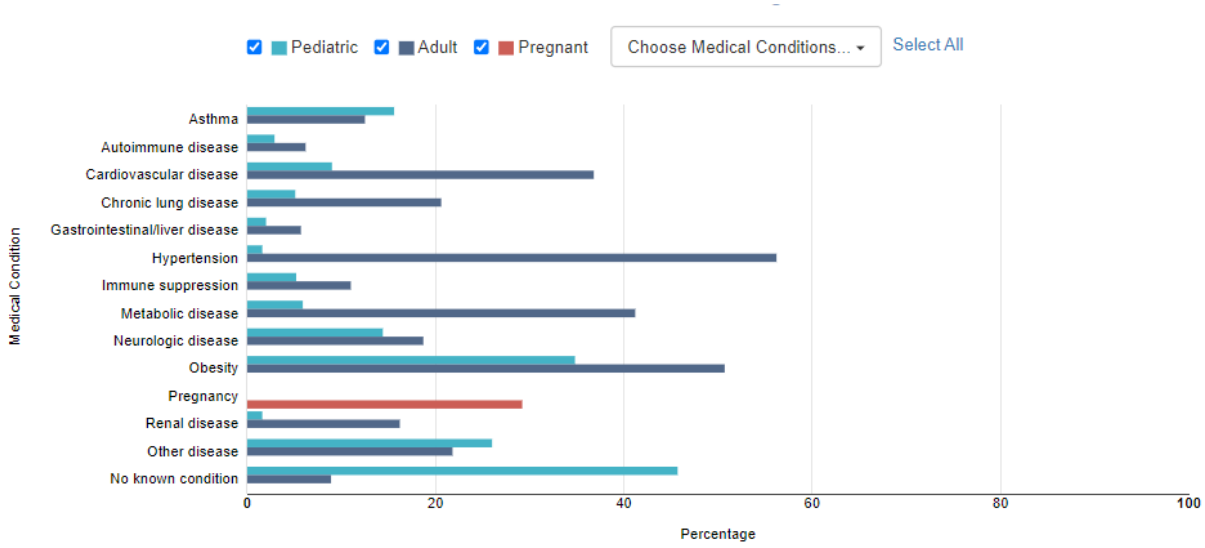
Age

Age has been identified as an independent risk factor for severe COVID-19 disease outcome (Booth 2021).

Medical condition

According to the CDC, the following conditions were found to have a significant association (with COVID-19 disease severity) in at least one meta-analysis or systematic review: cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), diabetes, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), smoking, obesity, pregnancy or recent pregnancy. The following conditions were found to have an association in cohort, case-control or cross sectional studies (including systematic review or meta-analysis that represents one condition in a larger group of conditions): children with certain underlying conditions, Down syndrome, Human Immunodeficiency Virus (HIV), neurologic conditions, obesity, other lung diseases ((including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension), sickle cell disease, solid organ of blood stem cell transplantation, substance use disorders and use of corticosteroids or other immunosuppressive medications (CDC 2021b). Figure 4 presents select underlying medical conditions in individuals with COVID-19 in the US from 01 March 2020 to 31 December 2021

Figure 4: Selected Underlying Medical Conditions (includes data from 01 March 2020 to 31 December 2021)



Data pooled from 31 European countries and reported to The European Surveillance System (TESSy) have identified the following as COVID-19 vulnerable health conditions: (cardiac disorders (excluding hypertension), diabetes, cancer malignancy, chronic lung disease (excluding asthma), current smoking, hypertension, neuromuscular disorder (chronic neurological), asthma, renal disease, obesity, liver disease, HIV (other immune deficiency), other endocrine disorders (excluding diabetes), haematological disorders, rheumatic diseases (including arthritis), tuberculosis, and asplenia (ECDC 2021a).

Table 3 below presents distribution by severity across the risk groups. Severe cases correspond to hospitalisations that required intensive care and/or respiratory support. Mild refers to cases that have not been reported as hospitalised or deaths.

Table 3: Distribution by Severity across risk groups in EU/EEA countries

Precondition	Mild		Hospitalised		Severe		Fatal	
	N	%	N	%	N	%	N	%
None	1415224	76.2	127508	36.3	16661	32.2	27231	25
Cardiac disorder, excluding hypertension	173141	9.3	83737	23.9	11760	22.8	31977	29.4
Diabetes	96336	5.2	60173	17.2	10606	20.5	20970	19.2
Cancer, malignancy	59767	3.2	32041	9.1	5205	10.1	12109	11.1
Chronic lung disease, excluding asthma	33365	1.8	12771	3.6	2249	4.4	3950	3.6
Current smoking	16327	0.9	386	0.1	93	0.2	53	0
Hypertension	14970	0.8	10202	2.9	1633	3.2	4168	3.8
Neuromuscular disorder, chronic neurological	13893	0.7	6458	1.8	716	1.4	2630	2.4
Asthma	10497	0.6	4328	1.2	685	1.3	1293	1.2
Other endocrine disorder (excl Diabetes)	6068	0.3	526	0.1	61	0.1	119	0.1
Liver-related condition, liver disease	5946	0.3	2416	0.7	349	0.7	613	0.6
Kidney-related condition, renal disease	5774	0.3	6265	1.8	986	1.9	2921	2.7
HIV / other immune deficiency	3217	0.2	2474	0.7	377	0.7	579	0.5
Obesity	2635	0.1	587	0.2	213	0.4	170	0.2
Rheumatic diseases including arthritis	752	0	165	0	18	0	38	0
Hematological disorders	278	0	799	0.2	55	0.1	122	0.1
Tuberculosis	53	0	22	0	3	0	6	0
Asplenia	13	0	4	0	1	0	0	0
Total	**1858256**	**100**	**350862**	**100**	**51673**	**100**	**108949**	**100**

In summary, 64.1% of fatalities were in populations with vulnerable preconditions, and only 17.2% of reported mild cases were from populations with vulnerable preconditions.

Among all fatal cases, 75% had one of the listed pre-existing conditions. The most common was cardiac disorder (excluding hypertension) (29.4% of all fatalities) followed by diabetes (19.2% of all fatalities), and cancer malignancy (11.1% of all fatalities) with other preconditions accounting for 15% or less of the fatalities. Two thirds (67.8%) of all severe hospitalisations were in patients with one of the listed pre-existing conditions. The most common were also cardiac disorder (excluding hypertension), diabetes and cancer (22.8%, 20.5% and 10.1% of all severe hospitalisations, respectively). A similar trend was observed among all hospitalised cases.

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 December 2021, five vaccines have been authorized for COVID prevention in the European Union including: Comirnaty® from Pfizer; Spikevax® previously COVID-19 Vaccine Moderna; Vaxzevria® previously COVID-19 Vaccine Astrazeneca, COVID-19 Vaccine Janssen, and Nuvaxovid® from Novavax. There are other additional vaccines currently under rolling review (Sputnik V [Gam-COVID-Vac], COVID-19 Vaccine [Vero Cell] Inactivated, Vidprevtyn, and VLA2001) (EMA 2021a). The cumulative uptake of full vaccination among adults (≥18 years-old) as of 52 week of 2021 was 37.9% (ECDC 2021d).

In the US, two vaccines are currently authorized for emergency use: Moderna and J&J/Janssen COVID-19 Vaccines. In the US, one vaccine was approved (BLA) on 23 August 2021: Pfizer BioNTech COVID19 Vaccine.

In addition, the following medicinal products have been authorized in the European Union: Kineret (anakinra), an immunosuppressive medicine; Paxlovid (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; and Xevudy (sotrovimab), human neutralizing monoclonal antibody. Additionally, the marketing authorisation for Olumiant® (baricitinib); an immunosuppressant and Lagevrio (molnupiravir); a medication that works by introducing errors into the SARS-CoV-2 virus' genetic code are under marketing authorization evaluation by the EMA (EMA 2021).

In the US, the following monoclonal antibodies were granted Emergency Use Authorizations (EUAs): Actemra® (Tocilizumab) since 24 June 2021, Sotrovimab since 26 May 2021, Bamlanivimab/etesevimab since 09 February 2021 and REGN-COV2 (casirivimab/imdevimab) since 21 November 2020 (FDA 2021). The FDA has also approved the antiviral drug Veklury (remdesivir) for adults and certain paediatric patients with COVID-19.

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 COVID-19 infection prevention and control living guideline: mask use in community settings, 22 December 2021 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. The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days. 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.

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. Thromboembolic events also occur in patients with COVID-19, with the highest risk in critically ill patients. The long-term sequelae of COVID-19 survivors are currently unknown (NIH 2020). SARS-CoV-2 has also been associated with a potentially severe multisystem inflammatory syndrome (MIS) in children (NIH 2020).

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). 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 et al Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine N Engl J Med 2021; 384:403-416. DOI: 10.1056/NEJMoa2035389

Beaudoin-Bussières 2020; Long 2020, Perreault 2020; Prévost 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). Longitudinal studies will provide an opportunity to monitor in more detail the progression of immunity over time.

Unlike adults, most adolescents with COVID-19 have mild symptoms and very low risk of death. However, some adolescents develop significant respiratory disease and need hospital admission. According to peer reviewed studies, one-third of the hospitalised paediatric patients with COVID-19 experience severe disease, which is often associated with underlying chronic conditions. Most common chronic conditions associated with hospitalised adolescents 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. Notably, critical illness is associated with increasing age of adolescents.

A very small subset of children experienced a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also referred to as Multisystem inflammatory syndrome in children (MIS-C), appearing 4-6 weeks after mild COVID-19 infection. The condition 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 persistent symptoms such as fatigue, dyspnoea, chest pain, cognitive impairment, and sleeping disturbances that last up to several months after infection. However, the exact burden of COVID-19 and its long-term consequences in the paediatric population is still to be determined and is a priority for further research (ECDC 2021e).

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

Table 4 summarises the key nonclinical findings and their relevance to safety in humans. In summary, the nonclinical package, which consisted of both studies performed with mRNA-1273 and with mRNA vaccines formulated in the same SM-102 lipid nanoparticle (LNP) vaccine matrix to support mRNA-1273 use in human, shows no important identified or potential risks. A developmental and reproductive study with mRNA-1273 in female Sprague-Dawley rats was completed in December 2020 with no adverse findings.

Table 4: 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	Several nonclinical studies (e.g., disease pathology, immunoprofiling) in several species have been generated to address the theoretical risk of disease enhancement with mRNA-1273. In summary, vaccination with mRNA-1273 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 mRNA-1273, 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 mRNA-1273, complete protection was observed. In animals dosed with low levels of mRNA-1273, 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. See further description below in text.	These nonclinical results show a lack of vaccine-enhanced pulmonary pathology post - challenge with mRNA-1273 in relevant animal species. In addition, the clinical Phase 3mRNA-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 mRNA-1273 as defined in the analysis plan. As a result of these assessments, no safety concerns have been identified.
Pharmacokinetics and Drug Metabolism		
Distribution Study	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	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

Study Type	Important Nonclinical Findings	Relevance to Human Use
	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.	persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen where it persisted in general 5 days.
Repeat-dose toxicity studies		
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.	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. 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. Clinical chemistry results indicated a decrease in albumin, increase in globulin, and a corresponding decrease in albumin/globulin ratio. In general, clinical pathology changes were dose-dependent and transient. 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. Macroscopic and microscopic changes were observed and included skin thickening at the injection site and enlarged lymph nodes.	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. Clinical findings such as increased body temperature, injection site pain, other inflammation related findings In ongoing clinical Phase 1 and 2a studies with mRNA-1273, 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.

Study Type	Important Nonclinical Findings	Relevance to Human Use
	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.	
Other Nonclinical Toxicology Studies		
Evaluation of mRNA-1273 at repeat doses, non-GLP immunogenicity rat study with non-terminal endpoints	mRNA-1273-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 mRNA-1273-related changes observed at 30, 60, and/or 100 µg/dose consisted of decreased red cell mass, reticulocytes, and lymphocytes and increased creatinine, triglyceride, cholesterol, and/or glucose. 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.	
Reproductive/development	A developmental and reproductive toxicity study was performed with mRNA-1273 in female Sprague-Dawley rats in December 2020 with no adverse findings noted. mRNA-1273 was at the clinical dose of 100 µg/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 µg/dose. The no observed adverse effect level is 100 µg, which on a mg/kg basis, provides a 137-fold safety margin to 60-kg woman.	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.

Study Type	Important Nonclinical Findings	Relevance to Human Use
Genotoxicity	SM-102, the novel lipid used in the mRNA-1273 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 mRNA-1273. 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. 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. 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.	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 mRNA-1273	N/A

CMV = cytomegalovirus; DSMB = data safety monitoring board; ERD = enhanced respiratory disease; GLP = Good Laboratory Practice; IgG = immunoglobulin B; 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 mRNA-1273 (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 mRNA-1273 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 mRNA-1273. 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 mRNA-1273.

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 mRNA-1273 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 mRNA-1273 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 mRNA-1273 (Baden 2020), confirming no clinical evidence for vaccine enhanced disease following vaccination with mRNA-1273 .

A conclusion of safety concerns for mRNA-1273 based on nonclinical data is summarised in Table 5.

Table 5: 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 mRNA-1273 are ongoing and reported below. Two of the seven 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 naive and previously vaccinated adults. The remaining five studies are a dose-confirming Phase 2a safety and immunogenicity study (mRNA-1273-P201); a Phase 2/3 safety, reactogenicity, and efficacy study in healthy adolescents ages 12 to < 18 years (mRNA-1273-P203); a Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV 2 vaccine in healthy children 6 months to less than 12 years of age (mRNA-1273-P204); 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) and a pivotal Phase 3 efficacy, safety, and immunogenicity study (mRNA-1273-P301).

