EU Risk Management Plan for COVID-19 mRNA vaccine

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

RMP version number: 1.1

Data lock point for this RMP: 21 December 2020

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Rationale for submitting an updated RMP: Updated based on list of questions during the procedure (Consolidated List of Questions 01 January 2021)

Summary of significant changes in this RMP:

Compared to the previously submitted COVID 19 Vaccine Moderna European Union (EU) RMP version 1.0, this RMP version 1.1 is updated to reflect non-significant administrative changes.

The list below shows the modifications/changes from the previous RMP version 1.0.

RMP Module:	**Significant Changes:**
Part I Product Overview	No changes
Part II Safety Specification	
1. Module SI Epidemiology of the indication(s) and target population(s)	No changes.
2. Module SII Non-clinical part of the safety specification	No changes.
3. Module SIII Clinical trial exposure	No changes.
4. Module SIV Populations not studied in clinical trials	No changes
5. Module SV Post-authorisation experience	No changes.
6. Module SVI Additional EU requirements for the safety specification	No changes.
7. Module SVII Identified and potential risks	No changes.
8. Module SVIII Summary of the safety concerns	No changes.
Part III Pharmacovigilance plan	Administrative changes and studies milestones updates.
Part IV Plans for post-authorisation efficacy studies	No changes.
Part V Risk minimisation measures	No changes.

Part VI Summary of the risk management plan	No changes
Part VII Annexes	Annex 2 – Milestones updates Annex 8 – updated to reflect the changes made from to the RMP.

Other RMP versions under evaluation: Not applicable

RMP version number: Not applicable

Submitted on: Not applicable

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Details of the currently approved RMP: Not applicable

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Approved with procedure: Not applicable

Date of approval (opinion date): Not applicable

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[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.

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LIST OF ABBREVIATIONS

Acronym	Definition
2019-nCoV	2019 novel coronavirus
Ab	antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARDS	acute respiratory distress syndrome
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
SARS	severe acute respiratory syndrome
SCRI	self-controlled risk interval

SmPC	Summary of Product Characteristics
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 Applicant	Moderna Biotech Madrid Spain
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area	COVID-19 Vaccine Moderna
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** The mRNA drug substance in COVID-19 Vaccine Moderna 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 (eg, toll-like receptors) (Desmet and Ishii 2012). 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** COVID-19 Vaccine Moderna 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 1.3.1
Indication(s) in the EEA	Current: Not applicable Proposed: COVID-19 Vaccine Moderna is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.
Dosage in the EEA	Current: Not applicable Proposed: COVID-19 Vaccine Moderna is administered as two 0.5 mL doses by the IM route. The recommended interval between two doses is28 days.
Pharmaceutical form(s) and strengths	Current: Not applicable Proposed: COVID-19 Vaccine Moderna is a dispersion for injection. It is supplied as a multidose-vial at the concentration of 0.20 mg/mL. Ten doses can be withdrawn from each multiple-dose vial. Each dose (0.5 mL) contains 0.10 mg mRNA.
Vaccine construct and the formulation	COVID-19 Vaccine Moderna 0.20 mg/mL is a dispersion for injection. One dose (0.5 mL) contains 0.10 mg mRNA encoding the prefusion stabilized spike glycoprotein of 2019 novel Coronavirus (SARS-CoV-2). The other ingredients are SM-102 (a novel lipid nanoparticle), cholesterol, DSPC, PEG2000-DMG, tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, sucrose, water for injection.
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: COVID-19 Vaccine

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

An outbreak of the CoV disease (COVID-19) caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019, and has spread globally (WHO 2020a and WHO 2020b). The World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020; however, by that time, there was already widespread community transmission in many locations. As of November 2020, more than 47 million cases and over 1.2 million deaths have been attributed to the COVID-19 pandemic globally (WHO 2020a and WHO 2020b). Widespread community transmission of SARS-CoV-2 has been reported in the Americas, Europe, Africa, Southeast Asia, and clusters of cases continue to be reported throughout Asia and Australia (WHO 2020a and WHO 2020b). Winter months coinciding with re-opening of some schools and increased indoor activities because of cooler temperatures have led to further increases in COVID-19 cases and deaths in some parts of the world.

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 28 April 2020, 63% of global mortality from SARS-CoV-2 was from the European Region (WHO 2019). In response, European countries implemented large-scale nonpharmaceutical interventions (NPIs), which varied between countries (Flaxmann et al 2020) but did temporarily decrease the incidence and mortality due to COVID-19.

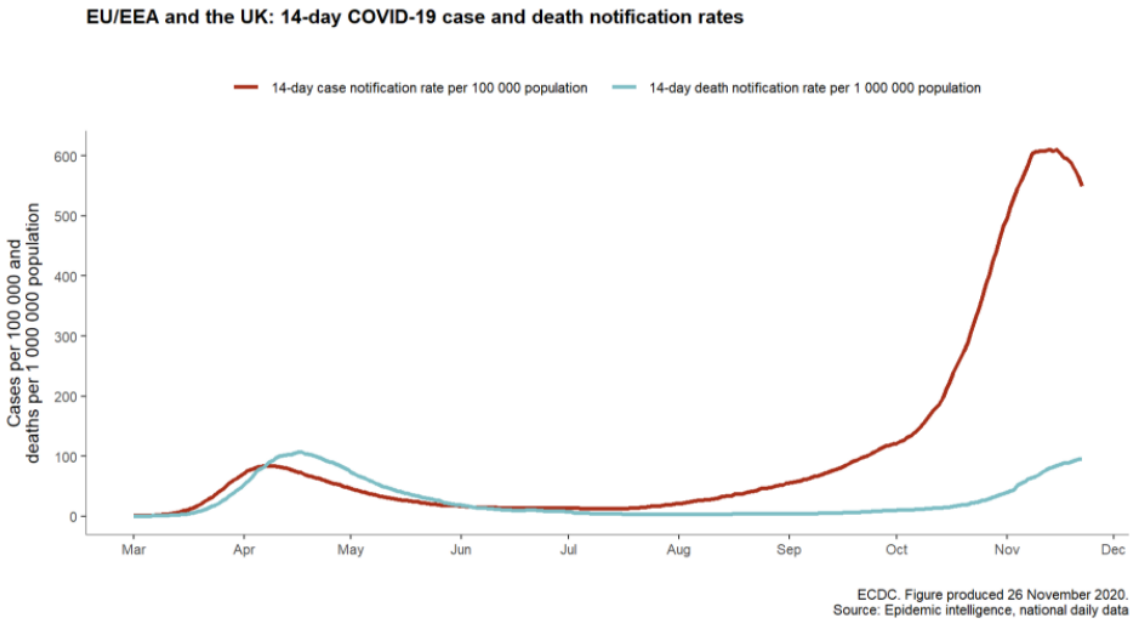
Unfortunately, similar to other parts of the world, Europe is experiencing a second surge in COVID-19 cases in fall 2020, potentially fuelled by relaxation of some NPIs (eg, border and school closures) and colder temperatures leading to increases in indoor gatherings. Data collected by the European Centre for Disease Prevention and Control (ECDC) from 31 countries indicated that the 14-day case notification rate for the European Union/European Economic Area (EU/EEA) and the UK at the end of week 47 of the pandemic (22 November 2020) was 549 (country range: 58-1,186) per 100,000 cases. The 14-day COVID-19 death rate for the EU/EEA and the UK, based on data collected by ECDC from official national sources from 31 countries, was 95.3 (country range: 2.4-226.7) per 1,000,000 persons (ECDC 2020a).

As of 26 November 2020 (ECDC 2020a), the 14-day number of COVID-19 deaths per 1,000,000 persons is currently highest in Czechia (226.7/1,000,000), Belgium (216.1/1,000,000), Bulgaria (169.7/1,000,000), Poland (148.8/1,000,000), and Hungary (139.4/1,000,000). The lowest 14-day number of COVID-19 deaths per 1,000,000 is currently in Finland (2.4/1,000,000), Norway (3.9/1,000,000), Denmark (7.1/1,000,000), Estonia (10.6/1,000,000), and Ireland (15.1/1,000,000).

As of 26 November 2020 (ECDC 2020a), the 14-day case-notification rate per 100,000 persons is currently highest in Luxembourg (1,186/100,000), Austria (1,065.7/100,000), Slovenia (961.7/100,000), Liechtenstein (896.3/100,000), and Croatia (876/100,000). The lowest 14-day case-notification rate per 100,000 persons is currently in Iceland (57.7/100,000), Finland (69.4/100,000), Ireland (107.8/100,000), Norway (154.1/100,000), and Latvia (253.3/100, 000).

Figure 1 provides more details about the case and death rate notifications in the EU/EEA and the UK.

