



**RECOMMENDATION FOR AN EMERGENCY USE LISTING  
OF COVID-19 mRNA VACCINE (nucleoside modified)  
SUBMITTED BY Moderna Biotech (Spain)**

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**Abstract**

*Moderna used its mRNA-based platform to develop mRNA-1273, a novel, lipid nanoparticle (LNP)-encapsulated, mRNA-based vaccine against SARS-CoV-2 (2019 novel coronavirus). The proprietary LNPs encapsulating the mRNA increase its delivery efficiency and improve vaccine tolerability. The vaccine is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2. The mRNA-1273 vaccine is administered by intramuscular (IM) injection, and mRNA is subsequently delivered into cells, primarily to antigen presenting cells at the injection site and draining lymph nodes. After delivery, the mRNA utilizes the cell's translational machinery to produce the spike protein, which after proper assembly and processing is trafficked to the cell membrane for display to the immune system.*

*The clinical data presented were generated from three trials. The vaccine was shown to be safe and immunogenic. In the phase III trial that enrolled 28,207 participants, the data cut on 25 November 2020, showed that 185 cases of COVID-19 occurred in the placebo group and 11 cases occurred in the group that received mRNA-1273, giving a vaccine efficacy of 94.1% (95% confidence interval, 89.3% – 96.8%) against symptomatic COVID-19.*

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

*The European Medicines Agency (EMA) is the regulatory authority of reference and has granted conditional Marketing Authorization for the use of COVID-19 Vaccine Moderna. The vaccine is endorsed by other regulatory authorities (e.g., the Food and Drug Administration of the United States of America and Health Canada).*

*This report was prepared by the product evaluation group (PEG) to be discussed by the technical advisory group for emergency use listing (TAG-EUL).*

## **1 Introduction**

### **1.1 Background**

The current COVID-19 pandemic is unprecedented in the 21<sup>st</sup> century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.

On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

Scientists around the world on COVID-19 met at the World Health Organization's Geneva headquarters on 11–12 February 2020<sup>1</sup> to assess what is known about the new severe acute respiratory coronavirus -2 (SARS-CoV-2) virus, agree on critical research questions that needed to be answered urgently, and find ways to collaborate to accelerate and fund priority research to curtail the pandemic.

The discussion led to an agreement on two main goals. The first was to accelerate innovative research to help contain the spread of the epidemic and facilitate care for those affected. The second was to support research priorities that contribute to global research platforms for the current pandemic response in order to be better prepared for the next epidemic.

The WHO Research & Development (R&D) Blueprint<sup>2</sup> aims to improve coordination between scientists and global health professionals, accelerate the research and development process, and develop new norms and standards to learn from and improve the global response. Building on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the R&D Blueprint has facilitated a coordinated and accelerated response to research into diagnostics, vaccines and therapeutics for the novel disease. This led to the establishment of an unprecedented program to develop a vaccine and strengthened channels for information sharing between countries.

### **1.2 COVID-19 vaccines**

Shortly after SARS-CoV emerged at the turn of the 21<sup>st</sup> century, the spike (S) protein (particularly in its native conformation) was identified as the immunodominant antigen of the virus.<sup>3</sup> Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response to SARS-CoV-2. The characteristics of this response would include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease.<sup>4</sup>

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<sup>1</sup> <https://www.who.int/news/item/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research>

<sup>2</sup> <https://apps.who.int/blueprint-brochure/>

<sup>3</sup> Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. *Nat Rev Microbiol.* 2009;7(3):226-236.

<sup>4</sup> Tseng CT, Sbrana E, Iwata-Yoshikawa N, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. *PLoS One.* 2012;7(4):e35421.

The current global COVID-19 public health emergency underscores the need to accelerate the development of COVID-19 candidate vaccines. The vaccine prioritization agenda has a public health and a vaccine component. The strategy includes the prioritization of vaccine platform approaches and/or candidates to be considered not only for development but also for evaluation in the context of the global COVID-19 outbreak. The pipeline of candidate vaccines for COVID-19 is reviewed and updated continuously. The vaccine development is carefully reviewed and discussed in order to assess their value in protecting against COVID-19 and a potential recommendation of use based on a careful benefit - risk approach.

The information available on COVID-19 candidate vaccines<sup>5</sup> and the new coronavirus (nCoV) epidemiology is closely monitored. The various platform technologies that are developed based on nucleic acids (both mRNA and DNA), viral vectored vaccine (e.g., MVA, VSV, Ad/ChAd), subunit proteins and the traditional platform of inactivated virus are reviewed. Some of the platforms may be easier and faster to manufacture at scale while other platforms may elicit a more rapid and robust protection. Technology platforms for which clinical experience, safety data and demonstrated usability already exist, could allow a more rapid advancement into final phases of clinical trials.

Vaccines that could exert protective immunity after a single dose are preferred. However, most of the current candidate vaccines for COVID-19 require two doses.

### **1.2.1 Moderna Covid-19 vaccine (mRNA-1273)**

Moderna has used its mRNA-based platform to develop mRNA-1273, a novel, lipid nanoparticle (LNP)-encapsulated, mRNA-based vaccine against SARS-CoV-2 (2019 novel coronavirus). The proprietary LNPs encapsulating the mRNA increase its delivery efficiency and improve vaccine tolerability. The vaccine is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2. Shortly after the SARS-CoV-2 genetic sequence was determined, mRNA-1273, a novel lipid nanoparticle (LNP) encapsulated messenger RNA-based vaccine encoding for a prefusion stabilized full-length spike (S) glycoprotein of the Wuhan-Hu-1 isolate of SARS-CoV-2, was developed.