Table 6. Summary of vaccination groups by dose (µg) in the ongoing studies Phase 1 (P101) 20-0003, P201 (Part A), P301 (Part A), P203, P204 (Part 1 and Part 2)

Study	Dose				
	25 µg	50 µg	100 µg	250 µg	Total
20-0003 (Phase 1 P101)	35	35	35	15	120
P201 Part A (Phase 2a)	0	200	200	0	400
P301 Part A (Phase 3)	0	0	15184	0	15184
P203 (Phase 2/3)	0	0	2486	0	2486
P204 Part 1 (Phase 2/3)[1]	0	380	371	0	751
P204 Part 2 (Phase 2/3)[1]	0	3007	0	0	3007

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
[1]Includes children 6 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 (mRNA-1273) 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 1.4 (08 May 2021); mRNA-1273-P204 study Data from ongoing trial as of 13 May 2021; 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).

Table 7. Summary of Vaccination groups by dose (µg) in the ongoing open label studies

Study	Dose		
	50 µg	100 µg	Total
P201 Part B	173	171	344
P301 Part B	0	27832	27832
P304	0	10	10

Note: Does not include P201 Part C.

Source:

mRNA-1273-P201 (Part B) study Table 14.1.1.1 Day 29 Interim Analysis (Data extraction date 11 June 2021); mRNA-1273-P304 study Data from ongoing trial as of 13 May 2021; mRNA-1273-P301 (Part B) study Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021).

Study 20-0003 (Phase 1)

The open-label dose-finding Phase 1 safety and immunogenicity study (NCT04283461) has enrolled 120 healthy adults 18 years of age and older to receive either 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273. Participants received 2 doses of mRNA-1273 given intramuscularly (IM) 28 days apart and will be followed up until Day 394. Participants in the trial will be offered the option to participate in a substudy in which they will receive a third mRNA-1273 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 will be followed for safety, reactogenicity, and immunogenicity endpoints through 12 months post third vaccination (Substudy Day 366).

Table 8: Participant Exposure by Gender in the Ongoing 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 (mRNA-1273) in Healthy Adults 26 October 2020.

Table 9: Participant Exposure by Age in the Ongoing 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 (mRNA-1273) in Healthy Adults 26 October 2020.

Table 10: Participant Exposure by Race/Ethnic Group in the Ongoing 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 (mRNA-1273) in Healthy Adults 26 October 2020.

Table 11: Summary of Vaccination Groups by Dose, Age Category, and Gender in the Ongoing 20-0003 Study

mRNA-1273 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)

mRNA-1273 dose	25 µg	50 µg	100 µg	250 µg
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 (mRNA-1273) in Healthy Adults 26 October 2020.

At the cut-off date 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 an ongoing 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 has enrolled 600 healthy adults 18 years of age and older in the US. Study participants were randomized 1:1:1 to receive placebo, mRNA-1273 50 µg, or mRNA-1273 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 mRNA-1273 or placebo given IM 28 days apart and will be 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 mRNA1273. Participants who received 1 or 2 doses of 50 µg or 100 µg mRNA-1273 in Part A were offered a single booster dose of mRNA-1273 (50 µg) in Part B. Part C is a proof-of-concept rollover study of approximately 60 participants who are currently enrolled in Moderna's Phase 3 mRNA-1273-P301 study, have already been unblinded, and have previously received 2 doses of mRNA-1273 at least 6 months earlier. Upon enrollment into Part C of this study, they received a single IM injection of mRNA1273.351 (20 µg or 50 µg) or mRNA-1273/mRNA-1273.351 mixture (50 µg total) at least 6 months after receiving the second vaccination in the mRNA-1273-P301 study.

Table 12: Duration of Exposure in the Ongoing mRNA-1273-P201 Study (Part A)

Duration of Exposure	Dose		
	50 µg	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)

Duration of Exposure	Dose		
	50 µg	100 µg	Total
≥ 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 13: Age Group and Gender in the Ongoing mRNA-1273-P201 Study (Part A)

Age Group	Dose		
	50 µg	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 14: Participant Race in the Ongoing mRNA-1273-P201 Study (Part A)

Race	Dose		
	50 µg	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 15: Participant Ethnicity in the Ongoing mRNA-1273-P201 Study (Part A)

Ethnicity	Dose		
	50 µg	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 16: Participant In the Ongoing mRNA-1273-P201 Open label Study (Part B)

Number of Participants (N)	**mRNA1273 Dose**	
	50 ug N= 200 n (%)	**100 ug N=200 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 Day 29 Interim Analysis (Data extraction date 11 June 2021).

Table 17: Participant Age Group in the Ongoing mRNA-1273-P201 Study (Part B)

Age group	**mRNA1273 Booster Dose**	
	50 ug N= 173	**100 ug N= 171**
Age ≥ 18 years and age < 55 years	80	82
Age ≥ 55 years	93	89

Source: Table 14.1.2.2.1 Day 29 Interim Analysis (Data extraction date 11 June 2021).

Table 18: Participant Gender in the Ongoing mRNA-1273-P201 Study (Part B)

Gender	**mRNA1273 Booster Dose**	
	50 ug N= 173	**100 ug N= 171**
Male	49	67
Female	124	104

Source: mRNA-1273-P201 Part B Table 14.1.3.7.1 Day 29 Interim Analysis (Data extraction date 11 June 2021).

Table 19: Participant Race in the Ongoing mRNA-1273-P201 Study (Part B)

Race	**mRNA1273 Booster Dose**	
	50 ug N= 173 n (%)	**100 ug N=171 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 Day 29 Interim Analysis (Extraction Date: 11 Jun 2021).

Table 20: Participant Ethnicity in the Ongoing mRNA-1273-P201 Study (Part B)

Ethnicity	mRNA1273 Booster Dose	
	50 ug N= 173 n (%)	100 ug N=171 n (%)
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 Day 29 Interim Analysis (Extraction Date: 11 Jun 2021).

In the Ongoing mRNA1273-P201 Part C, a total of 60 participants (20 per cohort) have been enrolled.

mRNA-1273-P203 (Phase 2/3)

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

Table 21: Duration of Exposure in the Ongoing mRNA-1273-P203 Study

Duration of Exposure	Number of Participants, n (%)
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	2453 (98.7)
≥ 28 and < 56 Days Since Second Injection	1366 (54.9)
≥ 56 Days Since Second Injection	1087 (43.7)
Study Duration from First Injection (Days)	
Mean (Standard Deviation)	87.9 (16.30)
Median	83.5
Quartile 1, Quartile 3	75.0, 99.0
Minimum, Maximum	30, 151

Source: mRNA-1273-P203 Table 1.4 (08 May 2021).

Table 22: Age Group and Gender in the Ongoing mRNA-1273-P203 Study

Age Group	Participants (N)
≥ 12 years and < 16 years	2767
≥ 16 years and < 18 years	959
Gender	
Male	1915
Female	1811

Source: mRNA-1273-P203 Table 1.3 (08 May 2021).

Table 23: Participant Race in the Ongoing mRNA-1273-P203 Study

Race	Participants (N)
White	3126
Black or African American	125
Asian	221
American Indian or Alaska Native	19
Native Hawaiian or Other Pacific Islander	2
Multiple	168
Other	36
Not Reported	22
Unknown	7
Total	**3726**

Source: mRNA-1273-P203 Table 1.3 (08 May 2021).

Table 24: Participant Ethnicity in the Ongoing mRNA-1273-P203 Study

Ethnicity	Participants (N)
Hispanic or Latino	432
Not Hispanic or Latino	3264
Not Reported	27
Unknown	3
Total	**3726**

Source: mRNA-1273-P203 Table 1.3 (08 May 2021).

mRNA-1273-P204 study

A Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 SARS-CoV 2 vaccine in healthy children 6 months to less than 12 years of age.

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. In total, 751 children 6 to < 12 years of age were enrolled to Part 1 (380 mRNA-1273 50 µg and 371 mRNA-1273 100 µg) and 4016 to Part 2 (3012 mRNA-1273 50 µg and 1004 placebo). Participants in Part 1 are distinct from those in Part 2.

Table 25: Summary of Study Duration by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study

	mRNA-1273 50 µg N=380	mRNA-1273 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 P204 Table 14.1.5.1
Data from ongoing trial as of 10 November 2021

Table 26: Summary of Blinded Study Duration in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study

	mRNA-1273 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)
≥ 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 P204 Table 14.1.5.2
Data from ongoing trial as of 10 November 2021

Table 27: Participant Demographics and Baseline Characteristics by Dose Level in Part 1 (Safety Set) in the Ongoing mRNA-1273-P204 Study

	mRNA-1273 50 µg N=380	mRNA-1273 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)
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)
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)
Not Reported	3 (0.8)	3 (0.8)	6 (0.8)
Unknown	1 (0.3)	3 (0.8)	4 (0.5)
Race and Ethnicity Group[a], n (%)			
White, non-Hispanic	208 (54.7)	230 (62.0)	438 (58.3)
Communities of Color	169 (44.5)	139 (37.5)	308 (41.0)
Missing	3 (0.8)	2 (0.5)	5 (0.7)
Weight, kg			
Mean (SD)	34.93 (12.472)	34.86 (11.834)	34.89 (12.153)
Median	32.05	32.27	32.18
Min, Max	16.8, 86.4	16.5, 85.6	16.5, 86.4
Baseline SARS-CoV-2 Status[b], n (%)			
Negative	327 (86.1)	322 (86.8)	649 (86.4)
Positive	28 (7.4)	30 (8.1)	58 (7.7)
Missing	25 (6.6)	19 (5.1)	44 (5.9)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = standard deviation.
Percentages are based on the number of participants in the Part 1 Safety Set.
a. White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
b. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.
Source: Study P204 Table 14.1.3.1.1
Data from ongoing trial as of 10 November 2021

Table 28: Participant Demographics and Baseline Characteristics in Part 2 (Safety Set) in the Ongoing mRNA-1273-P204 Study

	mRNA-1273 50 µg N=3007 n (%)	Placebo N=995 n (%)	Total N=4002 n (%)
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)
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)
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)
Race and Ethnicity Group[a], n (%)			
White, non-Hispanic	1542 (51.3)	536 (53.9)	2078 (51.9)
Communities of Color	1459 (48.5)	456 (45.8)	1915 (47.9)
Missing	6 (0.2)	3 (0.3)	9 (0.2)
Weight, kg			
Mean (SD)	33.33 (11.273)	33.52 (11.434)	33.38 (11.312)
Median	30.60	30.91	30.73
Min, Max	15.4, 112.0	14.2, 99.8	14.2, 112.0
Baseline SARS-CoV-2 Status[b], n (%)			
Negative	2703 (89.9)	880 (88.4)	3583 (89.5)
Positive	257 (8.5)	87 (8.7)	344 (8.6)
Missing	47 (1.6)	28 (2.8)	75 (1.9)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = standard deviation.
Percentages are based on the number of participants in the Part 2 Safety Set.
a. White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
b. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.
Source: Study P204 Table 14.1.3.2
Data from ongoing trial as of 10 November 2021

mRNA-1273-P304 study

This is a Phase 3b, open-label study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 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 mRNA-1273 28 days apart. The SOT recipients will be offered the opportunity to receive a third dose of mRNA-1273 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 29: Participants exposure by Age in mRNA-1273-P304 study

Age range	Participants (N)
>=18 and <65 years	9
>=65 and <75 years	1
Total	**10**

Data from ongoing trial as of 13 May 2021.

Table 30: Participant exposure by Gender in mRNA-1273-P304 study

Gender	Participants (N)
Male	4
Female	4
Missing	2
Total	**10**

Data from ongoing trial as of 13 May 2021.

Table 31: Participant exposure by Racial group in mRNA-1273-P304 study

Race	Participants (N)
White	4
Black	3
Missing	3
Total	**10**

Data from ongoing trial as of 13 May 2021

Table 32: Participant exposure by Ethnicity in mRNA-1273-P304 study

Ethnicity	Participants (N)
Not Hispanic or Latino	8
Missing	2
Total	10

Data from ongoing trial as of 13 May 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 mRNA-1273 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 μg of mRNA-1273 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. mRNA-1273 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 mRNA-1273 vaccine.