Figure 1: 14-Day COVID-19 Case and Death Notification Rates



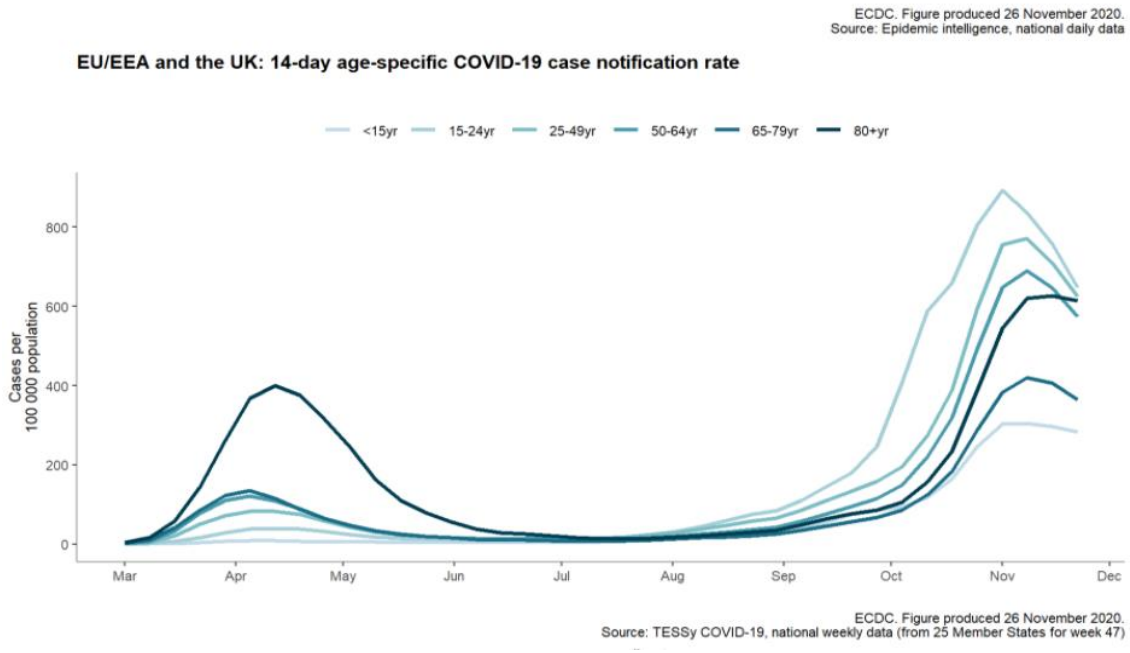
Risk Factors for COVID-19 in Europe

Age

Age has been identified as an independent risk factor for COVID-19 disease. Figure 2 describes the case notification rates per 100,000 persons stratified by different age groups in the EU/EEA and the UK. The case notification rate was significantly higher among elderly populations during the first 3 months of the pandemic.

Case notification rates remained steady across age groups during the summer months from June until September, when the second peak in case notification rates began. From September until December, cases of COVID-19 among individuals ≥ 65 years and older remain high, although the age distribution of the epidemic curve has begun to change, with younger age groups (15-24 years old) now having the highest case notification rate.

Figure 2: 14-Day Age-Specific COVID-19 Case Notification Rates



Comorbid Conditions

Data pooled from 31 European countries and reported to The European Surveillance System (TESSy) have identified the following as COVID-19 vulnerable health conditions (most vulnerable to least vulnerable): 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), hematological disorders, rheumatic diseases (including arthritis), tuberculosis, and asplenia (ECDC 2020b) .

Of all fatal cases (26,923 fatalities) reported to TESSy:

- 28% had cardiac disorders
- 17.8% had diabetes
- 15.6% had known preconditions
- 10.8% had cancer malignancies

- 8% had hypertension
- 6.3% had chronic lung disease
- 4.6% had neuromuscular diseases
- 4.4% had kidney-related conditions
- 2.2% had asthma
- 1-1% had HIV or other immune deficiencies
- 0.6% had liver-related conditions
- 0.3% had hematological disorders
- 0.1% were populations who smoke
- 0.1% were obese

Of all mild cases (365,643 mild cases) reported to TESSy:

- 80.2% had known preconditions
- 6.6% had cardiac disorders
- 3.7% had diabetes
- 3% had cancer malignancies
- 2.5% had chronic lung disease
- 0.8% had hypertension
- 0.8% were smokers
- 0.7% had neuromuscular disorders
- 0.4% had asthma
- 0.4% had kidney-related disorders
- 0.2% had liver-related disorders
- 0.2% had HIV or other immune deficiencies
- 0.2% were obese
- 0.1% had other endocrine disorders

In summary, 84.4% of fatalities were in populations with vulnerable preconditions, and only 20% of reported mild cases were from populations with vulnerable preconditions. Preconditions,

which have the most severe outcomes, include cardiac disorders, diabetes, cancer malignancy, hypertension, and chronic lung disease (excluding asthma). The elderly and other vulnerable populations are at increased risk for death due to COVID-19, and the proportion of elderly and vulnerable individuals in European countries is likely one reason for the observed COVID-19 mortality rates (IHME 2020a; IHME 2020b; Wyper et al 2020).

Main Existing Treatment Options

Until a safe and effective vaccine against COVID-19 is available, NPIs will continue to serve as the main public health tool to control and manage SARS-CoV-2 outbreaks. There is currently one EMA-approved vaccine against SARS-CoV-2. Without further increases in use of NPIs and in the absence of pharmaceutical interventions, almost 2.5 million COVID-19 deaths are projected globally by 01 February 2021 with daily deaths peaking at about 15,000/day during this time (IHME 2020c). 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.

Natural History of COVID-19 in the Unvaccinated Population

Current evidence suggests that SARS-CoV-2 is primarily transmitted via direct contact or person-to-person via respiratory droplets by coughing or sneezing from an infected individual (whether symptomatic or not). Airborne transmission may be possible during certain medical procedures and in indoor, crowded and poorly ventilated environments (WHO 2020c). Common symptoms of COVID-19 include fever and cough, and other symptoms can include shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. 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 $\geq$ 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). 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). Recently, SARS-CoV-2 has 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 et al 2020; Seydoux et al 2020; To et al 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 et al 2020; Grifoni et al 2020; Weiskopf et al 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 et al 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 (Beaudoin-Bussières et al 2020; Long et al 2020, Perreault et al 2020; Prévost et al 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 at al 2007; Kellam et al 2020). Longitudinal studies will provide an opportunity to monitor in more detail the progression of immunity over time.

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

Table 2 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 2: 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 (eg, 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. 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 3 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.

Study Type	Important Nonclinical Findings	Relevance to Human Use
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 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.	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 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	Reversible or reversing 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. There were hematology changes (ie, increases in white blood cells, neutrophils, eosinophils, and decreased lymphocytes); coagulation changes with increases in fibrinogen and activated partial thromboplastin time. Clinical chemistry changes were identified and included decreases in albumin, increases in globulin, and a corresponding decrease in albumin/globulin ratio. In general, clinical pathology changes were dose-dependent and transient. Transient cytokine increases were observed at ≥ 9 µg/dose at 6 hours postdose including interferon gamma protein, monocyte chemoattractant protein, and macrophage inflammatory protein alpha. Cytokine changes were generally reversing by the end of the 2-week recovery period. Macroscopic changes included skin thickening at the injection site and enlarged lymph nodes. Injection site changes completely recovered,	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. Laboratory abnormalities including increases in liver enzymes and functional tests and serum lipase levels following vaccination were observed in clinical trials with similar mRNA-based vaccines. These abnormalities were without clinical symptoms and returned toward baseline values. Of the events none fulfilled Hy's law criteria. The majority of the events were mild or moderate in severity and some were assessed as related to vaccine or placebo. 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

Study Type	Important Nonclinical Findings	Relevance to Human Use
	and lymph node changes were recovering by the end of the 2-week recovery period. Microscopic changes included mixed cell inflammation at the injection site; increased cellularity and mixed cell inflammation in the lymph nodes; decreased cellularity in the splenic periarteriolar lymphoid sheath; increased myeloid cellularity in the bone marrow; and hepatocyte vacuolation and Kupffer cell hypertrophy in the liver. Microscopic changes were generally reversing by the end of the 2-week recovery period.	concern. In the clinical Phase 3 P301 study, solicited systemic adverse reactions in the 7 days following administration, increased following the second dose. Solicited local adverse reactions, primarily injection site pain, were common but the incidence did not change from the first to second dose (Table 14.3.1.1.1 and 14.3.1.1.2).
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 observed on Day 1 and Day 22 of two separate IM injections on Day 1 and Day 22 at doses in rat starting at 30 µg/dose. 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 changes were observed starting at 30 µg/dose associated inflammation, 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 study with mRNA-1273 in female Sprague-Dawley rats was completed in December 2020 with no adverse findings. mRNA-1273 was assessed for developmental and reproductive toxicity in an embryo-fetal development rat study with peri-natal and post-natal assessments 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. Nonadverse, common skeletal variations consisting of wavy ribs and increase nodules were observed at 100 µg/dose. The no	The risk for adverse pregnancy outcomes 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
	observed adverse effect level is 100 µg, which on a mg/kg basis, provides a 137-fold safety margin to 60-kg woman.	
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, the 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 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 equivocal results are likely driven by micronuclei formation secondary to elevated body temperature induced by LNP-driven systemic inflammation 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

Abbreviations: 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 is a theoretical concern over the potential for vaccine associated disease enhancement in recipients of SARS-CoV-2 vaccines. The concern is that a SARS-CoV-2 vaccine could theoretically cause enhanced disease and specifically enhanced respiratory disease (ERD) in vaccines that are subsequently exposed to wild-type SARS-CoV-2. The potential for vaccination against SARS-CoV-2 to be associated with disease enhancement is 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 et al 2005; Deming et al 2006; Bolles et al 2011), the experience with feline infectious peritonitis virus and vaccines in cats (Takano et al 2008; Pedersen et al 2009; Pedersen et al 2012), and enhanced disease seen with respiratory syncytial virus, measles (Kim et al 1969; Polack 2007), and dengue vaccines in humans (Smatti et al 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 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 et al 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 et al 2020). These results were reassuring since the risk of enhanced disease has been previously associated with a Th2-directed immune response.

A conclusion of safety concerns for mRNA-1273 based on nonclinical data is summarised in Table 3.

Table 3: 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

Three clinical trials of mRNA-1273 are ongoing, which include a dose-ranging Phase 1 safety and immunogenicity study (20-0003), a dose-confirming Phase 2a safety and immunogenicity study (mRNA-1273-P201); and a pivotal Phase 3 efficacy, safety, and immunogenicity study (mRNA-1273-P301).