The precision and standardization of the mRNA platform enables rapid development and efficient manufacturing scale-up of safe and protective vaccines without reliance on systems that are specific to each pathogen. mRNA is highly precise in its translation into proteins that match viral antigens. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating and is expressed transiently. The estimated half-life for mRNA after injection is approximately 8 to 10 hours, before degradation by native RNases in the body, but the duration of effect also depends on the half-life of the expressed protein, which persists in the body for several days.

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<sup>5</sup> <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

The mRNA-1273 vaccine is delivered via intramuscular (IM) injection, and mRNA is subsequently delivered into cells, primarily to antigen presenting cells at the injection site and draining lymph nodes. After delivery, the mRNA utilizes the cell's translational machinery to produce the spike protein, which after proper assembly and processing is trafficked to the cell membrane for display to the immune system.

### **1.3 Emergency Use Listing**

The Emergency Use Listing (EUL) is a time limited benefit-risk assessment for emergency use of vaccines, medicines and in vitro diagnostics during a PHEIC when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the applicant is still expected to complete the development of the product and submit application for licensure and prequalification.

The issuance of an EUL for a product reflects WHO's recommendation for emergency use following a robust scientific benefit-risk assessment. However, each WHO Member States has the sole prerogative to allow the emergency use of a product under an EUL within their country.

## **2 Assessment process**

The COVID-19 vaccine manufactured by Moderna Biotech was assessed under the WHO EUL procedure based on rolling submissions. The WHO EUL application was submitted by Moderna Biotech, Spain. Vaccine batches will be released by European Medicine Agency (EMA).

The WHO prequalification procedure includes provision for a streamlined (or abbreviated) assessment procedure. The aim of this abbreviated assessment<sup>6</sup> is to increase efficiencies, avoid duplication of efforts and reduce the time to assess a product by focusing on aspects where WHO prequalification brings added value. The abbreviated approach applies to the prequalification of vaccines that have been licensed/authorized for emergency use by selected eligible NRAs willing to share information with WHO through a collaboration agreement.

The approach described above may be used to assess vaccines during public health emergencies following the EUL procedure. As EMA is the NRA of record for this vaccine, WHO conducted an abbreviated procedure of the dossier relying on the assessment done by the EMA. The WHO review focusses on issues relevant for the use of the vaccine in low- and middle-income countries (LMICs).

Emphasis was placed on the Risk Management Plan (RMP) because of the need to consider the perspectives and concerns of regulators from different regions, that might otherwise not be considered by the NRA of reference whose assessment is focused on issues related to its own jurisdiction.

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<sup>6</sup> WHO TRS 978 Annex 6

## 3 Scientific Review

### 3.1 Quality Overview

In accordance with the abbreviated review, the quality assessment by WHO of COVID-19 mRNA Vaccine (nucleoside-modified) manufactured by Moderna consisted in the evaluation of programmatic characteristics of the vaccine and its suitability for LMICs (see section 6.2 of this report). A summary of the quality aspects of the product, based on the EMA assessment report, is provided, nevertheless.

The drug substance is manufactured and controlled by Lonza, Visp, Switzerland, with GMP certification. Moderna, Norwood, USA is listed with GMP certification for quality control (QC) testing until method transfer is completed to Lonza, Visp. The drug product is manufactured and tested by Rovi Pharma Industrial Services, Spain (production and testing), and Eurofins BioPharma, Ireland (testing for stability).

### Drug Substance

Manufacture of COVID-19 mRNA vaccine drug substance is divided into 2 sequential steps: *in vitro* synthesis of the active substance and its inclusion in the mRNA-1273 lipid nano particle envelope. The active ingredient is the mRNA (also referred as CX-024414 mRNA) encoding the pre-fusion stabilised Spike protein (S protein) of 2019-novel Coronavirus (SARS-CoV-2). The S protein is composed of two subunits (S1 and S2) and is stabilised in the so-called pre-fusion conformation by two amino acid mutations, K986P and V987P. CX-024414 mRNA sequence includes a 5' cap, the 5' untranslated region (UTR), the Open Reading Frame (ORF), the 3' UTR, and the 3' polyA tail. The RNA contains modified N1-methylpseudouridine instead of uridine to minimise the indiscriminate recognition by pathogen-associated molecular pattern receptors (e.g., TLRs).

#### CX-024414 mRNA

The **manufacturing process** of CX-024414 mRNA consists of different steps as follows:

1. *in vitro* transcription of linearised plasmid DNA template into full-length, uncapped RNA using T7 RNA polymerase. The template is then degraded by DNase I. Input materials to the transcription and DNase reactions are sterile filtered prior to use;
2. First tangential flow filtration (TFF) is performed for buffer exchange and to concentrate the transcribed product;
3. Full-length, polyA tail-containing RNA is subsequently purified by chromatography;
4. A second TFF is performed to adjust the concentration and prepare the RNA for capping;
5. Enzymatic capping is then carried out. Inputs to the capping reaction are 0.2 µm filtered prior to use;
6. A third TFF is performed for buffer exchange and concentration adjustment;

7. Capped mRNA is subsequently purified by a second chromatography step;
8. A final TFF is performed to concentrate the mRNA and to change the buffer;
9. A final 0.2 µm filtration is carried out for clarification and sterilisation.