Table 33: Duration of Exposure in the Ongoing mRNA-1273-P301 Study (Part A)

Duration of Exposure	**mRNA-1273 (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

Duration of Exposure	mRNA-1273 (N=15184)
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 34: Age Group and Gender in the Ongoing mRNA-1273-P301 Study (Part A)

Age Group	mRNA-1273 (N=15184)
Adults, 18-64 years	11415
Elderly, 65-74 years	3112
Elderly, 75-84 years	616
Elderly 85 + years	41
Gender	
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 35: Participant Race in the Ongoing mRNA-1273-P301 Study (Part A)

Race	mRNA-1273 (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 36: Participant Ethnicity in the Ongoing mRNA-1273-P301 Study (Part A)

Ethnicity	mRNA-1273 (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 37: Comorbidities in the Ongoing mRNA-1273-P301 Study (Part A)

Age and Risk Group: ≥ 18 and < 65 Years	**mRNA-1273 (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 38: Risk Factors in the Ongoing mRNA-1273-P301 Phase 3 Study (Part A)

Age and Risk Group: ≥ 18 and < 65 Years	**mRNA-1273 (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 39: Participants Age group in the Ongoing mRNA-1273-P301 Phase 3 Study (Part B)

	>=18 and <65 Years			**>=65 Years**		
	Placebo-mRNA-1273 (N=9,256)	**mRNA-1273 (N=11,415)**	**Total (N=20671)**	**Placebo-mRNA-1273 (N=3,392)**	**mRNA-1273 (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 40: Participants Risk Factors / Comorbidities in the Ongoing mRNA-1273-P301 Phase 3 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-mRNA-1273 (N=9,256)	**mRNA-1273 (N=11,415)**	**Total (N=20,671)**	**Placebo-mRNA-1273 (N=3,392)**	**mRNA-1273 (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)
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 41: Participants Gender in the Ongoing mRNA-1273-P301 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-mRNA-1273 (N=9,256)	**mRNA-1273 (N=11,415)**	**Total (N=20671)**	**Placebo-mRNA-1273 (N=3,392)**	**mRNA-1273 (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 42: Participant Race in the Ongoing mRNA-1273-P301 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-mRNA-1273 (N=9,256)	**mRNA-1273 (N=11,415)**	**Total (N=20671)**	**Placebo-mRNA-1273 (N=3,392)**	**mRNA-1273 (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)
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 43: Participant Ethnicity in the Ongoing mRNA-1273-P301 Study (Part B)

	>=18 and <65 Years			>=65 Years		
	Placebo-mRNA-1273 (N=9256)	**mRNA-1273 (N=11415)**	**Total (N=21671)**	**Placebo-mRNA-1273 (N=3392)**	**mRNA-1273 (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).

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 44: 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)	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

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
prior to screening visit.			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.
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 mRNA-1273 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.

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
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 > 14 days in total within 6 months prior to Screening (for corticosteroids ≥ 20 mg/day of prednisone equivalent).	Allowance of these conditions would confound assessment of efficacy.	Yes	Not applicable.
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 ≥ 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 mRNA-1273 in these participants would be different from the rest of the population receiving mRNA-1273.

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

Rare Adverse Drug Reactions

The vaccine exposed population of the Phase 3mRNA-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 mRNA-1273 vaccine consists of two doses administered 28 days apart. There is no prolonged exposure to mRNA-1273. 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 sequalae due to vaccine exposure are expected.

In both the mRNA-1273 injection group and the placebo group in the Phase 3mRNA-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 45: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Paediatric participants	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 ≤ 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 mRNA-1273 (380 mRNA-1273 50 µg and 371 mRNA-1273 100 µg) in Part 1 (Table 14.1.5.1) and 4016 children 6 to < 12 years of age (3012 mRNA-1273 50 µg and 1004 placebo) in Part 2 (Table 14.1.5.2 (Data extraction date: 10 November 2021)).

Type of Special Population	Exposure
Pregnant women	Pregnant women were excluded from the clinical trials, although a small number of pregnancies were reported in the mRNA-1273 clinical program. As of the data lock point of this RMP, in mRNA-1273-P301 Part A, 16 pregnancies were reported in the mRNA-1273 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 mRNA-1273 group and 3 in the placebo group) experienced spontaneous abortion/miscarriage. In Part B, pregnancy was reported for 18 participants who received mRNA-1273 in Part A and 19 participants who received placebo in Part A and mRNA-1273 in Part B. Among the few known outcomes, spontaneous abortion/miscarriage was reported for 1 participant in the mRNA-1273 group and 3 participants in the placebo–mRNA-1273 group; elective termination was reported for 1 participant in the placebo–mRNA-1273 group. There is limited experience with use of Spikevax in pregnant women. A developmental and reproductive study with mRNA-1273 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. Administration of Spikevax in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.
Breastfeeding women	Lactating women were excluded from clinical trials. There have been no reports of women taking mRNA-1273 while breastfeeding in the mRNA-1273 clinical program. It is unknown whether Spikevax is excreted in human milk. Data are not available to assess the effects of Spikevax on the breastfed infant or on milk production/excretion.
Participants with relevant comorbidities[#]	
• Participants with hepatic impairment[1]	In the clinical trial mRNA-1273-P301 (Part A), 104 (0.7%) participants with hepatic disease have been exposed to mRNA-1273 (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 83 (0.7%) in placebo+mRNA-1273 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)).
• Participants with renal impairment	A Phase 3b open-label safety and immunogenicity study (mRNA-1273-Study mRNA-1273-P304) in target population of approximately 220 adult solid organ transplant recipients is ongoing.
• Participants with cardiovascular impairment[2]	In the Study mRNA-1273-P301 (Part A), 762 (5.0%) participants with significant cardiac diseases have been exposed to mRNA-1273 (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 675 (5.3%) in placebo+mRNA-1273 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)).

Type of Special Population	Exposure
• Immunocompromised participants	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 mRNA-1273 (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 81 (0.6%) in placebo+mRNA-1273 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 (mRNA-1273-Study mRNA-1273-P304) in target population of approximately 220 adult solid organ transplant recipients is ongoing.
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 3mRNA-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, 3126 (83.9%) participants were White, 125 (3.4%) were Black, 221 (5.9%) were Asian, 168 (4.5%) were multiracial and 432 (11.6%) were Hispanic or Latino (study mRNA-1273-P203 Table 1.3 and mRNA-1273-P203 Table 1.3).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Others	
1. Participants ≥ 75 years of age	In the Phase 3mRNA-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.
2. Diabetes (Type 1, Type 2)	In the Phase 3mRNA-1273-P301 study (Part A), 1460 (9.6%) participants with diabetes have been exposed to mRNA-1273 (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 1279 (10.1%) in placebo+mRNA-1273 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)).
3. Chronic lung disease[3]	In the Phase 3mRNA-1273-P301 study (Part A), 712 (4.7%) participants with chronic lung disease have been exposed to mRNA-1273 (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 658 (5.2%) in placebo+mRNA-1273 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)).
4. Severe obesity (BMI > 40 kg/m^2)	In the Phase 3mRNA-1273-P301 study (Part A), 1070 (7.1%) participants with severe obesity have been exposed to mRNA-1273 (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 925 (7.3%) in placebo+mRNA-1273 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)).

Type of Special Population	Exposure
5. HIV infection	In the Phase 3mRNA-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 mRNA-1273 (Table 14.1.6.2.8). While in mRNA-1273-P301 (Part B), 81 (0.6%) in placebo+mRNA-1273 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)).

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

[1]Hepatic disease including cirrhosis;

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

[3]Chronic 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), 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) (data retrieved on 01 January 2022). Cumulatively, as of 31 December 2021, a total of 827,274,740 doses of Spikevax (previously COVID 19 vaccine Moderna) have been distributed to 77 countries, and an estimated total of 559,872,937 doses of Spikevax had been administered. North America, Europe, and Asia accounted for >90% of Spikevax doses distributed and >70% of Spikevax doses administered (Table 46).

SV.1.2. Exposure

Table 46: Spikevax Doses Distributed and Administered through 31 December 2021

	Doses Distributed		Doses Administered	
	N	%	N	%
Total	**827,274,740**	**100**	**559,872,937**	**100**
North America	384,938,620	46.5	200,189,117	35.8
United States	350,231,980	42.3	193,650,993	34.6
Europe	211,273,900	25.2	112,474,294	19.6
European Economic Area	181,560,000	21.9	98,068,820	17.5
Asia	176,449,180	21.3	95,811,795	17.1
Middle East	15,553,380	1.9	7,776,690	1.4
Latin America	14,655,580	1.8	7,327,790	1.3
Oceana	10,223,200	1.2	5,111,600	0.9
Africa	14,180,880	1.7	7,090,440	1.3
Governmental donations	--	--	124,091,211	22.2

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

No new safety signals or new important potential or identified risks were identified in either part of study mRNA-1273-P204 that evaluated the safety, tolerability, reactogenicity, and effectiveness of Spikevax in healthy children 6 to < 12 years of age up to 10 November 2021. The safety data are consistent with events commonly seen in the paediatric population and with the reactogenicity known for Spikevax.

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

Table 47: Presentation of Important Identified Risks

Important Identified Risk	**Anaphylaxis**
Potential mechanisms	Immediate type (Type 1), hypersensitivity mediated by immunoglobulin (Ig) E. Naturally existing IgM and IgG can bind to various components commonly present in nanomedicines, (cholesterol, phospholipids and polyethylene glycol).
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from clinical studies and post authorisation.
Characterization of risk	In study mRNA-1273-P301 (Part A), in the anaphylaxis SMQ, 9 events were reported for 5 participants in the mRNA-1273 group and 18 events were reported for 8 participants in the placebo group (Table 14.3.1.22.8). Anaphylactic reaction of unknown cause was reported for 2 participants in the mRNA-1273 group as nonserious, moderate severity events approximately 2 months after the second dose; both were considered not related to investigational product and resolved on the same day with concomitant medications. Among the other terms in the SMQ, reported events in the mRNA-1273 group were all nonserious and described as follows: mild cough and mild eye pruritus for one participant on Day 47 after the second dose (not considered related); mild tachypnea on Day 29 after the first dose (which was reported on the day of the second dose), severe tachypnea on Day 1 after the second dose (which was the same day; event resolved on Day 64), and moderate urticaria beginning 30 minutes after the second dose and resolved in 1 hour with concomitant medication (all events considered related); and moderate dyspnea (considered related; reported as resolving) and severe swelling face (not considered related; resolving with prednisone) beginning on Day 34 after the second dose (Listing 16.2.7.28). In Part B of mRNA-1273-301, amongst the SAEs, a grade 3 anaphylaxis was reported in 2 participants in the

Important Identified Risk	**Anaphylaxis**
	placebo-mRNA-1273 group, both of which were considered unrelated to mRNA-1273. These 2 participants had history of asthma. The first participant was a 50s' years old female who experienced anaphylaxis 19 days after the first injection which resolved the same day; the participant did not receive the second dose. The second participant was a 50s' year old female who experienced anaphylaxis a few months after receiving the second dose of vaccine; however, it was not temporally related to mRNA-1273 and considered associated to a steroid injection per the investigator. In the placebo group, no anaphylaxis was reported. In the mRNA-1273 group, 1 participant experienced anaphylaxis due to antigen challenge allergy testing (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B]). During the post authorisation, cumulatively as of 30 June 2021, there were 1214 anaphylaxis cases reported. Out of those, 421 cases met the definition of anaphylaxis according to the Brighton Collaboration case definition, with 185 cases classified as Level 1, 204 as Level 2, and 32 as Level 3. The remaining 793 cases were categorized as Brighton Level 4 or 5 and did not meet the case definition. These 421 cases corresponded to an incidence rate of 0.23 cases per 100,000 doses administered.
Risk factors and risk groups	Any participant receiving the vaccine. However, participants with a known history of hypersensitivity to any component of the vaccine may be at risk of hypersensitivity reactions.
Preventability	Spikevax vaccine is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine or to a previous dose of the vaccine. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation is recommended following vaccination for 30 minutes for people with a history of an immediate allergic reaction of any severity to another vaccine or injectable therapy, and/or people with a history of anaphylaxis due to any cause. All other persons should be observed for 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Spikevax.
Impact on the benefit-risk balance of the product	Anaphylactic reaction is a potentially life-threatening event requiring medical intervention.
Public health impact	Anaphylaxis associated with vaccines typically occurs at a low incidence, which results in a low public health impact. Although the potential clinical consequences of an anaphylactic reaction are serious, this is a risk known to healthcare professionals.

Important Identified Risk	**Myocarditis**
Potential mechanisms	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 immunes disease and hypersensitive reactions. Numerous medications like antipsychotics (e.g., clozapine), antibiotics (penicillin, ampicillin, sulfonamides, tetracyclines), and antiphlogistic (e.g., mesalamine) can induce hypersensitivity eosinophilic myocarditis. Myocarditis has been reported following many different vaccines including flu vaccine, however the smallpox vaccine has the strongest association. During the influenza epidemic of the winter 1998-1999 there were several reports of patients who had preceding flu-like symptoms and fever and developed cardiac involvement between 4 and 7 days after the onset of influenza symptoms (Onitsuka 2001). Evaluation of the post-authorization safety data suggest a very rare risk of myocarditis following COVID-19 vaccination, the mechanisms involved in such vaccine-related myocarditis are not clear based on the data currently available.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from clinical trials and the post-authorisation safety.
Characterization of risk	In Study mRNA-1273-P301 (Part A), there were 15,184 participants exposed to the mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were no reported TEAEs of Myocarditis follow-up period after vaccination. No cases have been reported in Part B of the study (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B]). Using post authorization safety data, 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 reported event of myocarditis with insufficient evidence to meet level 1,2 or 3 of the case definition). 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.

Risk factors and risk groups	Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The annual prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men (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. 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.
Preventability	Myocarditis presents with a spectrum of symptoms ranging from mild dyspnea or chest pain that spontaneously resolves without treatment to cardiogenic shock and sudden death. The major long-term consequence is dilated cardiomyopathy (DCM) with chronic heart failure. Common viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated (Blauwet 2009). 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. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. For patients presenting with myocarditis or pericarditis after the 1st dose CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, it could consider proceeding with 2nd dose (Wallace 2021). Current SmPC and PIL adequately covers the information on this risk awareness to the health care professionals, caregivers and vaccinees.