Table 4: Summary of Vaccination Groups by Dose (µg) in the Ongoing 20-0003, mRNA-1273-P201, and mRNA-1273-P301 Studies

Dose	25 µg	50 µg	100 µg	250 µg	Total mRNA-1273 Participants (N)
20-0003 (Phase 1)	35	35	35	15	120
mRNA-1273-P201 (Phase 2a)	0	200	200	0	400
mRNA-1273-P301 (Phase 3)	0	0	15185	0	15185

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 Table 14.1.1.1 06 Nov 2020; mRNA-1273-P301 Table 14.1.6.2.1 25 Nov 2020.

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.

Table 5: 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 6: 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 7: 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 8: 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)
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.

Table 9: Number of Participants Completing Study Milestones (Including and After Day 36 Clinic Visit Follow-Up) Data Cutoff of 07 October 2020 in the Ongoing 20-0003 Study

	Day 36	Day 43	Day 57	Day 119	Day 209	Day 394
Study Group	**Clinic Visit Follow-Up n/N (%)**	**Clinic Visit Follow-Up n/N (%)**	**Clinic Visit Follow-Up n/N (%)**	**Clinic Visit Follow-Up n/N (%)**	**Clinic Visit Follow-Up n/N (%)**	**Clinic Visit Follow-Up n/N (%)**
18 to 55 years						
25 µg	15/15 (100)	15/15 (100)	15/15 (100)	15/15 (100)	1/15 (7)	0/15 (0)
50 µg	15/15 (100)	15/15 (100)	15/15 (100)	11/15 (73)	0/15 (0)	0/15 (0)
100 µg	15/15 (100)	15/15 (100)	15/15 (100)	15/15 (100)	2/15 (13)	0/15 (0)
250 µg	15/15 (100)	15/15 (100)	15/15 (100)	15/15 (100)	0/15 (0)	0/15 (0)
56 to 70 years						
25 µg	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	0/10 (0)	0/10 (0)
50 µg	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	0/10 (0)	0/10 (0)
100 µg	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	0/10 (0)	0/10 (0)
≥ 71 years						
25 µg	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	0/10 (0)	0/10 (0)
50 µg	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	0/10 (0)	0/10 (0)
100 µg	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)	0/10 (0)	0/10 (0)
All participants	120/120 (100)	120/120 (100)	120/120 (100)	116/120 (97)	3/120 (3)	0/120 (0)

Note: Percentages reflective of ongoing status of the trial.
Source: Table 2G 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 (Phase 2a)

mRNA-1273-P201 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.

Table 10: Duration of Exposure in the Ongoing mRNA-1273-P201 Study

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	174 (87.0)	177 (88.5)	351 (87.8)
≥ 28 Days Since Second Injection	142 (71.0)	153 (76.5)	295 (73.8)
< 28 Days Since Second Injection	53 (26.5)	45 (22.5)	98 (24.5)
≥ 28 and < 56 Days Since Second Injection	142 (71.0)	153 (76.5)	295 (73.8)
≥ 56 Days Since Second Injection	0	0	0
Study Duration from First Injection (Days)			
Mean (Standard Deviation)	59.9 (5.16)	60.5 (4.44)	60.2 (4.82)
Median	59.0	60.0	59.0
Quartile 1, Quartile 3	57.0, 62.0	57.0, 63.0	57.0, 63.0
Minimum, Maximum	30, 78	53, 79	30, 79

Source: mRNA-1273-P201 Table 14.1.6.1 (06 November 2020).

Table 11: Age Group and Gender in the Ongoing mRNA-1273-P201 Study

Age Group	Participants (N)
Adult, 18 – 64 years	307
Elderly, 65-74 years	79
Elderly, 75-84 years	11
Elderly, 85 + years	3
Gender	
Male	139
Female	261

Source: mRNA-1273-P201 Tables 14.1.6.2.1 and 14.1.6.2.3 (06 November 2020).

Table 12: Participant Race in the Ongoing mRNA-1273-P201 Study

Race	Participants (N)
White	376
Black or African American	13
Asian	4
American Indian or Alaska Native	3
Native Hawaiian or Other Pacific Islander	1
Multiple	1
Other	2
Total	400

Source: mRNA-1273-P201 Table 14.1.6.2.4 and Table 14.1.6.1 (06 November 2020).

Table 13: Participant Ethnicity in the Ongoing mRNA-1273-P201 Study

Ethnicity	Participants (N)
Hispanic or Latino	31
Not Hispanic or Latino	368
Not Reported	1
Total	400

Source: mRNA-1273-P201 Table 14.1.6.2.5 and Table 14.1.6.2.1 (06 November 2020).

mRNA-1273-P301 (Phase 3)

The Phase 3 study (mRNA-1273-P301) is a pivotal, 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.

Table 14: Duration of Exposure in the Ongoing mRNA-1273-P301 Study

Duration of Exposure	Number of Participants, n (%)
Received First Injection	15185 (100)
Received Second Injection	14715 (96.9)
≥ 49 Days Since First Injection	14095 (92.8)
≥ 56 Days Since First Injection	13767 (90.7)
≥ 2 Months Since First Injection	13498 (88.9)
≥ 28 Days Since Second Injection	13386 (88.2)
≥ 56 Days Since Second Injection	9406 (61.9)
≥ 2 Months Since Second Injection	8163 (53.8)
< 28 Days Since Second Injection	1329 (8.8)
≥ 28 and < 56 Days Since Second Injection	3980 (26.2)
≥ 56 Days Since Second Injection	9406 (61.9)
Study Duration from First Injection (Days)	
Mean (Standard Deviation)	88.8 (21.01)
Median	92.0
Quartile 1, Quartile 3	77.0, 105.0
Minimum, Maximum	1, 122

Source: mRNA-1273-P301 Table 14.1.6.2.1 (25 November 2020).

Table 15: Age Group and Gender in the Ongoing mRNA-1273-P301 Study

Age Group	Participants (N)
Adults, 18-64 years	11415
Elderly, 65-74 years	3112
Elderly, 75-84 years	617
Elderly 85 + years	41
Gender	
Male	7924
Female	7261

Source: mRNA-1273-P301 Tables 14.1.6.2.2 and 14.1.6.2.4 (25 November 2020).

Table 16: Participant Race in the Ongoing mRNA-1273-P301 Study

Race	Participants (N)
White	12032
Black or African American	1563
Asian	651
American Indian or Alaska Native	112
Native Hawaiian or Other Pacific Islander	35
Multiple	316
Other	321
Not Reported	96
Unknown	59
Total	15185

Source: mRNA-1273-P301 Table 14.1.6.2.5 and Table 14.1.6.2.1 (25 November 2020).

Table 17: Participant Ethnicity in the Ongoing mRNA-1273-P301 Study

Ethnicity	Participants (N)
Hispanic or Latino	3122
Not Hispanic or Latino	11921
Not Reported	104
Unknown	38
Total	15185

Source: mRNA-1273-P301 Table 14.1.6.2.6 and Table 14.1.6.2.1 (25 November 2020).

Table 18: Comorbidities in the Ongoing mRNA-1273-P301 Study

Age and Risk Group: ≥ 18 and < 65 Years	**Participants (N)**
Number of Participants at Risk (N)	2295
Chronic lung disease	473
Significant cardiac disease	316
Severe obesity	865
Diabetes	906
Liver disease	82
HIV infection	76
Age and Risk Group: > 65 Years	**Participants (N)**
Number of Participants at Risk (N)	1104
Chronic lung disease	237
Significant cardiac disease	436
Severe obesity	160
Diabetes	529
Liver disease	18
HIV infection	16

Source: mRNA-1273-P301 Table 14.1.6.2.8 (25 November 2020).

Table 19: Risk Factors in the Ongoing mRNA-1273-P301 Phase 3 Study

Age and Risk Group: ≥ 18 and < 65 Years	**Participants (N)**
At least one risk factor (N)	2295
One risk factor	1925
Two risk factors	328
Three risk factors	32
Four risk factors	9
Five risk factors	1
Six risk factors	0
Age and Risk Group: > 65 Years	**Participants (N)**
At least one risk factor (N)	1104
One risk factor	850
Two risk factors	219
Three risk factors	32
Four risk factors	3
Five risk factors	0

Source: mRNA-1273-P301 Table 14.1.6.2.9 (25 Nov 2020).

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

Due to exclusion criteria in the trials, special populations not studied included the paediatric age group (< 18 years old) as well as pregnant and breast-feeding women. A paediatric study plan has been agreed upon by the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research and a paediatric investigational plan by the EMA Paediatric Committee with the

clinical development plan for the evaluation of safety and effectiveness in the paediatric population. The Phase 3 P301 study included participants with age > 65 and participants with comorbidities, and was inclusive with respect to race and ethnicity (see Part II: Module SIII – Clinical Trial Exposure).

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 20: 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 has been submitted and is under ongoing review by the Agency.
Pregnant/Lactating women.	Clinical development generally does not initially investigate benefit/risk in pregnant women.	Yes	Not applicable
Acutely ill/febrile (temperature >38°C/100.4°F) prior to screening visit.	Allowance of these conditions would confound assessment of safety and these febrile participants might already be infected with SARS-CoV-2.	No	It is common medical practice to not administer vaccines in febrile participants. Febrile participants with minor illnesses could be enrolled at the discretion of the investigator. This is managed with the product prescribing information.
Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients.	Participants with medical history significant for allergic reactions following vaccines 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 other vaccines.
Bleeding disorder considered a contraindication to intramuscular injection or phlebotomy.	Participants have a potential risk of hematoma due to the puncture of the deep tissues. Allowance of these conditions would confound assessment of safety.	No	It is common medical practice to not administer a product by the intramuscular route in participants with coagulopathy or bleeding disorders although the use of a needle with proper gauge can decreased the risk.