Resulting CX-024414 mRNA is aseptically dispensed into 20 l bags and may be held at 2°C - 8°C prior to forward processing or stored at -15°C to -25°C. Reprocessing is not performed for any CX-024414 mRNA process step. DNA plasmid templates are manufactured in house and managed according to a 2-tiered bank system.

**Process validation** was conducted with 3 consecutive commercial mRNA batches between November and December 2020 for which critical process parameters (transcription reaction temperature, capping reaction temperature and chromatography elution temperature) have been identified and validated against.

**Quality control** of raw (buffers, enzymes, reagents) and starting (plasmid banks and nucleotides) is assured with compendial (mainly Ph.Eur. and USP) or in-house methods. Critical material attributes have been identified for a capping substrate and for plasmids. None of the materials used in the manufacturing process are of animal origin. CX-024414 mRNA is controlled with compendial (mainly Ph.Eur. and USP) or in-house based methods, as well. All methods are verified or validated. mRNA reference is prepared internally by the applicant.

**Stability** study at -20±5°C has been conducted and showed the nucleic acid is stable for 6 months at this temperature. Additional study at 5±3°C concluded CX-024414 mRNA is stable for 1 month. Finally, a freeze-thaw stability study was performed using a development batch and results demonstrated the stability of the product after 5 freezing and thawing cycles at room temperature.

#### mRNA-1273 lipid nanoparticle

The **manufacturing process** of mRNA-1273 lipid nanoparticle (mRNA-1273 LNP) consists in different steps as follows:

1. Mixing of CX-024414 mRNA with lipid stock solution containing novel excipient SM-102, cholesterol and 1,2-distearoyl-sn-glycero -3-phosphatidylcholine or DSPC;
2. Neutralisation and addition of PEG2000-DMG (LNP stabiliser and novel excipient);
3. Clarification by 0.8 and 0.2 µm dual-layer polyethersulfone (PES) filter;
4. Dispensing in sterile, single-use bags at a target fill volume, hold at an intermediate temperature, and freezing (-75°C) for long-term storage (between -60°C to -90°C).

Reprocessing is not performed for any mRNA-1273 LNP process step.

**Process validation** was conducted with 4 consecutive commercial LNP batches between December 2020 and January 2021 for which critical process parameters (CX-024414 mRNA thaw duration, diluted mRNA flow rate and lipid mixture flow rate) have been identified and validated against.

**Quality control** of raw (buffers and lipid solution) and starting (PEG2000-DMG) is assured with compendial (mainly Ph.Eur. and USP) or in-house methods. Critical material attributes have been identified for the pH of different buffers (mRNA dilution buffer, LNP cryoprotectant buffer and PEG2000-DMG addition buffer). None of the materials used in the manufacturing process are of animal origin. mRNA-1273 LNP is controlled with compendial (mainly Ph.Eur. and USP) or in-house based methods, as well. All methods are verified or validated. References are either developed in house or purchased.

**Stability** study at -60 to -90°C has been conducted and showed mRNA-1273 LNP is stable for 3 months at this temperature to date. Additional study at 5±3°C concluded LNP is stable for 1 month to date.

## Drug Product

The finished product is manufactured with a target of 0.2 mg/ml of mRNA-1273 LNP. Each vial contains 10 doses of vaccines with the following composition:

Component	Concentration in final product (mg/ml)	Function
CX-024414	0.20	Active ingredient
SM-102	2.15	Lipid components
Cholesterol	0.94	
DSPC	0.55	
PEG2000-DMG	0.23	
Tris	0.61	Buffer
Tris-HCL	2.35	
Acetic acid (Glacial)	0.085	LNP buffer
Sodium acetate	0.237	
Sucrose	87	cryoprotectant

The ingredients are diluted in water for injection (WFI) up to the target volume of 6.3 ml per vial.

**Production** of drug product is as follows:

1. Thawing of multiple batches of mRNA-1273 LNP;
2. Pooling of drug substance and dilution in buffer containing WFI, Tris, Tris-HCL and sucrose;
3. Clarification by 0.8 and 0.2 µm dual-layer PES filtering and sterile filtration by redundant passage on an asymmetric 0.8/0.2 µm PES membrane;
4. Filling, stoppering and capping of the sterile final bulk;
5. Visual inspection, labelling and storage at -20°C.

**Process validation** was conducted with 3 consecutive commercial batches between November 2020 and January 2021 for which critical process parameters at dilution, stoppering/capping, vial freezing and cumulative process duration have been identified and validated against. Media fill was also performed.

**Quality control** of excipients is performed with compendial (mainly Ph.Eur. and USP) or vendor-based methods. The product contains 2 novel excipients, SM-102 and PEG2000-DMG. Toxicity and safety have been assessed during non-clinical studies and clinical trials, respectively. Finished product is controlled with compendial (mainly Ph.Eur. and USP) or applicant-based methods. All testing methods are verified or validated. References are either developed in house or purchased.

A finished product shelf-life of 7 months at  $-20\pm 5^{\circ}\text{C}$  was proposed and accepted, based on a statistical model aligned with the WHO 2006 guidance document on stability evaluation of vaccines. Additionally, the vaccine is stable a period of 30 days at  $5\pm 3^{\circ}\text{C}$  (protected from light) plus 12 hours at  $25\pm 2^{\circ}\text{C}$ . **Stability** studies at those 3 temperatures are still ongoing. Additionally, in use stability study was performed and results showed the vaccine to be stable when held for 6 hours after first puncture in the dosing vial followed by 8 hours in the dosing syringe, at either ambient temperature or  $5\pm 3^{\circ}\text{C}$ .