Impact on the benefit-risk balance of the product	Based on the analysis of all the safety data, there have been very rare reports of myocarditis occurring after vaccination with Moderna COVID-19 Vaccine. Causal association between Spikevax and myocarditis is considered of at least a reasonable possibility. The majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended (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 mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were four TEAE of “Pericarditis” in P301: Two TEAEs in the Placebo arm, and two in the Vaccine arm of the safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the >18 to <65 years of age. The events in the vaccination arm were reported in a male in his 60s’ and a female in her 50s’. In Part B, one case of acute pericarditis (verbatim: “acute infective pericarditis”) was reported in a male in his 60s’ in the placebo group; the event occurred 24 days after a COVID-19 diagnosis. In addition, one case of pericardial effusion was reported as an SAE (resolving) in a 20s’ years old male in the placebo–mRNA-1273 group. No participant in the mRNA-1273 group

Important identified risk	Pericarditis
	experienced pericarditis (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B]). A review of the spontaneous reports from the company's global safety identified 68 case reports with the PTs of Pericarditis. All of the aforementioned reports were considered serious reports. As a difference with the Myocarditis reports, most of the Pericarditis reports (64.7%) involved persons >50 years of age. There was not an important difference between the reported genders, with 51% Males, and 47% females. There was not an important difference in the TTO for the pericarditis cases with 16% reporting a TTO less than 1 day, 18 % for each 2 to 3 days and 4 to 7 days. The majority of the reports reported a TTO of more than 8 days following last vaccination. Occurrence following dose 1 was very similar (37% of reports) to the one seeing following dose 2 (41%). Dose number was not reported in 22% of the cases. Evaluation of all the 68 cases identified as cases of Pericarditis, utilizing the WHO-UMC causality assessment, there were 18 reports that were classified as "Possible" according to the WHO-UMC causality assessment. Of these "Possible" 18 cases, there were 9 males and 9 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 mRNA-1273 vaccine, and 1 did not provided dose information. The reported TTO was between 1 days and 23 days (Mean 11.3 days). The rest of the 68 cases that reported Pericarditis, 11 cases (16.2%) were classified as "Conditional"; 21 cases (30.8%) were classified as "Unassessable/ Unclassifiable"; and 18 (26.5%) were classified as "Unlikely". The post-marketing reporting rate for pericarditis (without myocarditis) was 2.16 per 100, 000 person-years based on a 21-day risk window following each dose of vaccine administered.
Risk factors and risk groups	Acute pericarditis occurs when the bilayer pericardial sac becomes inflamed. In most cases, the cause of pericarditis is idiopathic or is assumed to be due to a viral infection for which the antecedent virus is not identified. There are several less common infectious and non-infectious causes of pericarditis, but most patients with acute pericarditis present with a history suggestive of recent or concurrent viral illness. Most cases resolve with no long-term sequelae. While pericardial effusions might develop as a result of pericarditis, they are usually minor and rarely result in cardiac tamponade (Sharif 2013). Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years (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). Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.
Preventability	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

Important identified risk	Pericarditis
	friction rub, electrocardiographic changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram (Hoit 2020). Pericarditis may result in one of two serious complications: cardiac tamponade and chronic constrictive pericarditis. Cardiac tamponade is considered a medical emergency and, if left untreated, can quickly become fatal. Very rare cases of myocarditis and pericarditis have been observed following vaccination with 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. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, could consider proceeding with 2nd dose (Wallace 2021).
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 48: Presentation of Important Potential Risks

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Potential mechanism(s)	Research points to disease enhancement being triggered by one of two major mechanisms although other mechanisms may also contribute. The first and least well characterised is when priming by the initial infection results in a Th2 biased immune response mediated more by myeloid lineage cells, including neutrophils and eosinophils with immune complex formation and complement activation. While this inflammatory phenotype may be preferred for parasitic infections it is not ideal for viruses, for which an adaptive T-cell and antibody mediated Th1 type response is preferable. This “Th2 biased” phenotype is most associated with enhanced disease as resulting from the formalin-inactivated measles and respiratory syncytial

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
	virus (RSV) vaccines. In these cases, post vaccination exposure of previously naïve vaccines resulted in an immune response characterised by high interleukin (IL) 4, 5 & 13 levels and localized tissue inflammation associated with neutrophil and eosinophil infiltration, immune complex deposition and pulmonary inflammation and obstruction. The second and far better characterised mechanism is antibody dependent enhancement (ADE). This results from the generation of binding but poorly neutralizing antibodies induced by heterologous antigens generated either by heterologous viral strains (e.g., dengue), by chemically disrupted antigens (e.g., formalin-inactivated RSV and measles) or by epitope altering mutations such as feline infectious peritonitis. These antibodies bind to but do not neutralize the virus and facilitate Fc receptor mediated entry of viable virus into macrophages. This can result in an accelerated and more marked viremia and more severe disease. This scenario is the one associated with dengue virus and its virus and vaccine-associated ADE. ADE for dengue can also result from sub-neutralizing concentrations of neutralizing antibodies, such as that seen in infants as maternal antibodies wane. It is likely that in many cases there are components of both mechanisms in enhanced disease.
Evidence source(s) and strength of evidence	No evidence of harm has been identified in nonclinical studies nor from the Phase 3 mRNA-1273-P301 harm monitoring at the time of the data lock point for the risk management plan where 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. As of 30 June 2021, no new information has been identified through post-authorisation safety data.
Characterization of risk	Not applicable as no evidence of harm has been identified.
Risk groups or risk factors	This is a potential risk and no increased risk to mRNA-1273 has been established. Therefore, no risks groups or risks factors can be identified. However, the generation of binding but poorly neutralizing antibodies in individuals may result in an accelerated and more marked viremia and more severe disease.
Preventability	Information is not available as the risk remains theoretical.
Impact on the benefit-risk balance of the product	In addition to possible early efficacy, the Data Safety Monitoring Board has monitored Phase 3 mRNA-1273-P301 study for vaccine harm. Based on these analyses no vaccine harm was identified. This risk is further evaluated in the ongoing Phase 3 mRNA-1273-P301 through continued trial follow up as well as pharmacovigilance activities.
Public health impact	The public health impact of mRNA-1273 in worsening COVID-19 disease is unknown but this could impact the benefit risk should this event be reported in a significant number of vaccinees.

Table 49: 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 mRNA-1273 in pregnant women from the clinical trials. A developmental and reproductive study with mRNA-1273 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 missing information	Targeted populations of the indication will include women of childbearing potential, thus, the use of mRNA-1273 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 mRNA-1273 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.
Missing Information	**Use in Immunocompromised subjects**
Evidence source	In the Phase 1 and 2a studies of mRNA-1273, participants with immunosuppression were excluded. Immunosuppression in these studies were defined as immunosuppressive or immunodeficient state, including HIV infection, asplenia, recurrent severe infections or systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the Screening Visit. These criteria were subsequently modified in the Phase 3 mRNA-1273-P301 to allow the participation in the study of HIV positive participants considered not immunosuppressed.
Anticipated risk/consequence of the missing information	In general, it is expected that participants with immunocompromised status may not reach the protective antibody level achieved in healthy individuals with vaccines. However, in the Phase 3 study mRNA-1273-P301, the results show an overwhelming vaccine efficacy in the overall population of the trial. mRNA-1273 vaccine is not a live attenuated vaccine, nor does it contain a viral vector. Therefore, no risk of transmission of an infection due to the vaccine construct is expected in this population. This population will be monitored via routine pharmacovigilance. To the extent that immunosuppressed patients are captured in the European post-authorisation safety study (PASS) and the US effectiveness study, these studies may inform use in subjects with immunosuppression. A Phase 3b open-label safety and immunogenicity study (Study mRNA-1273-P304) in a target population of approximately 220 adult solid organ transplant recipients is ongoing.
Missing Information	**Interactions with other vaccines**
Evidence source	No experience exists with vaccines within 28 days prior to the first dose or any dose of mRNA-1273 except for seasonal influenza vaccine <14 days.

Anticipated risk/consequence of the missing information	There is the theoretical question as whether a vaccine can create interference in the immune response to either vaccines or induce safety concerns. Due to the exclusion criteria in the mRNA-1273 clinical program no experience exists with vaccines within 28 days prior to the first dose or any dose of mRNA-1273 except for seasonal influenza vaccine <14 days. It is common medical practice to administer vaccines concurrently. Participants receiving mRNA-1273 may be administered seasonal flu vaccines during the vaccination period of the pandemic.
Missing Information	**Use in Frail Subjects With Unstable Health Conditions and Co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)**
Evidence source	The vaccine has been studied in participants with stable chronic diseases (e.g., patients with hepatic impairment and patients with cardiovascular impairment), however it has not been studied in frail participants with severe co-morbidities that may compromise immune function due to the condition or treatment of the condition.
Anticipated risk/consequence of the missing information	In general, there is a potential that frail participants with unstable health conditions and co-morbidities may experience a different outcome than achieved in healthy individuals administered vaccines. To the extent that frail participants can be classified in the European PASS and the US effectiveness study, these studies may inform use in frail participants.
Missing Information	**Use in Subjects With Autoimmune or Inflammatory Disorders**
Evidence source	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.
Anticipated risk/consequence of the missing information	In general, there is a potential that subjects with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines. To the extent that participants with autoimmune or inflammatory disorders are captured in the European PASS and the US effectiveness study, these studies may inform use in participants with autoimmune or inflammatory disorders.

Part II: Module SVIII – Summary of the Safety Concerns

Table 50: Summary of Safety Concerns

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

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

Anaphylaxis Questionnaire

The questionnaire is intended to collect structured information on severe cases of anaphylactic reaction including anaphylaxis. It is intended to assist with capturing information that can support case classification using the Brighton Collaboration case definition.

COVID- 19/Vaccine Failure Questionnaire

The questionnaire is intended to better characterise the extent and severity of COVID-19 disease reported after vaccination by Spikevax. This questionnaire is for use following the reporting of vaccine failure and/or COVID-19 disease cases and/or AESI associated with COVID-19 disease after Spikevax.

Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) is an Important Potential risk in the RMP. However, the broad spectrum of the COVID-19 disease manifestations in different populations and age groups makes it impossible, to determine how severe COVID-19 infection would have been in the absence of vaccination in the individual case. There is no uniformly accepted definition of vaccine-associated enhanced disease (VAED) or vaccine-associated enhanced respiratory disease (VAERD), and no single or combination of specific confirmatory tests to diagnose VAED. However, the case definition from the Brighton Collaboration will be used to the best possible extent for level of diagnostic certainty with respect to AE reports of potential VAED or VAERD (Munoz 2020).

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 51.

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

Table 51: 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 52: Product Surveillance List of Spikevax Signalling Strategy By Category

Category	Safety Topics (Updates may be Needed if New Adverse Events Emerge)
Safety concerns	- Anaphylaxis - Myocarditis - Pericarditis - Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) - 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
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, will become 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/544966/2020, at the start of the distribution of Spikevax, Moderna plans to prepare a Summary Monthly Safety Report (Table 53:) to submit to EMA in complement to the submission of routine periodic reports (Periodic Benefit-Risk Evaluation Reports). The need and frequency of submission of monthly reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions). Monthly reports and Periodic Safety Update Reports will include results of the O/E analyses for AESIs as appropriate.

Table 53: Spikevax Summary of Monthly Safety Report

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

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.

Moderna has made available Traceability and Vaccination Reminder cards, printed cards to vaccinators as of March 2021 for the Member States that wish to receive these. These cards may be completed at the time of vaccination when necessary for individual members states. The card is also accessible electronically and though a QR code, on the applicant's website.

The Traceability and Vaccination Reminder cards contain the following elements:

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

The vaccine carton 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, a US Post Authorization safety study, and a prospective observational pregnancy outcome study.

Study key detailed information is provided in text below and milestones in Table 54:.