Criterion	Reason for Exclusion	Included as Missing information (Yes/No)	Rationale (if not included as missing)
Known history of SARS-CoV-2 infection Of note, in Phase 3 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	Study P301 evaluated the safety and immunogenicity of participants who tested positive for SARS-CoV-2 at enrolment. Testing occurred on the day of vaccination with Dose 1, results were available subsequently. The incidence of solicited adverse reactions and unsolicited adverse events was similar regardless of baseline SARS-CoV-2 status (Source Tables 14.3.1.1.7, 14.3.1.1.8,14.3.1.7.7, 14.3.1.7.9, 14.3.1.8.7, 14.3.1.8.9, Module 5.3.5.1)
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 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 3 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 vaccination regimen is two doses administered 28 days apart, so 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, and there is a rapid degradation of the mRNA as demonstrated in the nonclinical biodistribution study; thus, no long term sequalae are expected.

In both the mRNA-1273 group and the placebo group in the Phase 3 P301 study, the median follow-up time after the first injection was 92.0 days (13 weeks) and the median follow-up time after the second injection was 63.0 days (9 weeks). Therefore, there has been limited 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 21: Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Paediatric participants	The safety of the vaccine has not yet been established in paediatric participants. mRNA-1273 will be evaluated in paediatric participants in a separate clinical plan.
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 risk management plan, all pregnancy and birth outcomes are pending with the exception of an elective termination and a spontaneous abortion which were both reported in participants who received placebo. A developmental and reproductive study with mRNA-1273 in female Sprague-Dawley rats was completed in December 2020 with no adverse findings. There is limited experience with use of COVID-19 Vaccine Moderna in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development. Administration of COVID-19 Vaccine Moderna in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Type of Special Population	Exposure
Breastfeeding women	Lactating women were excluded from clinical trials. There were no reports of women taking mRNA-1273 while breastfeeding in the mRNA-1273 clinical program. It is unknown whether COVID-19 Vaccine Moderna is excreted in human milk. Data are not available to assess the effects of COVID-19 Vaccine Moderna on the breastfed infant or on milk production/excretion.
Participants with relevant comorbidities[#]	
• Participants with hepatic impairment[1]	In the clinical trial P301, 100 (0.7%) participants with hepatic disease have been exposed to mRNA-1273 (Table 14.1.3.1.3).
• Participants with renal impairment	Not applicable.
• Participants with cardiovascular impairment[2]	In the Study P301, 752 (5.0%) participants with significant cardiac diseases have been exposed to mRNA-1273 (Table 14.1.3.1.3).
• Immunocompromised participants	In the clinical development program, participants with immunosuppression were generally excluded. In Study P301, participants with HIV who did not meet the exclusion criteria have been enrolled. A total of 92 (0.6%) participants with HIV were exposed to mRNA-1273 (Table 14.1.3.1.3).
Participants with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	While most participants enrolled in clinical trials were White, participants from other races or ethnicities were also enrolled. In the Phase 3 P301 study, 24024 (79.2%) participants were White, 3090 (10.2%) were Black or African American, 6235 (20.5%) were Hispanic or Latino, and 1382 (4.6%) were Asian (Table 14.1.3.1.1).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Others	
1. Participants ≥ 75 years of age	In the Phase 3 P301 study, a total of 1309 (4.3%) participants were 75 to 84 years of age and 90 (0.3%) were ≥ 85 years of age (Table 14.1.3.1.3).
2. Diabetes (Type 1, Type 2)	In the Phase 3 P301 study, 1435 (9.5%) participants with diabetes have been exposed to mRNA-1273 (Table 14.1.3.1.3).
3. Chronic lung disease[3]	In the Phase 3 P301 study, 710 (4.7%) participants with chronic lung disease have been exposed to mRNA-1273 (Table 14.1.3.1.3).
4. Severe obesity (BMI > 40 kg/m^2)	In the Phase 3 P301 study, 1025 (6.8%) participants with severe obesity have been exposed to mRNA-1273 (Table 14.1.3.1.3).
5. HIV infection	In the Phase 3 P301 study, participants with HIV who did not meet the exclusion criteria have been enrolled. A total of 92 (0.6%) participants with HIV have been exposed to mRNA-1273 (Table 14.1.3.1.3).

[#] In the Phase 3 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

As of 21 December 2020, mRNA-1273 vaccine has not been licenced in any country/region. Temporary emergency use authorisation was provided in the US on 18 December 2020 and in Canada (Interim Order) on 23 December 2020 after the data lock point of the risk management plan (RMP).

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

Reactogenicity

In accordance with the European Medicines Agency (EMA) requirements (coreRMP19 guidance), the reactogenicity profile of COVID-19 Vaccine Moderna is described below for local and systemic reactions, including observed differences between ages (younger and older groups) and after the first and second injections. The observed differences do not impact the safety profile of COVID-19 Vaccine Moderna.

The majority of solicited local adverse reactions (ARs) were considered risks with minimal and temporary clinical impact (Grade 1 and 2 severity) on the participants. The ADRs identified during the clinical development program include solicited local ARs at the injection site including pain, erythema (redness), swelling/induration (hardness), and localized axillary swelling or tenderness ipsilateral to the injection arm. Systemic ARs reported included headache, fatigue, myalgia,

arthralgia (aching in several joints), nausea/vomiting, fever. And chills. For Grades 3 and 4, the most common local and systemic events observed after any injection in the mRNA-1273 group included fatigue (10.1%), myalgia (9.1%), injection site pain (6.1%), headache (5.7%), arthralgia (5.3%). The median duration was 2 days (range: 1 to 45 days) for solicited local AR and 2 days (range: 1 to 83 days) for solicited systemic reactions (Table 14.3.1.4.1 and Table 14.3.1.1.3). Details on observed differences are presented below.

Local Adverse Reactions

Local reactogenicity was observed in 84.2% of participants treated with mRNA-1273 at the first injection and in 88.6% at the second injection. The incidence of solicited local ARs after the first injection, among participants who were baseline negative for SARS-CoV-2, was 84.5% and 19.7% (mRNA-1273 group and placebo group, respectively). For participants who were baseline positive, the incidence was 71.9% and 17.8%, in the mRNA-1273 and placebo groups, respectively (mRNA-1273-P301 Table 14.3.1.1.7). After the second injection, in baseline negative participants, the incidence of solicited local ARs was 88.8% in the mRNA-1273 group and 18.8% in the placebo group. In baseline positive participants, the incidence was 74.8% and 18.2% in the mRNA-1273 and placebo groups, respectively (mRNA-1273-P301 Table 14.3.1.1.8).

Systemic Adverse Reactions

Systemic reactogenicity was observed in 54.9% of participants treated with mRNA-1273 at the first injection and in 79.4% at the second injection. The incidence of solicited systemic ARs in the mRNA group for SARS-CoV-2 baseline negative participants was 54.7% after the first injection and 79.6% after the second injection. In baseline positive participants, the incidence was 61.4% and 65.2%, after the first and second injection, respectively (mRNA-1273-P301 Table 14.3.1.1.7 and Table 14.3.1.1.8).

Overall, the frequency of all solicited ARs was lower in baseline positive participants than in baseline negative participants (82.2% and 95.2%, respectively). The severity (Grade 3 and 4) of ARs was higher in baseline negative participants than in baseline positive participants (22.6% and 14.6%, respectively). Across both vaccinations, solicited systemic and local adverse events (Aes) that occurred in more than half the participants included injection site pain (92.0%), fatigue (70.0%), headache (64.7%), and myalgia (61.5%) (mRNA-1273-P301 Table 14.3.1.1.3). Greater reactogenicity was observed after the second vaccination.

A review of these events showed that the vast majority of the unsolicited TEAEs categorized as local injection or vaccination site reactions in the second week after immunization were a subset of the solicited local AR with a duration beyond Day 7 (mRNA-1273-P301 Table 14.3.1.6.6 and Table 14.3.1.6.7).

Reactogenicity by Age

At the time of the safety cut-off date (25 November 2020), the Phase 3 reactogenicity subset included 30, 342 participants (≥ 18 years of age). The reactogenicity data were collected from the participants' e-diaries for reporting prompted local reactions and systemic events for 7 days after each dose.

Reactogenicity was evaluated in subgroup analyses by age (18 to < 65 years of age and ≥ 65 year of age). Overall, reactogenicity was reported at similar rates in younger and older adults (95.4% and 93.3%, respectively, in the mRNA-1273 group). Systemic ARs in the mRNA-1273 group were more commonly reported by younger adults (≥ 18 to < 65 years; 86.0%) than older adults (≥ 65 years, 78.4% (mRNA-1273-P301 Table 14.3.1.1.6). Local reactogenicity was more commonly reported by younger adults (18 to < 65 years, 87.4% and 90.3% after the first and second injection of mRNA-1273, respectively) than older adults (≥65 years, 74.6% and 83.8% after the first and second injection of mRNA-1273, respectively; mRNA-1273-P301 Table 14.3.1.1.4 and Table 14.3.1.1.5).

Reactogenicity by SARS-CoV-2 Status

Solicited reactogenicity based on SARS-CoV-2 status at baseline (negative or positive) was comparable, 54.7% and 61.4%, respectively, for participants who received mRNA-1273 (mRNA-1273-P301 Table 14.3.1.1.7).

For baseline negative status, the mean durations for reactogenicity for local and systemic ARs were 3.4 days and 3.1 days (mRNA-1273 and placebo, respectively) after the first injection and 4.1 and 3.3 days, respectively, after the second injection. For baseline positive status, the mean durations for reactogenicity for local and systemic solicited ARs were 3.6 days and 3.4 days (mRNA-1273 and placebo, respectively) after the first injection and 3.3 and 3.9 days, respectively, after the second injection (Table 14.3.1.4.7 and Table 14.3.1.4.8).