### 3.2 Non-clinical overview

#### Discussion on nonclinical aspects

Generally, the reviewer is in agreement with both the discussion and conclusions of the CHMP evaluation on the nonclinical program undertaken by the sponsor with the mRNA-1273. Some of the relevant sections are re-produced here.

Study Number	Test system	Dose mRNA-1273	Method of administration; immunization schedule	Study
MOD-3937	BALB/C mice F only	1 or 10 $\mu\text{g}$	Intramuscular; prime/boost (2-week interval)	Vaccination and protein re-stimulation in young BALB/c mice with enhanced respiratory disease endpoint monitoring; challenged with SARS-CoV-2 10 $\mu\text{g}$ (+ alum)
MOD-3938/ MOD-3940	BALB/C mice F only	0.0025 through 20 $\mu\text{g}$	Intramuscular; prime/boost (3-week interval)	Evaluation of immunogenicity and determination of titres dynamic range of mRNA-1273
VRC01	BALB/cJ, C57BL/6J, and B6C3F1/J mice	0.01, 0.1, 1 or 10 $\mu\text{g}$	Intramuscular; prime only prime/boost (3-week interval) prime/boost (4-week interval)	Immunogenicity and protection from SARS-CoV-2 (0.01, 0.1, or 1 $\mu\text{g}$ (+ SAS-adjuvant) challenge of mice immunized with mRNA-1273
VRC02	BALB/c mice, >12 months age	0.1 or 1 $\mu\text{g}$	Intramuscular; prime/boost (3-week interval)	Efficacy of mRNA-1273 and enhanced disease in aged BALB/c mice – challenged with SARS-CoV-2 0.1 $\mu\text{g}$ (+ alum)
UTMB01	Syrian golden hamster M and F	1, 5, or 25 $\mu\text{g}$	Intramuscular; prime/boost (3-week interval)	Evaluation of immunogenicity and efficacy of mRNA-1273 in the Syrian golden hamster model
VRC04	Rhesus macaques	10 or 100 $\mu\text{g}$	Intramuscular; prime/boost (4-week interval)	Immunogenicity and protective efficacy of mRNA-1273 in rhesus macaques
VRC07	Rhesus macaques	2.5, 30, or 100 $\mu\text{g}$	Intramuscular; prime/boost (4-week interval)	Evaluation of immunogenicity and efficacy from expanded dose range of mRNA-1273 in rhesus macaques

#### Pharmacology

The nonclinical proof-of-concept studies reviewed included evaluation of immunogenicity and protective efficacy of mRNA-1273 in young and aged mice, hamsters and rhesus monkeys. The results showed that mRNA-1273 was well tolerated, immunogenic and provided protection from SARS-CoV-2 virus challenge.

At the clinically relevant dose(s) intramuscular administration of the vaccine elicited SARS-CoV-2-specific binding and neutralising antibody titres. Prime-only immunization generated high antibody titers, including neutralization antibodies, in all animals tested. Boosting with a second



dose of the vaccine resulted in increases in antibody titers. Antibodies were shown to bind to the S protein. The prime/boosting regimen also induced cellular immune responses: Th1-directed CD4+ T cell responses with no evidence of Th2-directed T cell responses.

A major potential concern in SARS-CoV-2 vaccine use is vaccine-associated antibody enhancement. This is associated with induction of non-neutralizing antibodies that can lead to immune complex formation, complement activation, Th2-responses and immunopathological complications. mRNA-1273 did not promote vaccine-associated enhancement of disease in mice, hamsters, and NHPs as demonstrated by balanced Th1/Th2-directed immune responses to immunization, the absence of increased lung pathology, and controlled viral replication after viral challenge when administered at doses predicted to be fully (optimal dose) or partially (suboptimal dose) protective.

In each animal model, IM administration of mRNA-1273 at clinically relevant dose(s) protected against SARS-CoV-2 virus challenge in both young and aged mice, hamsters and monkeys. Concurrent measurement of the cellular response in the immunised mice and nonhuman primates showed induction of a Th1-directed T-cell response characterised by IFN-g, IL-2 and TNF-a, and additionally IL-21-producing follicular helper T (Tfh) cells in rhesus monkeys. Dose-response relationship was established both for the binding and neutralising titres in both species, and for the CD4+ Th1-directed T cells and IL-21-producing Tfh cells in nonhuman primates.

#### Pharmacokinetics: biodistribution

No special studies were conducted with the proposed vaccine, mRNA-1273. Instead, the evaluation of mRNA-1273 distribution was based on a rat biodistribution study using a similar mRNA-based vaccine encoding CMV antigens (mRNA-1647). The rationale for using this study to evaluate biodistribution of mRNA-1273 is based on the fact that biodistribution of mRNA-based vaccines formulated in LNPs is dependent on that of the LNP. Therefore, any mRNA-based vaccine formulated within the same LNPs (eg, mRNA-1647) is expected to distribute similarly.

Following a single IM injection, mRNA-1647 were distributed throughout the body (including brain, heart, lung, eye, testis), and were rapidly cleared from plasma during the first 24 hours, with the T1/2 estimated in a range from 2.7 to 3.8 hours. The highest mRNA-1647 concentrations were at the injection site. Following plasma clearance, proximal and distal lymph nodes and spleen are the major distant organs to which mRNA-1647 distributed. For these tissues, Cmax was between 2 and 24 hours post-dose, and T1/2 was 14.9 hours for muscle of site of injection, 34.8 hours for proximal lymph nodes, 31.1 hours for distal lymph nodes, and 63.0 hours for spleen. Liver distribution of mRNA-1647 was also evident, consistent with the recognised LNP distribution pattern.