Table 54: Additional Pharmacovigilance Activities

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
20-0003 *US*	Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing	Open-label, dose-ranging study	Healthy male and non-pregnant female participants, ≥18 years of age	LPLV: 03 Jul 2021 Interim CSR: 01 May 2021 Final CSR Main

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
	Healthy Adults. Interventional *Ongoing*	Ab using different assays, SARS-CoV-2 spike-specific T-cell responses.			Study: 01 Nov 2022
mRNA-1273-P201 *US*	Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥ 18 Years Interventional *Ongoing*	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster	Randomized, observer-blind, placebo-controlled study	Generally healthy males and females (≥18 years of age) with no known history of SARS-CoV-2 infection, enrolled in 2 age cohorts (18 to <55 years of age and 55 years of age and older)	LPLV: 20 Aug 2021 Interim CSR: 01 Mar 2021 Final CSR: mid-Apr 2022
mRNA-1273-P203 *US*	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 *Ongoing*	Evaluate the safety, reactogenicity, and effectiveness	Randomized, observer-blind, placebo-controlled study	Healthy adolescents 12 to < 18 years of age	LPLV: 19 Apr 2022 Final CSR: 30 Sep 2022
mRNA-1273-	Phase 2/3, two-	Safety, tolerability,	Two-part,	The study	Study start:

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
P204 *US, Canada*	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 Interventional *Ongoing*	reactogenicity, and effectiveness of up to 3 doses of mRNA-1273 administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion 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	15 Mar 2021 Final CSR: 31 Mar 2024
mRNA-1273-P301 *US*	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 Interventional *Ongoing*	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	LPLV: 30 Sep 2022 Interim CSR: 15 Oct 2021 Final CSR: 31 Dec 2022

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
				COVID-19.	
Study mRNA-1273-P304 *US*	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. Interventional *Ongoing*	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of SARS-CoV-2 mRNA-1273 vaccine. 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 Jan 2024
mRNA-1273-P903 *US*	Post-Authorization Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity. Non-interventional *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	Secondary database analysis using retrospective analyses of pre-vaccination data as well as 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.	A sample of pediatric, adolescent and adult individuals enrolled in health plans contributing data to HealthVerity will be used for 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.	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 Dec 2022 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	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among	Secondary database analysis of observational data to estimate incidence	Pediatric, adolescent, and adult individuals within the catchment area of participating	Feasibility assessment: 31 Jan 2021 Protocol submission: 30 Jun 2021

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
	Real-World Safety of the mRNA-1273 Vaccine in the EU. Non-interventional *Ongoing*	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	rates of safety events of interest and other clinically significant events in cohorts of COVID-19 vaccine recipients in the EU.	data partners from the VAC4EU network	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**
		autoimmune or inflammatory disorders			
mRNA-1273-P905 *Denmark, Norway, Italy, Spain, United Kingdom*	Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries. Non-interventional Planned	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax? Primary objectives: - To determine whether exposure to the Moderna COVID-19 vaccine during pregnancy is associated with an increased risk of: a. Pregnancy complications b. Adverse pregnancy outcomes c. Major congenital malformations in the offspring (overall and organ-specific if feasible) d. Adverse neonatal outcomes Secondary objectives: - To describe utilization of COVID-19 Vaccine Moderna in pregnancy	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**
mRNA-1273-P902 *EU, Canada, US*	Moderna mRNA-1273 Observational pregnancy outcome study Non-Interventional *Ongoing*	Evaluate outcomes of pregnancies and birth in females exposed to mRNA-1273 vaccine during pregnancy. Evaluate infant outcomes.	Primary data collection cohort study.	Pregnant women exposed to mRNA-1273 recruited from the general population and live-born infants from Germany, Italy, Finland, Canada, and the United States. European Surveillance of Congenital Anomalies (EUROCAT) network data, Metropolitan Atlanta Congenital Defects Program (MACDP) data, and other published data will provide an external comparator.	Protocol submission: 31 Jan 2021 Interim updates: 31 Jul 2021, 31 Jan 2022, 31 Jul 2022, 31 Jan 2023, 31 Jul 2023, 31 Jan 2024 Final study report: 30 Jun 2024
mRNA-1273-P901 *US*	Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. Non-interventional *Ongoing*	Evaluate the vaccine effectiveness (VE) of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis (symptomatic and asymptomatic) and severe COVID-19 disease (hospitalizations and mortality) Primary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19	Prospective cohort study	Individuals ≥12 years of age	Protocol submission: 01 Mar 2021 Interim updates: 14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 14 Dec 2022; 14 Jun 2023; 14 Dec 2023 Final study report: 14 Apr 2025 Study milestones were updated due to a refinement of the initial assessment

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		diagnosis 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease Secondary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by age and by sex 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by race/ethnicity groups 3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals with chronic diseases (e.g., chronic kidney disease, lung disease including chronic obstructive pulmonary disease [COPD] and asthma, diabetes) 4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19			conducted during the start of the study. Interim updates were delayed by 6 weeks, and the final report was brought forward by 2 months.

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

Study Number *Country(ies)*	**Study Title** **Study Type** *Study Status*	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		19 diagnosis 9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis when given concomitantly with another vaccine 10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic COVID-19 11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic COVID-19 12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 13. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease 14. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing			

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		severe COVID-19 disease.			
mRNA-1273-P910 *Countries are yet to be determined*	Natural history and clinical outcomes of vaccine associated myocarditis *Initial development* *Planned*	Characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults	Observational cohort study	To be confirmed upon identification of study collaborators	Protocol submission: 28th February 2022 Interim report: 30 Aug 2022 28 Feb 2023 30 Aug 2023 28 Feb 2024 30 Aug 2024 Final study report: 28 February 2025

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 55: 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				
Study mRNA-1273-P301 Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Study Status: Ongoing	Evaluate long-term safety data and durability of vaccine effectiveness (VE)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis Pericarditis Long-term safety	Interim CSR	15 Oct 2021
			Final CSR	31 Dec 2022
Study mRNA-1273-P203 A Phase 2/3, Randomized, Observer-	Evaluate the safety, reactogenicity, and effectiveness of the vaccine	Anaphylaxis Myocarditis Pericarditis	Final CSR	30 Sep 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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		Long-term safety		
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 mRNA-1273 administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety	Study start Final CSR	15 Mar 2021 31 Mar 2024
Category 3 – Required pharmacovigilance activities				
Study 20-0003 Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults Study status: Ongoing	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses.	Anaphylaxis Myocarditis Pericarditis Long-term safety	Interim CSR Final CSR (Main Study)	01 May 2021 01 Nov 2022
Study mRNA-1273-P201 Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster	Anaphylaxis Myocarditis Pericarditis	Interim CSR Final CSR	01 Mar 2021 Mid-Apr 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
CoV-2 Vaccine in Adults ≥ 18 Years Study status: Ongoing				
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 SARS-CoV-2 mRNA-1273 vaccine. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.	Anaphylaxis Myocarditis Pericarditis Use in immunocompromised subjects AESI	Protocol submission	05 Feb 2021
			Interim report	31 Mar 2023
			Final CSR	31 Jan 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	Anaphylaxis 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 Dec 2022
			Final study report	30 Jun 2023
Study mRNA-1273-P904 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-	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	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including	Protocol submission	30 Jun 2021
			Interim Updates	30 Sep 2021, 31 Mar 2022, 30 Sep 2022 31 Mar 2023,

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
1273 Vaccine in the EU Study status: Ongoing	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	vaccine-associated enhanced respiratory disease (VAERD) Long-term safety 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		
			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: Planned	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax? Primary objectives: - To determine whether exposure to the Moderna COVID-19 vaccine during	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
	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			
Study mRNA-1273-P902 Moderna mRNA-1273 Observational pregnancy outcome study Study status: Ongoing	Evaluate outcomes of pregnancies and birth in females exposed to mRNA-1273 vaccine during pregnancy. Evaluate infant outcomes.	Use in pregnancy and while breast-feeding	Protocol submission	31 Jan 2021
			Interim updates	31 Jul 2021, 31 Jan 2022, 31 Jul 2022, 31 Jan 2023, 31 Jul 2023, 31 Jan 2024
			Final study report	30 Jun 2024
Study mRNA-1273-P901 Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. Study Status: Ongoing	Primary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease Secondary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by age and by sex	Use in immunocompromised subjects Interaction with other vaccines, as possible Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disorders)	Protocol submission	01 Mar 2021
			Interim updates	14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 14 Dec 2022; 14 Jun 2023; 14 Dec 2023
			Final study report	14 Apr 2025 Study milestones were updated due to a refinement of the initial assessment conducted during the start of the study. Interim

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by race/ethnicity groups 3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals with chronic diseases (e.g., chronic kidney disease, lung disease including chronic obstructive pulmonary disease [COPD] and asthma, diabetes) 4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals who are immunocompromised (e.g., HIV, cancer, transplant, immunosuppressive medications) 5. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals with autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus) 6. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in frail individuals 7. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in pregnant women 8. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis among individuals	Use in subjects with autoimmune or inflammatory disorders		updates were delayed by 6 weeks, and the final report was brought forward by 2 months.

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	with a history of COVID-19 diagnosis 9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis when given concomitantly with another vaccine 10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic COVID-19 11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic COVID-19 12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 13. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease 14. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease.			
mRNA-1273-P910 Natural history and clinical outcomes of vaccine associated myocarditis Study status: Planned	Characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults	Myocarditis	Protocol submission	28 February 2022
			Interim report	30 Aug 2022 28 Feb 2023 30 Aug 2023 28 Feb 2024 30 Aug 2024

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
			Final study report	28 February 2025

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 56: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Anaphylaxis	Routine risk communication: SmPC Section 4.3 Contraindications 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Ensure appropriate medical treatment and supervision to be always readily available in case of an anaphylactic reaction following administration of the vaccine. Recommendations for close observation for at least 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Spikevax (SmPC Section 4.4). Instructions to get urgent attention in case of signs and symptoms of allergic reactions is included in the PL section 4 Contraindication in subjects with prior hypersensitivity to any component of the vaccine is included in SmPC section 4.3 and PL Section 2. Other routine risk minimisation measures beyond the Product Information: None
Myocarditis	Routine risk communication: SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC Section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Other routine risk minimisation measures beyond the Product Information: None.
Pericarditis	Routine risk communication: SmPC 4.4 Special Warnings and Precautions for Use and 4.8 Undesirable Effects PL 2. What you need to know before you are given Spikevax; 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they

Safety Concern	Routine Risk Minimisation Activities
	develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. (SmPC Section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Other routine risk minimisation measures beyond the Product Information: None.
Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in pregnancy and while breast-feeding	Routine risk communication: 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? Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Long-term safety	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in immunocompromised subjects	Routine risk communication: SmPC Section 4.4 Special Warnings and Precautions for Use; PL: 2. What you need to know before you are given Spikevax Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Interaction with other vaccines	Routine risk communication: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction PL: 2. What you need to know before you are given Spikevax Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in frail subjects with unstable health	Routine risk communication:

Safety Concern	Routine Risk Minimisation Activities
conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	SmPC section 5.1 Pharmacodynamic properties. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: None.
Use in subjects with autoimmune or inflammatory disorders.	Routine risk communication: PL: 2. What you need to know before you are given Spikevax Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: 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 57: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Anaphylaxis	Routine risk minimisation measures: SmPC Sections - 4.3 Contraindications; 4.4 Special Warnings and Precautions for Use; 4.8 Undesirable effects; PL Sections 2 and 4. Ensure appropriate medical treatment and supervision to be always readily available in case of an anaphylactic reaction following administration of the vaccine. Recommendations for close observation for at least 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Spikevax (SmPC section 4.4). Instructions to get urgent attention in case of signs and symptoms of allergic reactions is included in the PL section 4. Contraindication in subjects with prior hypersensitivity to any component of the vaccine is included in SmPC section 4.3 and PL section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of anaphylactic reactions including anaphylaxis in individuals who have received Spikevax (see Section III.1). Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P903 (final CSR: 30 Jun 2023) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023) • Study mRNA-1273-P301 (final CSR: 31 Dec 2022) • Study mRNA-1273-P201 (final CSR: Mid-Apr 2022) • Study mRNA-1273-P204 (final CSR; 31 Mar 2024) • Study 20-0003 (final CSR [Main Study]: 01 Nov 2022; • Study mRNA-1273-P304 (final CSR: 31 Jan 2024) • Study mRNA-1273-P203 (final CSR: 30 Sep 2022)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis	Routine risk minimisation measures: 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). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of myocarditis or myopericarditis in individuals who have received Spikevax (see Section III.1). Additional pharmacovigilance activities (final CSR due date): • 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: 31 Dec 2022) • Study 20-0003 (final CSR [Main Study]: 01 Nov 2022; • Study mRNA-1273-P304 (final CSR: 31 Jan 2024) • Study mRNA-1273-P203 (final CSR: 30 Sep 2022) • Study mRNA-1273-P201 (final CSR: Mid-Apr 2022) • Study mRNA-1273-P910 (final CSR: 28 February 2025)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pericarditis	Routine risk minimisation measures: 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). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of pericarditis in individuals who have received Spikevax (see Section III.1). Additional pharmacovigilance activities (final CSR due date): • 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: 31 Dec 2022) • Study 20-0003 (final CSR [Main Study]: 01 Nov 2022; • Study mRNA-1273-P304 (final CSR: 31 Jan 2024) • Study mRNA-1273-P203 (final CSR: 30 Sep 2022) • Study mRNA-1273-P201 (final CSR: Mid-Apr 2022)
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of COVID-19 disease in individuals who have received Spikevax. The intent is to provide insight into potential cases of vaccine lack of effect or VAED (see Section III.1). Additional pharmacovigilance activities (final CSR due date): • 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: 31 Dec 2022)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnancy and while breast-feeding	Routine risk minimisation measures: SmPC Sections 4.6 Fertility, pregnancy and lactation; 5.3 Preclinical safety data; PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P905 (final CSR: 31 Dec 2023) • Study mRNA-1273-P902 (final CSR: 30 Jun 2024)
Long-term safety	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities (final CSR due date): • 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: 31 Dec 2022) • Study 20-0003 (final CSR [Main Study]: 01 Nov 2022; Study mRNA-1273-P203 (final CSR: 30 Sep 2022)
Use in immunocompromised subjects	Routine risk minimisation measures: SmPC Section 4.4 Special Warnings and Precautions for Use; PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P901 (final CSR: 14 Apr 2025) • Study mRNA-1273-P304 (final CSR: 31 Jan 2024)
Interaction with other vaccines	Routine risk minimisation measures: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction; PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P901 (final CSR: 14 Apr 2025) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Pharmacodynamic properties Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P901 (final CSR: 14 Apr 2025) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023)
Use in subjects with autoimmune or inflammatory disorders	Routine risk minimisation measures: PL Section 2 Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P901 (final CSR: 14 Apr 2025) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023)

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Spikevax (COVID-19mRNA vaccine)

This is a summary of the risk management plan (RMP) for Spikevax. The RMP details important risks of Spikevax, how these risks can be minimised, and how more information will be obtained about Spikevax's risks and uncertainties (missing information).

Spikevax's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Spikevax should be used.