Persistent Reactogenicity After the First and Second Injection

Solicited local reactogenicity that persisted beyond 7 days after the first injection was reported in 2.2% of participants (mRNA-1273) after the first injection and in 2.1% of participants (mRNA-1273) after the second injection compared to placebo (0.7% and 0.7% after the first and second injections, respectively). Solicited systemic reactogenicity that persisted beyond 7 days after the first injection was reported in 5.8% of participants (mRNA-1273) after the first injection and 5.7% of participants (mRNA) after the second injection, which was comparable to the incidence in the placebo group (5.7% and 4.9%, after the first and second injections, respectively; Table 14.3.1.6.1 and Table 14.3.1.6.2).

The ADRs associated with reactogenicity are identified risks described in the EU Summary of Product Characteristics (SmPC) and will continue to be monitored through continued trial follow up as well as routine pharmacovigilance.

Aspects of the Formulation

The mRNA-1273 vaccine dispersion for injection contains no preservative. Formulations without preservatives have the potential for the growth of bacteria and for being a vector for infections (ie, local abscess or sepsis). This may happen inadvertently when the stopper is penetrated by the needle. There is a higher risk when vials are for multiple uses. It is important that the vial and the materials used for withdrawing and injecting the medicine are sterile before use and that all precautions are taken to ensure that the vaccine and materials are not contaminated during the procedures. After first opening, the product should be used immediately and be discarded after 6 hours.

For additional support of the multiple-dose vial, a microbial challenge hold time study, also known as a growth promotion study, was performed from initial needle puncture/vial entry for the mRNA-1273 Drug Product. The study involved inoculating low levels of selected microorganisms (as specified in the USP <51> challenge test procedure, as well as an additional typical skin flora, *Staphylococcus epidermidis*) and evaluating the product's ability to promote or hinder growth of the microorganisms over a specified timeframe. The results show that growth of the inoculated microorganism is hindered for up to 24 hours at room temperature (ie, "No Increase" as defined in USP <51> passing criteria).

No local abscess or infections suspected due to a septic preparation were reported in the clinical studies. The risk appears low; however, in the context of mass vaccination, the risk of infection will be closely monitored via routine pharmacovigilance. The precautions for the preparation and handling of mRNA-1273 are described in the SmPC.

Degradation

The mRNA degradation products are not expected to represent functionally active mRNA molecules, are naturally metabolised, and are considered pharmacologically inactive.

The mRNA-1273 vaccine does not contain an adjuvant.

Adverse Events of Special Interest

For all routine and additional pharmacovigilance activities presented in the RMP, Moderna has taken into consideration the list of AESIs prepared by regulatory agencies and vaccine expert groups as follows.

- Brighton Collaboration (Safety Platform for Emergency vACcines; Law and Sturkenboom 2020)

- ACCESS protocol (Dodd et al 2020)
- US Center for Disease Control and Prevention (preliminary list of AESI for VAERS surveillance; Shimabukuro 2020)
- Medicines and Healthcare Regulatory Agency (unpublished guideline).

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Adverse drug reactions are identified risks. Not all potential or identified risks for the vaccine are considered to meet the level of importance/severity compared to the condition to be prevented necessitating inclusion in the list of safety concerns in the RMP.

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

Table 22: Important Identified Risks

Risk	Risk-Benefit Impact (Reasons for Classifications as Important Identified Risks)
Anaphylaxis	Anaphylaxis; a potentially life-threatening hypersensitivity reaction, can occur after any vaccination. Most persons recover fully with treatment, but serious complications can occur. (Su et al 2019). Reporting from selected health care organizations in the United States found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses administered to both children and adults. The estimated rate of anaphylaxis reported to Vaccine Adverse Event Reporting System during 1990 to 2016 after measles, mumps, and rubella vaccine was 0.6 per 1 million doses distributed, and after pneumococcal polysaccharide vaccine was 0.2 per 1 million doses distributed; during 2006 to 2016, the estimated rate after varicella vaccine was 1.2 per 1 million doses distributed. During 2010 to 2016, after influenza vaccine (all types) among persons aged 1 to 84 years, the median estimated annual rate was 0.2 (range, 0.1-0.4) per 1 million doses administered (Su et al 2019). Available data seem to suggest a particular patient profile for persons who experience anaphylaxis after vaccination: the vast majority have a history of atopy (history of atopic disease, such as asthma, allergic rhinitis, atopic dermatitis, or food or drug allergy) but they can occur among persons with no known history of hypersensitivity. In the Phase 3 study P301, 2 cases of anaphylaxis have been reported 1 case each in the placebo and the mRNA-1273 group. The cases happened 10 days after the first injection and 63 days after the second injection, respectively. Both cases were assessed unrelated to the study vaccine per the investigators. After the data lock of the Phase 3 P301 study on 25 November and before the data lock point (DLP) of the risk management plan (RMP), a second case of anaphylaxis was reported in the placebo group 60 days after the second injection. The case was nonserious and considered unrelated per the investigator. During emergency use authorisation, after the DLP of the RMP one case of anaphylaxis classified based on available information as a Level 2 according to Brighton Collaboration criteria was reported shortly after the intramuscular administration of mRNA-1273 vaccine.

Table 23: Important Potential Risks

Risk	Risk-Benefit Impact (Reasons for Classifications as Important Potential Risks)
Vaccine-associated enhanced disease	The concern is that a SARS-CoV-2 vaccine could theoretically cause enhanced disease and specifically enhanced respiratory disease (ERD) in vaccinees that are subsequently exposed to wild-type SARS-CoV-2. The potential for vaccination against SARS-CoV-2 to be

Risk	Risk-Benefit Impact (Reasons for Classifications as Important Potential Risks)
(VAED) including Vaccine-associated enhanced respiratory disease (VAERD)	associated with disease enhancement is a theoretical concern, given similar observations with other respiratory viruses in general, and in animal models of some highly pathogenic coronaviruses (Agrawal et al 2016). This concern has been triggered by preclinical work on SARS-CoV and MERS-CoV vaccines, the experience with feline infectious peritonitis virus and vaccines in cats, and enhanced disease seen with respiratory syncytial virus, measles, and dengue vaccines in humans. Importantly, VAED 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. To evaluate the theoretical concern of VAERD with mRNA-1273, nonclinical studies in several species have been performed (eg, disease pathology, immune profiling). These mRNA-1273 vaccine study results show immune signatures not predicted to associate with VAERD and a lack of vaccine-enhanced viral replication or pulmonary pathology after challenge with SARS-CoV-2 in relevant animal species. In addition, cytokine profiling of re-stimulated T cells from vaccinated Phase 1 study participants show a Th1- rather than Th2-directed response (Jackson et al 2020). The Phase 3 P301 study was designed to assess the risk of VAERD with prespecified rules for harm as defined in the analysis plan and evaluated through by the Data Safety Monitoring Board. No such safety concerns have been identified, and all cases of severe COVID-19 disease included in the first interim analysis of efficacy occurred in the placebo group. If VAED were to be identified as a risk, it could potentially impact the benefit risk.

SVII.3.2 Presentation of the Missing Information

Table 24: Important Missing Information

Missing Information	Risk-Benefit Impact (Reasons for Classifications as Important Identified Risks)
Use in pregnancy and while breast-feeding	The target indication for mRNA-1273 is adults ≥ 18 year of age thus will include women of childbearing potential. Pregnant women were excluded from the clinical trials, although a small number of pregnancies were reported in the mRNA-1273 clinical program. A developmental and reproductive study with mRNA-1273 in female Sprague-Dawley rats was completed in December 2020 with no adverse findings. However, it is necessary to follow up the pregnancies and evaluate the outcomes against the impact of the COVID-19 disease.
Long-term safety	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 P201, and 24 months in the Phase 3 study P301. At the time of the data lock point of the risk management plan, in the Phase 3 P301 the safety follow up is based on a median of 9 weeks of follow up post-second dose. The follow up time is through Day 119 for the Phase 1 study 20-0003 and through Day 57 for the Phase 2a study P201.
Use in immunocompromised subjects	In the clinical development program, subjects with immunosuppressive conditions or medications were to be excluded from the study. In study P301 subjects with stable HIV infection who were on HAART and had non-detectable viral load and a CD4+ T-cell count ≥350 were enrolled in the study. In general, it is expected that participants with immunocompromised status may not reach the protective antibody level achieved in healthy individuals with vaccines. In the Phase 3 study P301, the interim analysis shows an overwhelming vaccine efficacy in the overall population of the trial. mRNA-1273 vaccine is not a live

Missing Information	Risk-Benefit Impact (Reasons for Classifications as Important Identified Risks)
	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.
Interaction with other vaccines	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 attempt to administer vaccines at the same time. There is the theoretical question as whether a vaccine can create interference in the immune response to either vaccines or induce safety concerns. Participants receiving mRNA-1273 may be administered seasonal flu vaccines during the vaccination period of the pandemic.
Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	There is limited information on the safety of the vaccine in frail individuals with co-morbidities who are potentially at higher risk of severe COVID-19.
Use in subjects with autoimmune or inflammatory disorders	There is limited information on the safety of the vaccine in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.

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

Not applicable as this is the initial RMP for mRNA-1273.

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

Table 25: 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 emergency use authorisation.
Characterization of risk	In the Phase 3 study P301, 2 cases of anaphylaxis have been reported; 1 case each in the placebo and the mRNA-1273 group. The cases happened 10 days after the first injection and 63 days after the second injection, respectively. Both cases were assessed unrelated per the investigators. After the data lock of the Phase 3 P301 study on 25 November 2020 and before the data lock point (DLP) of the risk management plan (RMP), a second case of anaphylaxis was reported in the placebo group 60 days after the second injection. The case was non serious and considered unrelated per the investigator. During emergency use authorisation, after the DLP of the RMP one case of anaphylaxis classified based on available information as a Level 2

	according to Brighton Collaboration criteria was reported shortly after the intramuscular administration of mRNA-1273 vaccine.
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	Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine Moderna.
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.