This study demonstrated that the mRNA constructs do not persist past 1 to 3 days in tissues other than muscle (injection site), proximal popliteal and distal axillary lymph nodes, and spleen.

#### Toxicology

For the toxicological assessment of the mRNA-1273, stated was that data were submitted from only two studies: a non-good laboratory practices (GLP) compliant repeat-dose toxicity study and

a GLP-compliant developmental and reproductive toxicology (DART) study. The DART study was not listed in the sponsor's data package.

#### *Repeat-dose toxicity study*

All doses of the mRNA/LNP vaccines administered in the repeat-dose toxicity studies were well-tolerated. Treatment-related effects were observed at all tested concentrations in a dose-dependent manner. Generally, local inflammatory responses towards LNP-mRNA injection in rats was not only observed in the direct vicinity of the injection site, but also in adjacent tissues and/or organs. The spread of inflammation into adjacent tissues of the injection sites was in part due to the large difference in body surface area between rats and humans, and that the dose volume administered resulted in higher concentrations of drug product at the site of injection in rats compared to humans with safety margin of ~ 375. Therefore, it is considered that these severe local inflammations bear no clinical relevance.

During the assessment of the study conducted with the proposed product, mRNA-1273, the following observations were made possibly attributable to inflammatory responses after LNP-mRNA product administration in rats:

- Alterations in erythropoiesis: decrease in mean reticulocyte count and increase in red cell distribution width (also observed in other repeat-dose studies with other mRNA vaccines);
- Decrease in RBC mass (erythrocytes, haemoglobin and/or haematocrit).

The potential clinical relevance of these findings is unknown; however, they were reversible after the two-week recovery period.

Hepatic changes with corresponding changes in clinical chemistry were frequently but not consistently observed in most of the studies, suggesting that these hepatic changes may not be a direct result of LNP-mRNA administration but rather secondary to systemic inflammation.

Of concern were the following findings observed in the studies although the toxicological potential for humans are considered to be low. Throughout the studies, increases in activated partial thromboplastin time (APTT, up to ~ 30%) and fibrinogen (up to ~ 2.5-fold) as well as increases in eosinophil counts were consistently observed. These findings are mentioned in the SmPC (Section 5.3, under General Toxicity). The attention of the clinical evaluator is drawn to these findings.

In general, the repeat-dose toxicity of the products were similar, suggesting that any observed toxicities were not product-specific but rather as a consequence of the immunologic responses towards the translated antigens or due to the LNP formulation. These effects were resolved at the end of the 2-week recovery period.

#### *Genotoxicity*

As pointed out in the European public assessment report (EPAR), with regards to the submitted genotoxicity studies, the administered mRNA/SM-102 concentrations in the positive genotoxicity study were much higher than the actual concentrations in the clinical setting (>27mg/kg SM-102). The vaccine will be administered twice only, and a low dose containing around 1 mg SM-102 per dose will be administered. Moreover, a different route of administration was used in the

micronucleus study compared to the intended clinical route (IV vs. IM), and thus significantly lower systemic exposure to the individual excipients can be expected in the clinical setting. The SM-102 specific in vitro bacterial reverse mutation test and in vitro mammalian cell micronucleus test in human peripheral blood lymphocytes did not indicate any genotoxic potential for this novel excipient. Therefore, a relevant genotoxic risk is thus not expected for mRNA-1273.

#### *Developmental and reproductive toxicity study*

The potential DART effects of mRNA-1273, the vaccine development candidate, was assessed when administered intramuscularly on Study Days 1 and 15 (28 and 14 days prior to mating, respectively) and Gestation Days 1 and 13 on fertility and pre and postnatal development in the pregnant and lactating female Sprague Dawley CD (CrI:CD[SD]) rat.

In the F0 generation, a significantly lower pregnancy index (68.2%) was observed in the natural delivery group only and was ascribed to random distribution of pregnant and non-pregnant animals between the C-section and natural delivery cohorts. The overall pregnancy index was numerically lower in mRNA-1273 vaccinated female rats (84.1%), compared to control animals (93.2%), but remained within the Test Facility's historical control range (low range being 75%).

There were no mRNA-1273-related effects on female fertility, embryo-foetal or post-natal survival, growth or development in the F1 offspring. The mRNA-1273-related non-adverse effects vs control group treated with Tris/Sucrose were limited to an increase in the number of foetuses with common skeletal variations of 1 or more rib nodules and 1 or more wavy ribs, with no effect on the viability and growth on the F1 generation pups.

SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in fetuses and offspring. Although maternal-to-foetal and maternal-to pup transfer of antibodies was observed, no data are available on vaccine placental transfer or excretion in milk.

The DART study did not address the direct embryotoxic effect of the components of the vaccine formulation. No vaccine dose was administered during early organogenesis to address the direct embryotoxic effect of the components of the vaccine formulation. However, such a risk is considered low in humans, given the non-live organism nature of mRNA-1273 and the low risk of genotoxic effect of SM-102-containing LNP in humans.

In conclusion, no mRNA-1273 related effect on pregnancy is expected from these data.

#### **Package inserts (Summary of Product Characteristics)**

The following preclinical information in the proposed SmPC are acceptable.

#### Fertility, pregnancy and lactation

##### *Pregnancy*

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 (see section 5.3).