This summary of the RMP for Spikevax 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 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 years of age and older. The active substance in Spikevax is mRNA encoding the SARS-CoV-2 Spike protein embedded in lipid nanoparticles and it is given by intramuscular route.

Further information about the evaluation of Spikevax 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, together with measures to minimise such risks and the proposed studies for learning more about Spikevax'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 is not yet available, it is listed under "missing information" below.

In the case of Spikevax, 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 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. 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 58: List of Important Risks and Missing Information

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

II.B Summary of Important Risks

Table 59: Important Identified Risk: Anaphylaxis

Important Identified Risk: Anaphylaxis	
Evidence for linking the risk to the medicine	Data to evaluate the safety concern were derived from clinical studies and post authorisation.
Risk factors and risk groups	Any participant receiving the vaccine. However, participants with a known history of hypersensitivity to any component of the vaccine may be at risk of hypersensitivity reactions.

Important Identified Risk: Anaphylaxis	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3 Contraindications 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects PL Sections 2 and 4 Ensure appropriate medical treatment and supervision to be always readily available in case of an anaphylactic reaction following administration of the vaccine. Recommendations for close observation for at least 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Spikevax (SmPC section 4.4). Instructions to get urgent attention in case of signs and symptoms of allergic reactions is included in the Package Leaflet (PL) section 4. Contraindication in subjects with prior hypersensitivity to any component of the vaccine is included in SmPC section 4.3 and PL section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P301 Study mRNA-1273-P201 Study mRNA-1273-P204 Study 20-0003 Study mRNA-1273-P304 Study mRNA-1273-P203 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 60: 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	Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The annual prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men. Patients are usually between the ages of 20 and 50. Acute myocarditis and hyperthyroidism are also common diseases that often present in young, otherwise healthy patients. The spontaneous reports included in the 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

Important Identified Risk: Myocarditis	
	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.
Risk minimisation measures	Routine risk minimisation measures: 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 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). Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P910 Study mRNA-1273-P301 Study mRNA-1273-P304 Study mRNA-1273-P203 Study 20-0003 Study mRNA-1273-P201 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 61: 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	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. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years

Important Identified Risk: Pericarditis	
	identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65. Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.
Risk minimisation measures	Routine risk minimisation measures: 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). Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 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 20-0003 Study mRNA-1273-P201 See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 62: Important Potential Risk: Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD) Disease

Important Potential Risk: Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)	
Evidence for linking the risk to the medicine	No evidence of harm has been identified in nonclinical studies nor from the Phase 3 mRNA-1273-P301 harm monitoring at the time of the data lock point for the risk management plan where 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. As of 30 June 2021, no new information has been identified through post-authorisation safety data.
Risk factors and risk groups	This is a potential risk and no increased risk to mRNA-1273 has been established. Therefore, no risks groups or risks factors can be identified. However, the generation of binding but poorly neutralizing antibodies in individuals may result in an accelerated and more marked viremia and more severe disease.

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

Table 63: Missing information: Use in Pregnancy and While Breast-Feeding

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P905 Study mRNA-1273-P902 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 64: Missing information: Long-Term Safety

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P903 Study mRNA-1273-P904 Study mRNA-1273-P204 Study mRNA-1273-P301 Study 20-0003 Study mRNA-1273-P203 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 65: Missing information: Use in Immunocompromised Subjects

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special Warnings and Precautions for Use

	PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P901 Study mRNA-1273-P304 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 66: Missing information: Interaction with Other Vaccines

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P901 Study mRNA-1273-P904 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 67: Missing information: Use in Frail Subjects With Unstable Health Conditions and Co-morbidities (e.g., Chronic Obstructive Pulmonary Disease (COPD), Diabetes, Chronic Neurological Disease, Cardiovascular Disorders)

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P901 Study mRNA-1273-P904 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 68: Missing information: Use in Subjects With Autoimmune or Inflammatory Disorders

Risk minimisation measures	Routine risk minimisation measures: PL Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study mRNA-1273-P901 Study mRNA-1273-P904

	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

The following studies are conditions of the marketing authorisation:

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
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 mRNA-1273 administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age

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 I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults (DMID Protocol No. 20-0003 [NCT04283461])	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses.
A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥ 18 Years (mRNA-1273-P201)	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster.
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 mRNA-1273 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)	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives:

Study Title and Number	Purpose of the Study
Signal Evaluation in HealthVerity (mRNA-1273-P903)	-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?
Moderna mRNA-1273 Observational Pregnancy Outcome Study (mRNA-1273-P902)	Evaluate outcomes of pregnancies and birth in females exposed to mRNA-1273 vaccine during pregnancy. Evaluate infant outcomes.
Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the U.S (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).
Natural history and clinical outcomes of vaccine associated myocarditis (mRNA-1273-P910)	Characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults

Part VII: Annexes

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Follow-Up Forms

Anaphylaxis Questionnaire

COVID-19 / Vaccine Failure Questionnaire

Myocarditis / Pericarditis Questionnaire

moderna

MCN:

Vaccine Hypersensitivity/Anaphylaxis Follow-up Form

Please complete this form and return via email to ModernaPV@modernatx.com or via fax to .

If you have any questions about completing this form, please call .

INFORMATION ABOUT PERSON COMPLETING THIS FORM	INFORMATION ABOUT FACILITY WHERE VACCINE WAS GIVEN
Form completed by (name):_____ Country:_____ Address:_____ City_____State/Province_____Postal Code_____ Phone:_____ Email:_____ **Relationship to Patient:** ☐Self ☐Family Member ☐ Other_____ ☐Healthcare Professional (specify below) ☐Physician ☐Nurse ☐Office staff ☐Other:_____	**Type of Facility:** ☐ Doctor's office, urgent care, or hospital ☐ Pharmacy ☐ Workplace Clinic ☐ Public health clinic ☐ School or student health clinic ☐ Nursing home or senior living facility ☐ Other: **Facility/Clinic Name**:_____ Country:_____ Address:_____ City:_____State/Province:_____Postal Code_____ Phone:_____Fax:_____

Best doctor/healthcare professional to contact about the adverse event:_____

Phone:_____ Fax:_____ Email:_____

MODERNA VACCINE INFORMATION			
Dose 1 – Date:_____/____/_____ Time: ____ :____ ☐ am ☐ pm Lot/Batch #: _____ ☐Unk Route & Body site: _____ Dose/volume: _____☐Unk	**Dose 2** – ☐Not received Date:_____/____/_____ Time: ____ :____ ☐ am ☐ pm Lot/Batch #: _____ ☐Unk Route & Body site: _____ Dose/volume: _____☐Unk	**Dose 3** – ☐Not received Date:_____/____/_____ Time: ____ :____ ☐ am ☐ pm Lot/Batch #: _____ ☐Unk Route & Body site: _____ Dose/volume: _____☐Unk	**Dose 4** – ☐Not received Date:_____/____/_____ Time: ____ :____ ☐ am ☐ pm Lot/Batch #: _____ ☐Unk Route & Body site: _____ Dose/volume: _____☐Unk

PATIENT INFORMATION	
Initials: **Gender:** ☐ Male ☐ Female ☐ Unknown	**Race** (check all that apply):☐White ☐Black ☐Middle Eastern ☐N American Indian/Inuit/Métis ☐South Asian ☐East/Southeast Asian ☐Native Hawaiian/Pac Islander ☐Unknown ☐Other:_____
Age (in years) at vaccination or Date of birth:	
If female, pregnant? ☐ No ☐ Yes ☐ Unknown	**Ethnicity:** ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

Height: _____ ☐ inches ☐ centimeters **Weight:** _____ ☐ pounds ☐ kilograms

ALLERGY HISTORY

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

Anaphylaxis: ☐Unknown ☐No ☐Yes
Hypersensitivity reactions: ☐Unknown ☐No ☐Yes
Hives/urticaria: ☐Unknown ☐No ☐Yes
Asthma: ☐Unknown ☐No ☐Yes
Hay fever: ☐Unknown ☐No ☐Yes

Any previous history of allergic/hypersensitivity reactions to vaccines? ☐Unknown ☐None ☐**Yes – Describe below**

Vaccine	Start date (DD/MMM/YYYY)	Describe the Reaction
	____/____/_____	
	____/____/_____	

Any previous history of other allergic/hypersensitivity reactions (medications, foods, environmental, etc.)?
☐Unknown ☐None ☐**Yes – Describe below**

Other causes of allergic/ hypersensitivity reactions	Start date (DD/MMM/YYYY)	Describe the Reaction
	____/____/_____	
	____/____/_____	
	____/____/_____	
	____/____/_____	

GENERAL HEALTH/MEDICAL HISTORY

Acute illnesses at the time of vaccination and up to one month before: ☐ None ☐Unknown	Start date (DD/MMM/YYYY)	Ongoing?	Stop date (DD/MMM/YYYY)
	_____/_____/_____	☐ Yes ☐ No	_____/_____/_____
	_____/_____/_____	☐ Yes ☐ No	_____/_____/_____

moderna

MCN:

Vaccine Hypersensitivity/Anaphylaxis Follow-up Form

Please complete this form and return via email to ModernaPV@modernatx.com or via fax to .

If you have any questions about completing this form, please call .

Other chronic/long-standing health conditions: ☐ None ☐ Unknown	Start date (DD/MMM/YYYY)	Recent change in status of chronic condition (i.e. significant worsening or improvement; treatment changes, etc)? **If yes, please describe.**
	____/____/_____	☐ No ☐ Yes:
	____/____/_____	☐ No ☐ Yes:
	____/____/_____	☐ No ☐ Yes:
	____/____/_____	☐ No ☐ Yes:
	____/____/_____	☐ No ☐ Yes:

Prescriptions, over-the-counter medications, dietary supplements, or herbal remedies being <u>taken at time of vaccination</u>:
☐ None ☐ Unknown

Product name:	Strength/ Frequency	Route	Indication for use	Start date (DD/MMM/YYYY)	Still taking?	If no longer taking, stop date:
				____/____/_____	☐ Yes ☐ No	____/____/_____
				____/____/_____	☐ Yes ☐ No	____/____/_____
				____/____/_____	☐ Yes ☐ No	____/____/_____
				____/____/_____	☐ Yes ☐ No	____/____/_____
				____/____/_____	☐ Yes ☐ No	____/____/_____

OTHER VACCINES GIVEN ON THE SAME DAY AS MODERNA COVID-19 VACCINE

Vaccine (type/brand)	Manufacturer	Lot number	Route	Body side/site	Dose number in series
					_____ of _____
					_____ of _____

OTHER VACCINES RECEIVED WITHIN ONE MONTH PRIOR TO MODERNA COVID-19 VACCINE

Vaccine (type/brand)	Manufacturer	Lot number	Route	Body side/site	Dose number in series	Date Given (dd/mmm/yyyy)
					____ of ____	____/____/_____
					____ of ____	____/____/_____

ADVERSE EVENT INFORMATION

What was the final diagnosis for the reported reaction? ☐Hypersensitivity reaction ☐Anaphylactic reaction ☐Anaphylactoid reaction ☐Anaphylactic shock ☐Other – please specify: _____

Reaction start date/time:
_____/_____/_____ _____ : _____ ☐ am ☐pm
DD/ MMM / YYYY

Reaction stop date/time:
_____/_____/_____ _____ : _____ ☐ am ☐pm
DD/ MMM / YYYY

Describe the first observation of the reaction:

Please indicate all signs and symptoms experienced by the patient (check all that apply).

☐Itching/pruritus: ☐*Generalized* or ☐*Local* ☐Redness/erythema: ☐*Generalized* or ☐*Local* ☐Rash: ☐*Generalized* or ☐*Local*

☐Hives/urticaria: ☐*Generalized* or ☐*Local*
☐Irregular heart rate/palpitations
☐Heart rate >100 beats per min
☐Systolic blood pressure <90 mmHg
☐Reduced central pulse volume
☐Capillary refill >3 secs
☐Nausea/vomiting
☐Diarrhea
☐Abdominal cramping
☐Swelling of upper airway (lips, tongue, throat, uvula, or larynx)
☐Sensation of throat closing
☐Red/itchy eyes
☐Angioedema
☐Sneezing/runny nose
☐Difficulty breathing
☐Use of respiratory accessory muscles
☐Respirations >20 per min
☐Difficulty swallowing
☐Bronchospasm /wheezing
☐Hoarseness
☐Chest tightness
☐Stridor
☐Cough
☐Cyanosis
☐Decreased level of consciousness
☐Chills
☐Unusual taste
☐Prickling/Tingling sensation
☐Numbness
☐Feeling hot
☐Flushing

Did the event cause the patient to seek medical care? ☐ No ☐ Yes (select below)

☐ Doctor's office/urgent care visit
☐ Emergency room/department
☐ Admitted to hospital - Dates of hospitalization:
_____/_____/_____ to _____/_____/_____
DD/ MMM / YYYY DD/ MMM / YYYY

moderna

MCN:

Vaccine Hypersensitivity/Anaphylaxis Follow-up Form

Please complete this form and return via email to ModernaPV@modernatx.com or via fax to .

If you have any questions about completing this form, please call .

VITAL SIGNS/DIAGNOSTIC RESULTS

Please provide vital signs measurements during the onset of the reaction. Enter date/time of vital signs measurement in the top row with results for each measure below the corresponding date/time or check "Not done" if not done at that time.