Table 26: 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 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 (eg, dengue), by chemically disrupted antigens (eg, 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.

Important Potential Risk	**Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)**
	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 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 of 9 weeks of follow up post-second dose.
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 P301 study for vaccine harm. Based on these analyses no vaccine harm was identified. This risk is further evaluated in the ongoing Phase 3 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 27: Presentation of Missing Information

Missing Information	**Use in Pregnancy and While Breast-Feeding**
Evidence source	There is no data from the use of mRNA-1273 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.
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. A non-interventional study (pregnancy cohort) 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 in the ongoing Phase 1 study 20-0003, Phase 2a study P201 and, 24 months in the Phase 3 study P301. At the time of the DLP of the RMP, in the Phase 3 P301 the safety follow-up is based on a median of 9 weeks of follow up post-second dose. The follow up time is through

	Day 119 for the Phase 1 study DMID 20-0003 and through Day 57 from the Phase 2a study 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 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 P301, the IA shows 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 4 safety and immunogenicity study is also planned in adults who are immunocompromised.
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. However, in the United States where mRNA-1273 had emergency use authorisation, the US Centers for Disease Control and Prevention has recommended that mRNA COVID-19 vaccines be given alone, with a minimum interval of 14 days before or after administration with any other vaccines. 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 (eg, 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 28: Summary of Safety Concerns

Summary of Safety Concerns	
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

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

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance will be conducted for mRNA-1273 along with the additional actions part of the pharmacovigilance plan. Due to the special circumstances of the pandemic, enhancement of routine activities will be undertaken.

Moderna has a safety surveillance and reporting system in place to organize the collection, data entry in the company global safety database and evaluation of any AEs reported to Moderna.

A call center will be available in countries for vaccine providers (eg, healthcare professionals and individuals who administer the vaccine) and recipients, to assist with medical inquiries, collect product quality complaints and AEs.

All AE/serious AE cases will undergo follow-up and for serious AEs, hospital records including autopsy reports, will be queried to the reporter, as possible.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific adverse reaction follow-up questionnaires for mRNA-1273

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 mRNA-1273. 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 mRNA-1273 vaccination.

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 et al 2020).

Signal Detection

The Moderna signal management process for mRNA-1273 vaccine 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 the mRNA-1273 vaccine is described in the product safety strategy form. It describes the data sources, type and frequency of the signal detection analyses summarised in Table 29.

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

Table 29: mRNA-1273 Vaccine Signal Data Sources and Frequency of Evaluations

Data Source	Frequency of Safety Evaluations
Company global safety database	Ongoing monitoring of individual cases of Suspected Unexpected Serious Adverse Reaction (SUSAR), safety concerns, and Adverse Events (AE) of Special Interest. Weekly aggregated review of AE cases 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 the mRNA-1273 vaccine. 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 Individual Case Safety Reports (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 (ie, 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 disproportionality analyses of the combination of AEs as appropriate. In case of disproportionality, Moderna will present these results in the monthly summary safety reports or upcoming Periodic Safety Update Reports (eg, as part of the interval and cumulative number of reports per MedDRA high-level term and system organ class).

Table 30: Product Surveillance List of the mRNA-1273 Vaccine Signaling Strategy By Category

Category	Safety Topics (Updates may be Needed if New Adverse Events Emerge)
Safety concerns	- Anaphylaxis - 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 as follows (AESIs will be updated at lease 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 et al 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 mRNA-1273 vaccine 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.

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 mRNA-1273, Moderna plans to prepare a Summary Monthly Safety Report (Table 31) 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 31: mRNA-1273 Vaccine 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 (eg, pregnant women)
Interval and cumulative number of reports per HLT and SOC
Summary of the 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 will create Traceability and Vaccination Reminder cards (Annex 7), printed cards to vaccinators as of March 2021, that may be completed at the time of vaccination when necessary for individual members states. The card will be 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 targets by the end of February 2021 the implementation of inclusion of stickers (two stickers per dose, containing printed batch/lot information, product identification and 2D bar code) either in cartons or to be shipped along with each shipment.

III.2 Additional Pharmacovigilance Activities

In addition to actions targeted at identified and potential risks described in the safety specifications, the Sponsor intends to address general safety through continued clinical trial follow-up, a European Post -Authorisation Safety Study, and a US Post Authorization safety study. The sponsor is also proposing to establish an observational pregnancy outcome study, a study to evaluate safety and immunogenicity in immunocompromised adults, and conduct a long-term effectiveness study. The Applicant believes the results from the long-term effectiveness study conducted in the Kaiser

Permanente Southern California (KPSC) healthcare system in the US can be extrapolated to the European context because of similarities in the demographics and major underlying comorbid conditions between the two populations; similarities in access to vaccines for KPSC members and Europeans (financial barriers removed and/or greatly reduced); similarities in general access to healthcare for KPSC members and almost all European countries which have healthcare available for all citizens; the populations prioritized for initial supply of COVID-19 vaccines are similar between KPSC and Europe; risk factors for COVID-19 disease and mortality are similar between KPSC and Europe; and because circulating variants of the SARS-CoV-2 virus appear to be similar between the US and Europe.

Study key detailed information is provided in text below and milestones in Table 32.

Table 32: 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 Healthy Adults. Interventional *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. Follow up period extended by an additional 12 months for 24 months follow up total after the second dose. Assessment of a booster dose	Open-label, dose-ranging study	Healthy male and non-pregnant female participants, ≥18 years of age	LPLV: 03 Jul 2021 Interim CSR: 1 May 2021 Final CSR: 01 Nov 2022

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
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: 1 Mar 2021 Final CSR: 18 Nov 2021

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
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 COVID-19.	LPLV: 30 Sep 2022 Interim CSR: 30 June 2021 Final CSR: 31 Dec 2022
Safety and immunogenicity in immunocompromised adults *US*	**S**tudy of the Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Immunocompromised Adults Interventional *Planned*	Safety and reactogenicity and adverse events for 1 year after receiving 2 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 arm study	Immunocompromised adults	Protocol submission: 05 Feb 2021 Interim Report: 31 March 2022 Final CSR: 31 Jan 2023

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
Post authorization safety of SARS-CoV-2 mRNA-1273 vaccine in the US *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 *Planned*	This study will monitor anaphylaxis, Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), and long-term safety. It will also monitor AESI and emerging validated safety signals.	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 45 million patients similar to US census distribution estimates for age and sex 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 July 2021, 31 October 2021, 31 Jan 2022, 30 Apr 2022, 31 July 2022, 31 October 2022, 31 December 2022 Final study report: 30 Jun 2023

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
EU post-authorization safety study *EU*	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Non-interventional *Planned*	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine, use in pregnancy and while breast-feeding,* interaction with other vaccines, use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders.	Secondary database analysis of observational data to estimate incidence rates of safety events of interest and other clinically significant events in cohorts of COVID-19 vaccine recipients in the EU	General population data sources in multiple member states. A proposal from ACCESS/VAC 4EU is being developed.	Feasibility assessment: 31 Jan 2021 Protocol submission: 30 Jun 2021 Interim updates: , 30 Sep 2021, 31 Dec 2021, 31 Mar2022, 30 Jun 2022, 30 Sep 2022, 31 Dec 2022, 31 Mar 2023, 30 Jun 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**
Moderna mRNA-1273 Observational pregnancy outcome study *EU, Canada, US*	Moderna mRNA-1273 Observational pregnancy outcome study Non-Interventional *Planned*	Evaluate outcomes of pregnancies in females exposed to mRNA-1273 vaccine during pregnancy.	Primary data collection cohort study.	Pregnant women exposed to mRNA-1273 recruited from the general population and live-born infants from Germany, Italy, Ireland, Canada, and the United States. European Surveillance of Congenital Anomalies (EUROCAT) network data and Metropolitan Atlanta Congenital Defects Program (MACDP) data will provide an external comparator.	Protocol submission: 31 Jan 2021 Interim updates: 31 July 2021, , 31 Jan 2022, , 31 July 2022, , 31 Jan 2023, , 31 July 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 *Planned*	Evaluate the real-world effectiveness and long-term effectiveness of mRNA-1273 in preventing COVID-19 and severe COVID-19 disease. -Effectiveness stratified by age, sex, race/ethnicity, comorbid conditions. -Effectiveness of two doses of vaccine in preventing COVID-19 among	Prospective cohort study	US Adults ≥18 years of age	Protocol submission: 01 Mar 2021 Interim updates: 01 Aug 2021; 01 Nov 2021; 01 Feb 2022; 01 Nov 2022; 01 May 2023; 01 Nov 2023 Final study report: 30 Jun 2025

Study Number ***Country(ies)***	**Study Title** **Study Type** ***Study Status***	**Rationale and Study Objectives**	**Study Design**	**Study Population(s)**	**Milestones**
		immunocompromised patients. -Frail individuals and participants with autoimmune and inflammatory disorders will be evaluated to the extent that it is feasible. Considering current Advisory Committee on Immunization Practice recommendations to not co-administer other adult vaccines (eg, seasonal flu vaccine) in participants, Moderna will evaluate this schedule as possible. -Durability of one or two doses of COVID19 Vaccine Moderna against COVID-19 and severe COVID-19 disease will also be assessed.			