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.

#### *Fertility*

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

#### *Preclinical safety data*

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

#### *General Toxicity*

General toxicity studies were conducted in rats (intramuscularly receiving up to 4 doses exceeding the human dose once every 2 weeks). Transient and reversible injection site oedema and erythema and transient and reversible changes in laboratory tests (including increases in eosinophils, activated partial thromboplastin time, and fibrinogen) were observed. Results suggests the toxicity potential to humans is low.

#### *Genotoxicity/Carcinogenicity*

In vitro and in vivo genotoxicity studies were conducted with the novel lipid component SM-102 of the vaccine. Results suggests the genotoxicity potential to humans is very low. Carcinogenicity studies were not performed.

#### *Reproductive toxicity*

In a developmental toxicity study, 0.2 mL of a vaccine formulation containing the same quantity of mRNA (100 micrograms) and other ingredients included in a single human dose of COVID-19 Vaccine Moderna was administered to female rats by the intramuscular route on four occasions: 28 and 14 days prior to mating, and on gestation days 1 and 13. SARS-CoV-2 antibody responses were present in maternal animals from prior to mating to the end of the study on lactation day 21 as well as in foetuses and offspring. There were no vaccine-related adverse effects on female fertility, pregnancy, embryo foetal or offspring development or postnatal development. No data are available of mRNA-1273 vaccine placental transfer or excretion in milk.

In conclusion the primary pharmacology studies indicate the vaccine is immunogenic, fully protects animals from viral challenge, and does not promote vaccine-associated enhancement of disease. The biodistribution study with mRNA-1647 within similar LNP as used with mRNA-1273 showed that mRNA constructs do not persist beyond three days in tissues other than muscle of injection site and draining lymph nodes and the spleen. It is likely the mRNA-1273 will distribute similarly without persisting in the body. Repeat dose toxicity studies with the proposed and similar mRNA vaccines in animals in general raised no major safety issues. Findings were consistent with immune stimulation and inflammatory responses (injection site inflammation, increased body temperature, leucocytosis, increased large unstained cells, fibrinogen and acute phase proteins and hypercellularity of lymphohematopoietic tissues). The toxicity of the LNP

formulation and novel excipients was assessed. Neither the mRNA nor the lipid excipients of the LNP formulation are expected to have genotoxic potential in humans.

In general, the data from the nonclinical studies demonstrate that mRNA-1273 is safe and well tolerated. Therefore, there are no nonclinical objections, provided efficacy of the prime-boost regimen has been satisfactorily addressed by clinical studies.

### 3.3 Clinical Overview

There are three ongoing clinical studies with mRNA-1273 summarized in the Table-1 below.

**Table 1: Ongoing Clinical Studies of mRNA-1273**

Study Number	Study Design	Age Groups (years) / Dose (Planned Participants)	Vaccine Dose and Schedule
Study 301	Phase 3, randomized, stratified, observer-blind, placebo-controlled	<b>Age Groups:</b> 18+ (n=30000) <b>Dose Groups:</b> Placebo (n=15000) mRNA-1273 100 µg (n=15000) <b>Stratification:</b> Age and, if they are < 65 years of age, based on the presence or absence of risk factors for severe illness from COVID-19 based on CDC recommendation as of Mar 2020	100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart
Study 201	Phase 2a, randomized, observer-blind, and placebo-controlled	<b>Age Groups:</b> <b>Cohort 1:</b> ≥ 18 to < 55 (n=300) <b>Cohort 2:</b> ≥ 55 (n=300) <b>Dose Groups:</b> Placebo (n=200) mRNA-1273 50 µg (n=200) mRNA-1273 100 µg (n=200)	50 or 100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart
Study 101	Phase 1, open-label, dose ranging	<b>Age Groups:</b> 18 to 55 (n=75) 56 to 70 (n=40) ≥ 71 (n=40) <b>mRNA-1273 Dose Groups:</b> 10 µg (n=15) <sup>a</sup> 25 µg (n=35) 50 µg (n=35) 100 µg (n=35) 250 µg (n=35) <sup>b</sup>	10, 25, 50, 100, or 250 µg mRNA-1273 2 IM injections, 28 days apart

Abbreviations: IM = intramuscular.

<sup>a</sup> In Study 101, Cohort 13 (10 µg, 18–55 years, n=15) was not enrolled.

<sup>b</sup> In Study 101, dosing at the 250 µg level was discontinued after Cohort 3 (18–55 years, n=15) and prior to enrollment in Cohorts 6 (56–70 years, n=10) and 9 (≥ 71 years, n=10).

The evidence to support COVID-19 mRNA VACCINE (nucleoside modified) listing comes from interim results of a Phase 1 (study 20-003) open-label, dose-ranging study of the safety and immunogenicity of mRNA-1273 in healthy adults, a Phase 2a randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in adults aged 18 years and older (18-54 years, ≥55 years), and a 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. The three studies are still ongoing at the time of dossier submission.

The design and results of the trials are reviewed in line with the documents “Considerations for evaluation of Covid-19 vaccines: Points to consider for manufacturers of Covid-19 vaccines” Version 25, November 2020, and “WHO Target Product Profiles for Covid-19 Vaccines” Version 3-29 April 2020.