Date/Time of measurement:					
Body temperature ☐°C or ☐°F	☐Not done	☐Not done	☐Not done	☐Not done	☐Not done
Heart rate (beats per minute)	☐Not done	☐Not done	☐Not done	☐Not done	☐Not done
Respiratory rate (breaths per minute)	☐Not done	☐Not done	☐Not done	☐Not done	☐Not done
Blood pressure (mmHg)	☐Not done	☐Not done	☐Not done	☐Not done	☐Not done

Please provide results of the following laboratory results or check here if ☐No lab/diagnostic tests done or ☐Results not available:

Test Type	Date/time sample collected	Result with units	Reference range	Comments
Mast cell tryptase ☐ Not done				
IgE ☐ Not done				
Complement ☐ Not done				
Pathology exam – specify: ☐ Not done				
Other – specify:				
Other – specify:				

TREATMENT FOR THE EVENT

Please indicate below the details of treatment provided or check here if ☐None or ☐Unknown:

Treatment	Dose/Frequency	Route	Start date (DD/MMM/YYYY)	Still taking?	If no longer taking, stop date:
☐Epinephrine/ Adrenaline			____/____/_____	☐ Yes ☐ No	____/____/_____
☐Antihistamines – specify: _____			____/____/_____	☐ Yes ☐ No	____/____/_____
☐Steroids – specify: _____			____/____/_____	☐ Yes ☐ No	____/____/_____
☐Oxygen			____/____/_____	☐ Yes ☐ No	____/____/_____
☐Other – specify: _____			____/____/_____	☐ Yes ☐ No	____/____/_____

CAUSALITY AND OUTCOME

Was the adverse event most likely caused by mRNA-1273? ☐ No ☐ Yes ☐ Unknown

Were there any other potential causes? ☐ No ☐ Unknown ☐ Yes - please describe:

Event Outcome:

☐ Recovered
Date recovered:___/____/_____
☐ Ongoing/Not recovered
☐ Unknown

☐ Recovered with residual effects
Date recovered:_____/_____/_____
Residual effects:_____

☐ Event resulted in death
Date of death:___/_____/_____
Cause of death_____
Autopsy done:☐ Yes ☐ No ☐ Unk

MCN:

Vaccine Hypersensitivity/Anaphylaxis Follow-up Form

Please complete this form and return via email to ModernaPV@modernatx.com or via fax to .

If you have any questions about completing this form, please call .

Describe the adverse event(s), including any additional signs/symptoms, clinical course, and treatments with dates/timelines (use additional pages or attach records, if necessary):

☐ Additional records attached

Completed by:_____ Date:_____/_____/_____ (DD/MMM/YYYY)

MCN:

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

Patient Initials/Gender:
Patient DOB/Age:
Reported Event(s):

Please provide details of all SARS-CoV2 testing performed: Unknown☐ Not done ☐

Date of Test DD/MMM/YYYY	Source of Sample (nasopharyngeal, saliva, serum, etc)	Type of Test (RT-PCR, rapid antigen, IgG, IgM)	Quantitative Results	Qualitative/ Titer Results, if applicable
			☐ Positive-detected ☐ Negative-not detected	
			☐ Positive-detected ☐ Negative-not detected	
			☐ Positive-detected ☐ Negative-not detected	
			☐ Positive-detected ☐ Negative-not detected	

****

Did the patient have any of the following high-risk medical conditions prior to COVID-19 diagnosis?

Condition		If yes, please specify:
Cardiovascular disease	☐ No ☐ Yes	Start date: Diagnoses:
Chronic respiratory conditions	☐ No ☐ Yes	Start date: Diagnoses:
Diabetes	☐ No ☐ Yes	Start date: Diagnoses:
Cancer	☐ No ☐ Yes	Start date: Diagnoses:
HIV/AIDS	☐ No ☐ Yes	Start date:
Other immune-deficiency conditions/immunosuppressive medications	☐ No ☐ Yes	Start date: Diagnoses/Indications:
Liver-related conditions	☐ No ☐ Yes	Start date: Diagnoses:
Obesity (BMI ≥ 30)	☐ No ☐ Yes	Start date: Most recent BMI, if known:
Other – specify:	☐ No ☐ Yes	Start date: Diagnoses:

Did any of the conditions above worsen during COVID-19 illness? ☐ No ☐ Yes – Please describe:

MCN:

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

Patient Initials/Gender:
Patient DOB/Age:
Reported Event(s):

Please complete the table below concerning the patient's vital signs at any medically attended clinic visits and/or during hospitalization:

Did the patient have any measurements at rest of:		If yes, please provide the following details:	
a respiratory rate ≥ 30 per minute?	☐ No ☐ Yes	Start date: Respiratory rate range:	End date:
a heart rate ≥ 125 beats per minute?	☐ No ☐ Yes	Start date: Heart rate range:	End date:
an oxygen saturation of ≤ 93% on room air?	☐ No ☐ Yes	Start date: Oxygen saturation range:	End date:
a systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg?	☐ No ☐ Yes	Start date: Blood pressure range:	End date:

****

Please indicate COVID-19 symptoms experienced by the patient in the table below:

Fever	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐ Temperature max:_____ ☐Fahrenheit ☐Celsius
Chills	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Shortness of breath	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Cough	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Muscle aches	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Headache	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Nausea/vomiting	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Diarrhea	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Nasal congestion/ runny nose	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Loss of taste	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Loss of smell	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐
Other (specify):	☐ No ☐ Yes	Duration (# of days):_____Ongoing? ☐

****

Did the patient have clinical and/or radiographical evidence of pneumonia?

☐ No ☐ Yes – Please provide details with dates:

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

Patient Initials/Gender:
Patient DOB/Age:
Reported Event(s):

Did the patient require non-invasive supplemental oxygen?

☐ No ☐ Yes – Please provide details:

Oxygen delivery method (nasal cannula, high-flow face mask, etc)	Oxygen delivery rate in L/hr	Start date	End date

****

Please provide details of treatment provided for SARS-CoV-2 infection:

Treatment	Dose/ Frequency	Route	Start Date/Time	Stop Date/Time

****

(If patient was hospitalized)

Did the patient require admission to an intensive care unit (ICU)?

☐ No ☐ Yes – If yes, please provide date of admission to ICU and length of stay:

Date of ICU transfer/admission	**Number of nights spent in ICU**

****

(If patient was hospitalized)

Did the patient require treatment with vasopressors?

☐ No ☐ Yes – Please provide details:

Medication	**Dose**	**Frequency**	**Route**	**Start date dd/mmm/yyyy**	**Stop date dd/mmm/yyyy**	**Ongoing**
						☐
						☐
						☐

****

(If patient was hospitalized)

Did the patient require respiratory ventilator support or ECMO?

☐ No ☐ Yes – Please provide details with dates:

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

Patient Initials/Gender:
Patient DOB/Age:
Reported Event(s):

**During their illness, did the patient exhibit signs or symptoms of new/worsening dysfunction in any of the following categories? *****see additional instructions below table for any "Yes" responses:*		
Multiorgan failure?	☐ No ☐ **Yes**	Start date: End date:
Gastrointestinal dysfunction? Hepatic dysfunction Abdominal pain Other – specify:	 ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes**	Start date: End date:
Acute renal dysfunction?	☐ No ☐ **Yes**	Start date: End date:
Neurologic dysfunction? Encephalopathy Convulsions/seizures Meningitis Altered level of consciousness Other – specify:	 ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes**	Start date: End date:
Respiratory dysfunction? Acute respiratory distress syndrome (ARDS) Acute respiratory failure Dyspnea/tachypnea Other – specify:	 ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes**	Start date: End date:
Acute cardiac injury? Myocardial infarction Arrhythmia Heart failure Myocarditis, pericarditis Stress cardiomyopathy Microangiopathy Other – specify:	 ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes**	Start date: End date:

(continued on next page)

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

Patient Initials/Gender:
Patient DOB/Age:
Reported Event:

**During their illness, did the patient exhibit signs or symptoms of new/worsening dysfunction in any of the following categories? *****see additional instructions below table for any "Yes" responses:*		
Hematologic/Vascular disorders? Deep vein thrombosis Pulmonary embolus Cerebrovascular stroke Limb ischemia Hemorrhagic disease Thrombocytopenia Other – specify:	 ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes**	Start date: End date:
Dermatologic disorders? Erythema multiforme Single organ cutaneous vasculitis Chillblain-like lesions Other – specify:	☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes** ☐ No ☐ **Yes**	Start date: End date:

****If yes to any, please describe the clinical course and provide details of supporting laboratory/diagnostic investigations (medical records/additional pages can be attached, if needed):**

Please provide the following laboratory test details:

Test Type/Name	**Completed?**	**If yes, date collected with results including units and reference ranges (records may be attached, if needed):**
Lymphocytes (i.e. CD4, CD8 counts)	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Cytokines	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Procalcitonin	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Erythrocyte sedimentation rate	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:

(continued on next page)

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

Patient Initials/Gender:
Patient DOB/Age:
Reported Event:

Test Type/Name	Completed?	If yes, date collected with results including units and reference ranges (records may be attached, if needed):
C-reactive protein	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Ferritin	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Lactate dehydrogenase (LDH)	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
D-dimer	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Fibrinogen	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
PT/INR, PTT	☐ Yes ☐ No ☐ Unknown	Test Name/Date(s): Results with units: Normal range:
PaO2/FiO2, PaCO2	☐ Yes ☐ No ☐ Unknown	Test Name/Date(s): Results with units: Normal range:
Venous/Arterial blood pH	☐ Yes ☐ No ☐ Unknown	Test Name/Date(s): Results with units: Normal range:
Histopathology/ immunopathology of organs involved	☐ Yes ☐ No ☐ Unknown	Date(s): Results:
Diagnostic Imaging (Magnetic Resonance Imaging, Computed Tomography, Ultrasound, doppler)	☐ Yes ☐ No ☐ Unknown	Test / Date / Result (/ /) (/ /) (/ /)
Other relevant results (attach additional pages, as needed)	☐ Yes ☐ No ☐ Unknown	Test / Date / Result w/units / Normal range (/ / /) (/ / /) (/ / /)

moderna

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 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	☐ No ☐ Yes ☐ Unk		☐ Ongoing	
Pericarditis	☐ No ☐ Yes ☐ Unk		☐ Ongoing	
Hypertension	☐ No ☐ Yes ☐ Unk		☐ Ongoing	
Thrombosis (blood clots) – e.g. pulmonary embolism, deep vein thrombosis (DVT), etc.	☐ No ☐ Yes ☐ Unk		☐ Ongoing	
Cardiac arrythmia (e.g. atrial fibrillation (afib), supraventricular tachycardia (SVT), etc.)	☐ No ☐ Yes ☐ Unk		☐ Ongoing	
Myocardial infarction (heart attack)	☐ No ☐ Yes ☐ Unk		☐ Ongoing	
Coronary artery disease	☐ No ☐ Yes ☐ Unk		☐ Ongoing	
Other heart or vascular condition -specify: _____	☐ No ☐ Yes ☐ Unk		☐ 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)	☐ No ☐ Yes ☐ 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.)	☐ No ☐ Yes ☐ Unk	Start date: Diagnosis: Treatment with dates: Date recovered:
Fungal Infections in the last 6 months (e.g. yeast infections (Candida), Aspergillus, Histoplasma, etc.)	☐ No ☐ Yes ☐ Unk	Start date: Diagnosis: Treatment with dates: Date recovered:
Tick-borne disease (Lyme disease, Ehrlichiosis, Babesiosis, etc.)	☐ No ☐ Yes ☐ 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.)	☐ No ☐ Yes ☐ Unk	Start date: Diagnosis: Treatment with dates:
HIV	☐ No ☐ Yes ☐ Unk	Start date: Treatment with dates: Current status of disease:
Use of Immunosuppressant medications	☐ No ☐ Yes ☐ Unk	Start date: Medication: Condition treated: Stop date:

(continued on next page)

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	☐ No ☐ Yes ☐ Unk	Start date: Diagnosis: Treatments with dates: Current status of disease:
Radiation and/or Chemotherapy treatment	☐ No ☐ Yes ☐ 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.

☐ New onset chest pain/pressure Start date: Duration:	☐ Cough Start date: Duration:	☐ Abnormal tiredness Start date: Duration:	☐ Abdominal pain Start date: Duration:
☐ Shortness of breath Start date: Duration:	☐ Weakness Start date: Duration:	☐ Swelling in feet/ankles Start date: Duration:	☐ Dizziness/Fainting Start date: Duration:
☐ Sudden, excessive sweating Start date: Duration:	☐ Nausea, vomiting, or diarrhea Start date: Duration:	☐ Shoulder/upper back pain Start date: Duration:	☐ Palpitations/Irregular heart beats Start date: Duration:

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	☐ Yes ☐ No ☐ Unknown	Pulsus Paradoxus: ☐ No ☐ Yes – If yes: Expiratory SBP_____; Inspiratory SBP_____ Pericardial friction rub: ☐ Yes ☐ No Other abnormal findings:
Troponin T	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Troponin I	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
CK-MB	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
C-reactive protein (CRP)	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
D-dimer	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Erythrocyte sedimentation rate (sed rate, ESR, Westergren sed rate)	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:

(continued on next page)

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	☐ Yes ☐ No ☐ Unknown	Date:	Interpretation/results:
Electrocardiogram (EKG)	☐ Yes ☐ No ☐ Unknown	Date:	Interpretation/results:
Echocardiogram	☐ Yes ☐ No ☐ Unknown	Date:	Interpretation/results:
Magnetic Resonance Imaging (MRI)/Cardiac MRI	☐ Yes ☐ No ☐ Unknown	Date:	Interpretation/results:
Computed Tomography/CT scan	☐ Yes ☐ No ☐ Unknown	Date:	Interpretation/results:
Pericardial/ Endomyocardial biopsy	☐ Yes ☐ No ☐ Unknown	Date: Results:	

REFERENCES

Baden et al Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine N Engl J Med 2021; 384:403-416. DOI: 10.1056/NEJMoa2035389

Beaudoin-Bussières G, Laumaea A, Anand SP, Prévost J, Gasser R, Goyette G, et al. Decline of humoral responses against SARS-CoV-2 Spike in convalescent individuals. mBio. 2020;11(5):e02590-20.