* As the EU PASS proceeds, the applicant will be able to ascertain where national recommendations might result in significant exposure in pregnant women. In conjunction with the first interim report due 30 Jun 21, the applicant will engage with the agency to select appropriate data sources/registers which can be incorporated into the study plan based on vaccine uptake and usage in pregnancy.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 33: Ongoing and Planned Additional Pharmacovigilance Activities

Study 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				
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 Long term safety	LPLV Interim CSR Final CSR	30 September 2022 30 June 2021 31 December 2022
Category 3 – Required pharmacovigilance activities				
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. Follow up period extended by an additional 12 months for 24 months follow up total after the second dose. Assessment of a booster dose	Anaphylaxis Long term safety	LPLV Interim CSR Final CSR	03 July 2021 1 May 2021 01 November 2022
Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100	Anaphylaxis	LPLV	20 August 2021

Study Title and categories **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥18 Years Study status: Ongoing	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		Interim CSR Final CSR	1 March 2021 18 November 2021
Safety and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Immunocompromised Adults Aged 18 Years and Older Study status: Planned	Evaluate the safety and reactogenicity of the vaccine in immunocompromised adults Evaluate the immunogenicity of the vaccine in immunocompromised adults	Anaphylaxis Use in immunocompromised subjects	Protocol submission Interim Report Final CSR	05 Feb 2021 31 March 2022 31 Jan 2023
Post Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US Study status: Planned	Enhanced pharmacovigilance study to provide additional evaluation of AESI and emerging validated safety signals. The study has three 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 Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety AESI and emerging validated safety signals.	Protocol submission Interim updates Final study report	31 January 2021 30 Apr 2021, 31 July 2021, 31 October 2021, 31 Jan 2022, 30 Apr 2022, 31 July 2022, 31 October 2022, 31 December 2022 30 June 2023

Study Title and categories **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Study status: Planned	Enhanced pharmacovigilance study to provide additional evaluation of AESI and emerging validated safety signals in European populations. Electronic database assessment of use in pregnant women	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in pregnancy and while breast-feeding 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	Feasibility assessment Protocol submission Interim Updates Final study report	31 January 2021 30 June 2021 30 September 2021, 31 December 2021, 31 March 2022, 30 June 2022, 30 September 2022, 31 December 2022, 31 March 2023, 30 June 2023 31 December 2023
Moderna mRNA-1273 Observational Pregnancy Outcome Study Study status: Planned	Evaluate outcomes of pregnancies in females exposed to mRNA-1273 vaccine during pregnancy	Use in pregnancy and while breast-feeding	Protocol submission Interim updates Final study report	31 Jan 2021 31 July 2021,, 31 Jan 2022,, 31 July 2022, , 31 Jan 2023, 31 July 2023, 31 Jan 2024 30 June 2024

Study Title and categories **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. Study Status: Planned	Evaluate the real-world effectiveness and long-term effectiveness of mRNA-1273 in preventing COVID-19 and severe COVID-19 disease. -Effectiveness stratified by age, sex, race/ethnicity, comorbid conditions. -Effectiveness of two doses of vaccine in preventing COVID-19 among immunocompromised patients. -Frail individuals and participants with autoimmune and inflammatory disorders will be evaluated to the extent that it is feasible. Considering current Advisory Committee on Immunization Practice recommendations to not co-administer other adult vaccines (eg, seasonal flu vaccine) in participants, Moderna will evaluate this schedule as possible. -Durability of one or two doses of COVID19 Vaccine Moderna against COVID-19 and severe COVID-19 disease will also be assessed.	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,	Protocol submission Interim updates Final study report	01 March 2021 01 Aug 2021; 01 Nov 2021; 01 Feb 2022; 01 Nov 2022; 01 May 2023; 01 Nov 2023 30 June 2025

Part IV: Plans for Post-Authorisation Efficacy Studies

Not currently 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 34: 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 COVID-19 vaccine Moderna; 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 and the recommendations for close observation for at least 15 minutes following vaccination (SmPC Section 4.4). Instruction to subjects to get urgent attention in case of signs and symptoms of allergic reactions is included in Section 4 of the PL A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 vaccine Moderna (SmPC Section 4.4). Contraindication in subjects with prior hypersensitivity to any component of the vaccine is included in Section 4.3 and 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

Safety Concern	**Routine Risk Minimisation Activities**
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 COVID-19 vaccine Moderna? 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 COVID-19 vaccine Moderna 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 COVID-19 Vaccine Moderna Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

Safety Concern	Routine Risk Minimisation 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 communication: 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 COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna.

V.3 Summary of Risk Minimisation Measures

Table 35: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Anaphylaxis	Routine risk communication : 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 COVID-19 vaccine Moderna (SmPC section 4.4). Patients 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 section 4.3 and PL section 2. Additional risk minimisation: 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 mRNA-1273 vaccine (see Section III.1). Additional pharmacovigilance activities (final CSR due date): • Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US (final CSR: 30 June 2023) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023) • Phase 3 P301 (final CSR: 31 December2022) • Phase 2a P201 (final CSR: 18 November 2021) • Phase 1 20-0003 (final CSR: 01 November 2022) • Safety and Immunogenicity in Immunocompromised Adults (final CSR: 31 January 2023)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine and enhanced 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 mRNA-1273 vaccine. 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): • Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US (final CSR: 30 June 2023) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023) • Phase 3 P301 (final CSR: 31 December 2022)
Use in pregnancy and while breast-feeding	Routine risk communication: SmPC Sections 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data PL Section 2 Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023) • Moderna mRNA-1273 Observational Pregnancy Outcome Study (final CSR: 30 June 2024)
Long-term safety	Routine risk communication: None Additional risk minimisation: None	Additional routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Additional pharmacovigilance activities (final CSR due date): • Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US (final CSR: 30 June 2023) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023) • Phase 3 P301 (final CSR: 31 December 2022) • Phase 1 20-0003 (final CSR: 01 November 2022)
Use in immunocompromised subjects	Routine risk communication: SmPC Section 4.4 Special Warnings and Precautions for Use PL Section 2 Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. (final CSR: 30 June 2025) • Safety and Immunogenicity in Immunocompromised Adults (final CSR: 31 January 2023)
Interaction with other vaccines	Routine risk communication: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction PL Section 2 Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. (final CSR: 30 June 2025) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU if concomitant administration occurs and can be captured (final CSR: 31 December 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. Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. (final CSR: 30 June 2025) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023)
Use in subjects with autoimmune or inflammatory disorders	Routine risk minimisation measures: None PL Section 2 Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. (final CSR: 30 June 2025) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023)

Part VI: Summary of the Risk Management Plan

This is a summary of the risk management plan (RMP) for COVID-19 Vaccine Moderna. The RMP details important risks of COVID-19 Vaccine Moderna, how these risks can be minimised, and how more information will be obtained about COVID-19 Vaccine Moderna risks and uncertainties (missing information).

The COVID-19 Vaccine Moderna's summary of product characteristics (SmPC) and its package leaflet provides essential information to healthcare professionals and patients on how COVID-19 Vaccine Moderna should be used.

This summary of the RMP for COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna RMP.

I The Medicine and What it is Used for

COVID-19 Vaccine Moderna is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The active substance in COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna benefits can be found in the COVID-19 Vaccine Moderna EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: www.ema.europa.eu/medicines/human/EPAR/covid-19-vaccine-moderna

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

Important risks of COVID-19 Vaccine Moderna, together with measures to minimise such risks and the proposed studies for learning more about COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of COVID-19 Vaccine Moderna 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 COVID-19 Vaccine Moderna. 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 36: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
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

List of Important Risks and 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) Use in subjects with autoimmune or inflammatory disorders

II.B Summary of Important Risks

Table 37: Important Identified Risk: Anaphylaxis

Important Identified Risk: Anaphylaxis	
Evidence for linking the risk to the medicine	In the Phase 3 study P301, 2 cases of anaphylaxis have been reported; 1 case each in the placebo and the mRNA-1273 group. The cases happened 10 days after the first injection and 63 days after the second injection, respectively. Both cases were assessed unrelated per the investigators. After the data lock of the Phase 3 P301 study on 25 November 2020 and before the data lock point (DLP) of the risk management plan (RMP), a second case of anaphylaxis was reported in the placebo group 60 days after the second injection. The case was non-serious and considered unrelated per the investigator. During emergency use authorisation, after the DLP of the RMP one case of anaphylaxis classified based on available information as a Level 2 according to Brighton Collaboration criteria was reported shortly after the intramuscular administration of mRNA-1273 vaccine.
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 communication : 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 COVID-19 vaccine Moderna (SmPC section 4.4). Patients 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 section 4.3 and PL section 2. Additional risk minimisation: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the European Union (EU) Phase 3 P301 Phase 2a P201 Phase 1 20-0003 Safety and Immunogenicity in Immunocompromised Adults See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 38: 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-associatedEnhanced Respiratory Disease (VAERD)	
Evidence for linking the risk to the medicine	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. This "Th2 biased" phenotype is most associated with enhanced disease as resulting from the formalin-inactivated measles and respiratory syncytial 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 (eg, dengue), by chemically disrupted antigens (eg, 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. No evidence of harm has been identified in non-clinical studies nor from the Phase 3 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 of 9 weeks of follow up post-second dose.
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: Post Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Phase 3 P301 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 39: 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:

	Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Moderna mRNA-1273 Observational pregnancy outcome study See section II.C of this summary for an overview of the post-authorisation development plan.

Table 40: Long-Term Safety

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU • Phase 3 P301 • Phase 1 20-0003 See section II.C of this summary for an overview of the post-authorisation development plan.

Table 41: 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:

	• Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Safety and Immunogenicity in Immunocompromised Adults See section II.C of this summary for an overview of the post-authorisation development plan.

Table 42: 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: • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU See section II.C of this summary for an overview of the post-authorisation development plan.

Table 43: 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 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

	• Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU See section II.C of this summary for an overview of the post-authorisation development plan.

Table 44: 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: • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU 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

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).