### **3.3.1 Vaccine efficacy**

A 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 (P301):

The study was designed to evaluate the safety and efficacy of the Investigational Product (IP) in adults 18 years of age and older who have no known history of SARS-CoV-2 infection but whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection. The study planned to enroll at least 25% and up to 50% of participants most at risk for severe complications of COVID-19, including those  $\geq 65$  years of age or  $< 65$  years of age with comorbid medical conditions such as diabetes mellitus (Type 1, Type 2, or gestational), significant cardiac disease, chronic pulmonary disease, severe obesity, liver disease, and controlled human immunodeficiency virus infection. The Sponsor had the intention to enroll a representative population of communities of color that have been disproportionately affected by COVID-19. The percentage of participants enrolled who self-reported as Black or African American (10.3% in mRNA-1273 group and 10.1% in placebo group) or Hispanic or Latino (20.6% in mRNA-1273 group and 20.5% in placebo group) approached that of the US population (US Census Bureau 2019: Black [13.4%], Hispanic or Latino [18.5%]). Communities of color represented 37% of the study population (Table 10 clin overview). Study 301 included equal proportions of males and females, more than 40% of participants in each group were at high risk for severe COVID-19 (i.e. the sum of participants  $< 65$  and at risk and  $\geq 65$  years). The majority (25.1%) of participants with a specified occupational risk for acquisition of SARS-CoV-2 were healthcare workers (Table 14.1.3.1.3 clin overview). The proportion of participants in each demographic category were generally similar between the 2 study groups.'

*Primary Efficacy Endpoint Assessment:* To be considered as a **case of COVID-19** for the evaluation of the Primary Efficacy Endpoint, the following criteria must be met:

The participant must have experienced at least two of the following systemic symptoms:

Fever ( $\geq 38^{\circ}\text{C}$ ), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s),

**OR**

The participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia;

**AND**

The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

The primary analysis showed that the vaccine efficacy (VE) of mRNA-1273 to prevent symptomatic COVID-19 in baseline seronegative participants was 94.1% (95% CI: 89.3%, 96.8%; p-value  $< 0.0001$ ). There were 196 COVID-19 cases, with 11 cases occurring in the

mRNA-1273 group and 185 cases occurring in the placebo group, starting 14 days after the second injection based on adjudication committee assessments in the per-protocol (PP) Set.

These results confirmed the interim analysis of efficacy, which was performed on 95 cases, with 5 cases occurring in the mRNA-1273 group and 90 cases occurring in the placebo group. In the interim analysis, the VE point estimate was 94.5% (95% CI: 86.5, 97.8). Therefore, the results from the interim and the primary analyses were highly consistent with each other. The VE based on incidence rate (94.1% [primary analysis]; 94.5% [interim analysis]) was the same as the VE based on hazard ratio. Sensitivity analyses based on the modified intent-to-treat (mITT) Set gave similar results: VE based on hazard ratio was 93.6%, with a 95% confidence interval (CI) of 88.5%, 96.4% for the primary analysis and 93.4%, with a 95% CI of 84.8%, 97.1% for the interim analysis.

**Table 11: Primary Efficacy Analysis of Study 301 (Starting 14 Days After Second Injection; Per-Protocol Set)**

	11 Nov 2020 Dataset <sup>a</sup>		25 Nov 2020 Dataset <sup>b</sup>	
	mRNA-1273 (N=13934)	Placebo (N=13883)	mRNA-1273 (N=14134)	Placebo (N=14073)
Number of participants with COVID-19, n (%)	5 (<0.1)	90 (0.6)	11 (<0.1)	185 (1.3)
Vaccine efficacy based on hazard ratio (95% CI) <sup>c</sup>	94.5% (86.5%, 97.8%)		94.1% (89.3%, 96.8%)	
P value <sup>d</sup>	<0.0001		<0.0001	
Person-years <sup>e</sup>	2716.9	2697.5	3304.9	3273.7
Incidence rate per 1,000 person-years (95% CI) <sup>f</sup>	1.84 (0.60, 4.30)	33.365 (26.83, 41.01)	3.33 (1.66, 5.96)	56.51 (48.66, 65.27)
Vaccine efficacy based on incidence rate (95% CI) <sup>g</sup>	0.945 (0.87, 0.98)		0.941 (0.89, 0.97)	

<sup>a</sup> Interim efficacy analysis.

<sup>b</sup> Primary efficacy analysis.

<sup>c</sup> Vaccine efficacy is defined as 1 – hazard ratio (mRNA-1273 vs. placebo), and 95% CI was estimated using a stratified Cox proportional hazard model with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor.

<sup>d</sup> One-sided p-value from stratified Cox proportional hazard model to test the null hypothesis VE ≤ 0.3.

<sup>e</sup> Person-years is defined as the total years from randomization date to the date of COVID-19, last date of study participation, or efficacy data cutoff date, whichever is earlier.

<sup>f</sup> Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI was calculated using the exact method (Poisson distribution) and adjusted by person-years.

<sup>g</sup> Vaccine efficacy is defined as 1 – ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio was calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Source: mRNA-1273-P301 [Table 14.2.2.1.1.1.1](#) (11 Nov 2020) and [Table 14.2.2.1.1.1.1](#) (25 Nov 2020).