Blauwet LA, Cooper LT. Myocarditis. Prog Cardiovasc Dis. 2010;52(4):274-288. doi:10.1016/j.pcad.2009.11.006

Bolles M, Deming D, Long K, Agnihothram S, Whitmore A, Ferris M, et al. A double inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice and induces increased eosinophilic proinflammatory pulmonary response upon challenge. J Virol. 2011;85(23):12201-15.

Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PLoS One 2021; 16(3):e0247461. Available at: Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. — Department of Experimental Psychology (ox.ac.uk)

Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, et al. SARS-CoV-2 reactive T cells healthy donors and patients with COVID-19. Nature. 2020;587(7833):270-4.

Brighton Collaboration Myocarditis Case Definition (Pandemic Emergency Response Process_Draft Release) Level of Certainty (LOC) Classification Version_1.4.2_30.May.2021

Cascella M, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19). Treasure Island (FL): StatPearls Publishing; 2021 Jan

Centers for Disease Control and Prevention (CDC). COVID Data tracker weekly review [Internet]. 01 Jan 2022 [cited 2022 Feb 11]. Available. Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/covid-view-past-summaries.html?Sort=Posted%20Date%3A%3Adesc

Centers for Disease Control and Prevention (CDC). Science Brief: Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. 10 Jan 2022 2022b. Available at: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html

Centers for Disease Control and Prevention (CDC). COVID-19 Vaccinations in the United States. 2022. Available at: https://.cdc.gov/covid-data-tracker/#vaccinations

Chowdhury SD, Oommen AM. Epidemiology of COVID-19. Journal of Digestive Endoscopy. 2020;11(1):3-7.

Corbett KS, Flynn, B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. N Engl J Med. 2020 Oct 15;383(16):1544-55.

Czub M, Weingartl H, Czub S, He R, Cao J. Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets. Vaccine. 2005;23(17-18):2273-9.

Deming D, Sheahan T, Heise M, Yount B, Davis N, Sims A, et al. Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. PloS Med. 2006;3(12):e525. Correction in: PloS Med. 2007;4(2):e80.

Desmet CJ, Ishii KJ. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. Nat Rev Immunol. 2012;12(7):470-91.

Dodd C, Willame C, Sturkenboom M. vACCine COVID-19 monitoring readinESS (ACCESS). Background rates of adverse events of special interest for monitoring COVID-19 vaccines. Protocol, v1.1. 2020 Sep 21. 54p.

European Centre for Disease Prevention and Control (ECDC). COVID-19 country overviews [Internet]. 202220a [cited 2022 Feb 11]. Available at: https://covid19-surveillance-report.ecdc.europa.eu/archive-COVID19-reports/archive/2021W52_country_overview_report_20220105.zip .

European Centre for Disease Prevention and Control (ECDC). Covid-19 surveillance report [Internet]. 202220b [cited 2022 Feb 11]. Available at: https://covid19-surveillance-report.ecdc.europa.eu/archive-COVID19-reports/archive/2021W52_country_overview_report_20220105.zip.

European Centre for Disease Prevention and Control (ECDC). COVID-19 country overviews – Week 52 2021 [Internet]. 2022a [cited 2022 Feb 11]. Available at: https://covid19-surveillance-report.ecdc.europa.eu/archive-COVID19-reports/archive/2021W52_country_overview_report_20220105.zip

European Centre for Disease Prevention and Control (ECDC). Interim public health considerations for COVID-19 vaccination of adolescents in the EU/EEA. 11 Feb 2022. Stockholm: ECDC; 2021b. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Interim-public-health-considerations-for-COVID-19-vaccination-of-adolescents.pdf

European Centre for Disease Prevention and Control (ECDC). Data on the 14-day age-specific notification rate of new COVID-19 cases. 11 Feb 2022. Stockholm: ECDC; 2021c. Available at: https://www.ecdc.europa.eu/en/publications-data/covid-19-data-14-day-age-notification-rate-new-cases

European Centre for Disease Prevention and Control (ECDC). COVID-19 Vaccine Tracker. 31 Dec 2021. Stockholm: ECDC; 2022d. Available at: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab

European Centre for Disease Prevention and Control (ECDC). Interim public health considerations for COVID-19 vaccination of adolescents in the EU/EEA. 10 Feb 2022e. Stockholm: ECDC; 2021. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Interim-public-health-considerations-for-COVID-19-vaccination-of-adolescents.pdf

European Medicines Agency (EMA). COVID-19 Vaccines. 13 Feb 2022a. Amsterdam. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines

European Medicines Agency (EMA). COVID-19 treatments. 2022b. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments

European Centre for Disease Prevention and Control. COVID-19 Vaccine rollout overview. Week 52, 2021. Available at: https://covid19-vaccine-report.ecdc.europa.eu/#6_Reported_data

Fechter P, Brownlee GG. Recognition of mRNA cap structures by viral and cellular proteins. J Gen Virol. 2005;86(5):1239-49.

Federal Office of Public Health (FOPH). COVID-19 Switzerland. 01 July 2021. Available at: https://www.covid19.admin.ch/en/epidemiologic/vacc-doses

Flaxman S, Mishra S, Gandy A, Unwin HJT, Mellan TA, Coupland H, et al. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Nature, 2020;584(7810):257-61.

Food and Drug Administration (FDA). Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19 (October 2020). Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19.

Food and Drug Administration (FDA). Emergency Use Authorisation. 13 July 2021. Available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep. ePub: 6 July 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7027e2

Golpour, A., Patriki, D., Hanson, P. J., McManus, B. & Heidecker, B. Epidemiological Impact of Myocarditis. J Clin Medicine 10, 603 (2021)

Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell. 2020;181(7):1489-1501.

Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral immune response to SARS-CoV-2 in Iceland. N Engl J Med. 2020;383(18):1724-34.

Hoit BD. The Merck Manual. Professional edition. Case Western Reserve University. Nov 2020.

Imazio, M. et al. Myopericarditis versus viral or idiopathic acute pericarditis. Heart 94, 498 (2008).

Imazio, M., Gaita, F. & LeWinter, M. Evaluation and Treatment of Pericarditis: A Systematic Review. Jama 314, 1498–1506 (2015)

Institute for Health Metrics and Evaluation (IHME). GBD Results Tool. Seattle: University of Washington; 2020a. http://ghdx.healthdata.org/gbd-results-tool. Accessed 27 November 2020.

Institute for Health Metrics and Evaluation (IHME). Global Health Data Exchange (GHDx). Seattle: University of Washington; 2020b. http://ghdx.healthdata.org/. Accessed 27 November 2020.

Institute for Health Metrics and Evaluation (IHMEs). 2020c. Available at: covid19.healthdata.org. Accessed on 07 December 2020.

Jackson LA, Anderson EL, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 – preliminary report. 2020. N Engl J Med; 383(20):1920-1931.

Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity. 2005;23(2):165-75.

Kellam P, Barclay W. The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential for reinfection. The Journal of general virology. 2020 May 20.

Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969;89(4):422-34.

Kozak M. Structural features in eukaryotic mRNAs that modulate the initiation of translation. J Biol Chem. 1991;266(30):19867-70.

Kytö, V., Sipilä, J. & Rautava, P. Clinical Profile and Influences on Outcomes in Patients Hospitalized for Acute Pericarditis. Circulation 130, 1601–1606 (2014).

Long Q-X, Tang X-J, Shi Q-L, Li Q, Deng H-J, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020;26(8):1200-4.

Munoz FM, Cramer JP, Dekker CL, Dudley MZ, Graham BS, Gurwith M, et al. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data [Internet]. 21Sep 2020 [cited 29 December 2020]. Available from: https://brightoncollaboration.us/wp-content/uploads/2020/10/JVAC-S-20-02520_mzd.pdf.

National Institute of Health (NIH). Overview of COVID-19: Epidemiology, Clinical Presentation, and Transmission. [Internet]. 2020 [cited XX Month YYYY]. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/.

Ni L, Ye F, Cheng M-L, Feng Y, Deng Y-Q, Zhao H, et al. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. Immunity. 2020;52(6):971-7.e3.

Onitsuka, H. et al. Clinical manifestations of influenza a myocarditis during the influenza epidemic of winter 1998-1999. J Cardiol 37, 315–23 (2001).

Pedersen NC, Liu H, Dodd KA, Pesavento PA. Significance of coronavirus mutants in feces and diseased tissues of cats suffering from feline infectious peritonitis. Viruses. 2009;1(2):166-84.

Pedersen NC, Liu H, Scarlett J, Leutenegger CM, Golovko L, Kennedy H, et al. Feline infectious peritonitis: role of the feline coronavirus 3c gene in intestinal tropism and pathogenicity based upon isolates from resident and adopted shelter cats. Virus Res. 2012;165(1):17-28.

Perreault J, Tremblay T, Fournier M-J, Drouin M, Beaudoin-Bussières G, Prévost J, et al. Longitudinal analysis of the humoral response to SARS-CoV-2 spike RBD in convalescent plasma donors bioRxiv. 2020.

Polack FP. Atypical measles and enhanced respiratory syncytial virus disease (ERD) made simple. Pediatr Res. 2007;62(1):111-5.

Prévost J, Gasser R, Beaudoin-Bussières G, Richard J, Duerr R, Laumaea A, et al. Cross-sectional evaluation of humoral responses against SARS-CoV-2 Spike. Cell Rep Med. 2020;1(7):100126.

Public Health Agency of Canada. Canadian COVID-19 vaccination coverage report. 01 July 2021. Available at: https://health-infobase.canada.ca/covid-19/vaccination-coverage/

Ritchie H, Ortiz-Ospina E, Beltekian D, Mathieu E, Hasell J, et al. Coronovirus Pandemic (COVID-19). 01 July 2021. Published online at Ourworldindata.org. Available at: https://ourworldindata.org/covid-vaccinations.

Rozenski J, Crain P, McCloskey J. The RNA modification database: 1999 update. Nucleic Acids Res. 1999;27(1):196-7.

Seydoux E, Homad LJ, MacCamy AJ, Parks KR, Hurlburt NK, Jennewein MF, et al. Analysis of a SARS-CoV-2- infected individual reveals development of potent neutralizing antibodies with limited somatic mutation. Immunity. 2020;53(1):98-105.e5.

Sharif N, Dehghani P. Emergency files: acute pericarditis, myocarditis, and worse!. Can Fam Physician. 2013;59(1):39-41.

Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, et al. Preliminary Findings of mRNA COVID-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021;384(24):2273-2282.

Smatti MK, Al Thani AA, Yassine HM. Viral-induced enhanced disease illness. Front Microbiol. 2018;9:2991.

Takano T, Kawakami C, Yamada S, Satoh R, Hohdatsu T. Antibody-dependent enhancement occurs upon re-infection with the identical serotype virus in feline infectious peritonitis virus infection. J Vet Med Sci. 2008;70(12):1315-21.

To KK-W, Chan W-M, Ip JD, Chu AW-H, Tam AR, Liu R, et al. Unique clusters of severe acute respiratory syndrome coronavirus 2 causing a large coronavirus disease 2019 outbreak in Hong Kong. Clinical Infectious Diseases. 2020.

Wallace M and Oliver S. COVID 19 vaccines in adolescents and young adults: benefit-risk discussion. ACIP Committee meeting. June 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html

Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Okba NMA, Endeman H, et al. Phenotype and kinetics of SARS-CoV-2- specific T-cells in COVID-19 patients with acute respiratory distress syndrome. Sci Immunol. 2020;5(48):eabd2071.

World Health Organization (WHO) 2019. Coronavirus disease (COVID-19) pandemic. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/novel-coronavirus-2019-ncov.

WHO Timeline of WHO's response to COVID-19. 2020a. Available from: https://www.who.int/news/item/29-06-2020-covidtimeline.

WHO World health assembly charts course for COVID-19 response and global health priorities. 2020b. Available from: https://www.who.int/news/item/05-11-2020-world-health-assembly-charts-course-for-covid-19-response-and-global-health-priorities.

WHO COVID-19 infection prevention and control living guideline: mask use in community settings, 22 December 2021 . 2022c. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-IPC_masks-2021.1

WHO. Global situation. WHO Coronavirus (COVID-19) Dashboard. Accessed on 11 Feb 2022a. Available at: https://covid19.who.int/

WHO. Tracking SARS-CoV-2 Variants. 2021b. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

Wu L-P, Wang N-C, Chang Y-H, Tian X-Y, Na D-Y, Zhang L-Y, et al. Duration of antibody responses after severe acute respiratory syndrome. Emerg Infect Dis. 2007;13(10):1562-4.

Wyper GMA, Assunção, R., Cuschieri, S, Devleeschauwer B, Fletcher E, Haagsma JA, et al. Population vulnerability to COVID-19 in Europe: a burden of disease analysis. Arch Public Health. 2020;78:47.