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. Follow up period extended by an additional 12 months for 24 months follow up total after the second dose. Assessment of a booster dose.
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.
Study of the Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Immunocompromised Adults	Safety and reactogenicity and adverse events for 1 year after receiving 2 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) Signal Evaluation in HealthVerity.	This study will monitor anaphylaxis, Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD), and long-term safety. It will also monitor AESI and emerging validated safety signals.
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU	Assessment of occurrence of safety events of interest, including severe or atypical COVID-19 in real-world use of COVID-19 mRNA vaccine, use in pregnancy and while breast-feeding, concomitant administration observed with non-COVID vaccines, use in frail participants with unstable health conditions and co-morbidities, and use in participants with autoimmune or inflammatory disorders.
Moderna mRNA-1273 Observational Pregnancy Outcome Study	Evaluate outcomes of pregnancies in females exposed to mRNA 1273 vaccine during pregnancy.
Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the U.S	Evaluate the real-world effectiveness and long-term effectiveness of mRNA-1273 in preventing COVID-19 and severe COVID-19 disease. Effectiveness stratified by age, sex, race/ethnicity, comorbid conditions. Effectiveness of two doses of vaccine in preventing

	COVID-19 among immunocompromised patients. Frail individuals and participants with autoimmune and inflammatory disorders will be evaluated to the extent that it is feasible. Considering current Advisory Committee on Immunization Practice recommendations to not co-administer other adult vaccines (eg, seasonal flu vaccine) in participants, Moderna will evaluate this schedule as possible. Durability of one or two doses of COVID19 Vaccine Moderna against COVID-19 and severe COVID-19 disease will also be assessed.

Part VII: Annexes

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Follow-Up Forms

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Anaphylaxis Reporting Form

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:_____ **Relation to Patient:** ☐Self ☐Family Member ☐ Other_____ ☐Healthcare Professional (select 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

Vaccine (type/brand)	Manufacturer	Lot number / Batch number	Route	Needle length / gauge	Dose Volume (mL)	Body site	Dose number in series	Date/Time Given
COVID-19 / mRNA-1273	**Moderna**					☐ Left ☐ Right	Dose 1	_____/_____/_____ _____:_____ ☐ am ☐ pm
COVID-19 / mRNA-1273	**Moderna**					☐ Left ☐ Right	Dose 2	_____/_____/_____ _____:_____ ☐ am ☐ pm

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:_____
If female, pregnant? ☐ No ☐ Yes ☐ Unknown	
Age at vaccination or Date of birth:	Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown
Height: _____ ☐ inches ☐ centimeters Weight: _____ ☐ pounds ☐ kilograms	Allergies to medications, food, and other products:

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	_____/_____/_____

Previous allergic reaction history: **Does the patient have a history of allergic or hypersensitivity reactions?** ☐ No ☐ Yes ☐ Unknown **Date** ___/_____/_____ DD/ MMM / YYYY **If yes, please indicate if these are observed in relation to previous vaccines/immunisation** ☐ No ☐ Yes ☐ Unknown **Date** ___/_____/_____ DD/ MMM / YYYY	**Please identify if patient has a history of any of the following medical conditions?** Anaphylaxis ☐ No ☐ Yes ☐ Unknown Hypersensitivity reactions ☐ No ☐ Yes ☐ Unknown Asthma ☐ No ☐ Yes ☐ Unknown Hay fever ☐ No ☐ Yes ☐ Unknown Urticaria/hives ☐ No ☐ Yes ☐ Unknown

Concurrent signs and symptoms and chronic or long-standing	**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.**

Anaphylaxis Reporting Form

health conditions: ☐ None ☐ Unknown		
	______/______/______	☐ No ☐ Yes:
	______/______/______	☐ No ☐ Yes:
	______/______/______	☐ No ☐ Yes:
	______/______/______	☐ No ☐ Yes:
	______/______/______	☐ No ☐ Yes:
	______/______/______	☐ No ☐ Yes:

Prescriptions, over-the-counter medications, dietary supplements, or herbal remedies being taken prior to, at time of vaccination and after the event:

☐ 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 site	Dose number in series

PRIOR IMMUNISATION HISTORY

Vaccine (type/brand)	Manufacturer	Lot number	Route	Body site	Dose number in series	Date Given (dd/mmm/yyyy)
						________/_______/_______
						________/_______/_______
						________/_______/_______

ADVERSE EVENT INFORMATION

What is the diagnosis for the reported reaction?	Please check which of the following signs or symptoms were experienced by the patient?	Treatment
What is the diagnosis for the reported reaction? Hypersensitivity reaction ☐ Anaphylactic reaction ☐ Anaphylactoid reaction ☐ Anaphylactic shock ☐ Other - please specify:	Pruritus ☐ Indicate: Generalized ☐ Local ☐ Urticaria ☐ Indicate: Generalized ☐ Local ☐ Redness/erythema ☐ Indicate: Generalized ☐ Local ☐ Bronchospasm or wheezing ☐ Indicate: Unilateral ☐ Bilateral ☐ Nausea or vomiting ☐ Angioedema ☐ Hoarseness ☐ Diarrhea ☐ Stridor ☐ Capillary refill time >3 s ☐ Reduced central pulse volume ☐ Abdominal cramps ☐ Generalized prickle sensation ☐ Red and itchy eyes ☐ Cough ☐ Tachypnea ☐ Difficulty breathing ☐ Sensation of throat closure ☐ Sneezing/rhinorrhea ☐ Feeling hot ☐ Tingling ☐ Flushing ☐ Chest tightness ☐ Difficulty swallowing ☐ Chills/rigors ☐ Taste perversion ☐ Cyanosis ☐ Decrease level of consciousness ☐ Tachycardia ☐	**Was the patient treated?** ☐ No ☐ Yes ☐ Unknown If yes, which treatment below: **Adrenaline** ☐ **Antihistamines** ☐ - Oral - please list: - Injection - please list: **Steroids** ☐ - Oral - please list: - Injection - please list: **Oxygen** ☐ **Other** - please list:

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Anaphylaxis Reporting Form

	Arrhythmia ☐ Numbness ☐ Increased use of accessory respiratory muscles ☐ Upper airway swelling (lip, tongue, throat, uvula, or larynx) ☐	
Adverse Event Start Date and Start/Stop Time: (e.g. DD/MMM/YYYY)	**How long did the event last?** _____/_____/_____ DD/ MMM / YYYY _____ : _____ ☐ am ☐pm _____ : _____ ☐ am ☐pm How long did the event last?	**First observation:** **Please describe patient vitals:** Hypotension - **blood pressure readings**: _____(Value), _____ (Units) Fever - **body temperature readings**: _____(Value), _____ (Units) Rash - **please describe**: Any other symptoms- **please describe**:
Did the event cause the patient to seek medical care?	**Was the patient hospitalized?** ☐No ☐ Yes (select below) ☐ Doctor's office/urgent care visit ☐ Emergency room/department ☐ Admitted to hospital Dates of hospitalization _____/_____/_____to _____/_____/_____ DD/ MMM / YYYY	**Laboratory Results** **Date of labs drawn** _____/_____/_____ DD/ MMM / YYYY _____ **Time of labs drawn** _____ ☐ am ☐ pm **Check all that apply** **Mast cell tryptase** ☐ _____(Value), _____ (Units) **IgE** ☐ _____(Value), _____ (Units) **Complement** ☐ _____(Value), _____ (Units) **Laboratory reference ranges:** **Pathology Findings** **Date** ___/_____/_____ DD/ MMM / YYYY _____ **Time** _____ ☐ am ☐ pm
Was the adverse event most likely caused by mRNA-1273?	☐ No ☐ Yes ☐ Unknown	
Were there any other potential causes other than mRNA-1273?	☐ Yes - please specify: _____ ☐ No ☐ Unknown	
Event Outcome:	☐ Recovered Date recovered:____/___/____ ☐ Recovered with residual effects Date recovered:_____/_____/_____ Residual effects:_____ ☐ Ongoing/Not recovered ☐ Unknown ☐ Event resulted in death Date of death:____/____/_____ Cause of death_____ Autopsy done: ☐ Yes ☐ No	

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Anaphylaxis Reporting Form

Describe the adverse event(s), including signs/symptoms, clinical course, and treatments with dates/timelines including exposures other than the immunization 24 h before and after the immunization (e.g. foods, environmental). ***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:

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	

Has the patient been treated with immunomodulating or immunosuppressing medications or received any other vaccines around the time of the COVID-19 vaccination?	☐ No ☐ Yes, specify:	**Date(s):**

****

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:

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:

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:

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: End date: Respiratory rate range:
a heart rate ≥ 125 beats per minute?	☐ No ☐ Yes	Start date: End date: Heart rate range:
an oxygen saturation of ≤ 93% on room air?	☐ No ☐ Yes	Start date: End date: Oxygen saturation range:
a systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg?	☐ No ☐ Yes	Start date: End date: Blood pressure range:

****

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? ☐

****

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:

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

☐ No ☐ Yes – Please provide details with dates:

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**
						☐
						☐
						☐

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:

****

(If patient was hospitalized)
Did the patient require respiratory ventilator support or ECMO?
☐ No ☐ Yes – Please provide details with dates:

**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:

(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):
Erythrocyte sedimentation rate	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
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:
PT	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
PTT	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
INR	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
Fibrinogen	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
PaO2/FiO2	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
PaCO2	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
pH	☐ Yes ☐ No ☐ Unknown	Date(s): Results with units: Normal range:
SpO2/FiO2	☐ Yes	Date(s):

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):**			
	☐ No ☐ Unknown	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, etc.)	☐ Yes ☐ No ☐ Unknown	Test	Date	Result	
Other relevant results	☐ Yes ☐ No ☐ Unknown	Test	Date	Result w/units	Normal range