## Subgroup analysis of efficacy

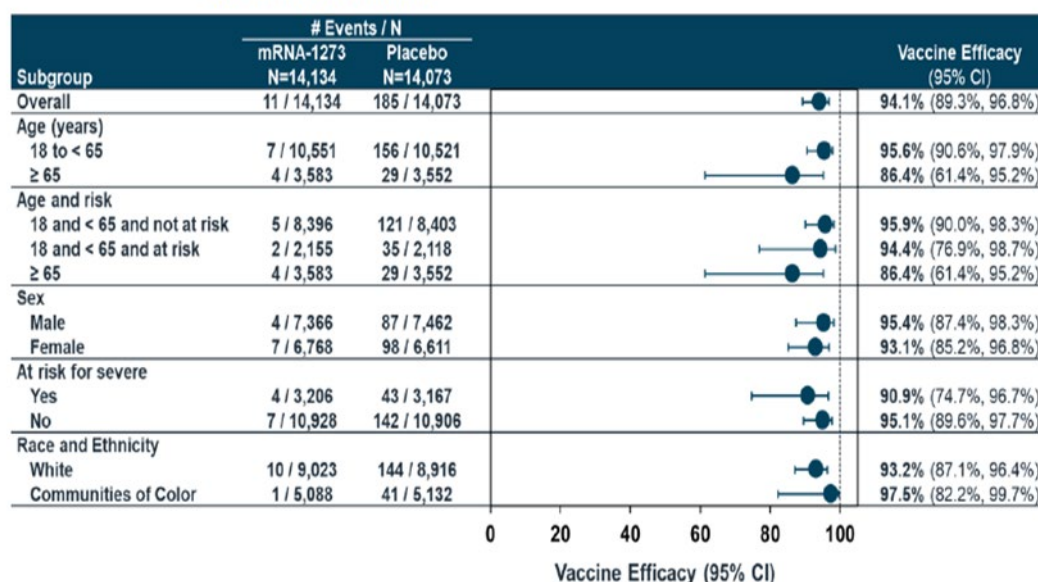
The efficacy of mRNA-1273 for the primary efficacy endpoint was consistent across major demographic and baseline characteristic subgroups in table and figure below. With respect to the subgroup analysis for ethnicity, limited numbers of participants in each ethnic group contributed to the primary efficacy endpoint. Therefore, the data were pooled together into a “communities of color” group for this analysis to ensure that two subpopulations in the study would be large enough for meaningful analyses.

Table 13: Subgroup Analyses, by Race, of VE of mRNA-1273 to Prevent COVID-19 in Study 301 (Per-Protocol Set; 25 Nov 2020 Dataset)

	# Events/N		Vaccine Efficacy (95% CI)
	mRNA-1273	Placebo	
Overall	11/14,134	185/14073	94.1% (89.3, 96.8)
White	11/11,253	166/11,174	93.5% (88.0, 96.5)
Black or African American	0/1,385	6/1,349	100%
Asian	0/620	5/689	100%
American Indian or Alaskan Native	0/108	1/111	100%
Native Hawaiian or Other Pacific Islander	0/35	0/31	100%
Other	0/299	2/295	100%
Multiple	0/295	3/307	100%
Not Reported	0/86	1/64	100%
Unknown	0/53	1/53	100%

Source: mRNA-1273-P301 Table 14.2.2.1.1.6.5.1 (25 Nov 2020).

Figure 3: Forest Plot of Subgroup Analyses of VE of mRNA-1273 to Prevent COVID-19 in Study 301 (Per-Protocol Set; 25 Nov 2020 Dataset<sup>a</sup>)



### 3.3.2 Vaccine Safety

The safety profile is based on administration of mRNA-1273 to more than 15,693 adults across 3 clinical studies, monitored for solicited local/systemic reactions, unsolicited adverse events (AEs) and serious adverse events (SAEs). There have been no emergent safety concerns, and the AE profile has been observed to be largely characterized by mild to moderate reactogenicity of a median duration of 2-3 days. Vaccination with mRNA-1273 results in transient local injection site and systemic reactions. The incidence of unsolicited AEs and AEs leading to discontinuation of study vaccine were similar between the treatment groups. Less common but clinically significant AEs, such as SAE and deaths, were reported at similar rates for placebo and vaccine recipients. The overall safety profile observed in the Phase 3 trial was generally consistent with the safety profile observed to date in the Phase 1 and 2 studies.



*The detailed safety evaluation of mRNA-1273 in the ongoing Phase 3 study P301:* At the latest data cut-off (25 November 2020), 30,351 subjects were enrolled (vaccine = 15,185, placebo 15,166), of whom 14,715 subjects in the vaccine arm and 14,613 subjects in the placebo arm have received the second dose of the respective treatment. The median study follow-up after the second injection was 63.0 days.

The safety and reactogenicity of mRNA-1273 100 µg compared with placebo administered 28 days apart were assessed in participants 18 years of age and older at increased risk for acquiring COVID-19 based on occupation or location and living circumstances.

Reactogenicity (solicited local and/or systemic ARs) was observed in the majority of participants in the mRNA-1273 group and generally increased after the second injection. The rates of local and systemic reactions were higher in the mRNA-1273 group than in the placebo group after each injection. The majority of solicited ARs in the mRNA-1273 group were grade 1 to grade 2 in severity and generally resolved within 3 days or less. The incidence rates of unsolicited AEs and severe AE during the 28 days after injection were also generally similar in participants who received mRNA-1273 and those who received placebo. Deaths and SAEs were reported at a similar incidence in the mRNA-1273 and placebo groups. There was no evidence of enhanced disease, as fewer cases of severe COVID-19 and COVID-19 were observed in participants who received mRNA-1273 than in those who received placebo.

### **Subgroup analysis of safety**

The overall incidence of unsolicited AEs within 28 days after any IP injection regardless of relationship was comparable in younger adults (18 to < 65 years of age) and older adults (≥ 65 years of age) who received mRNA-1273. As noted in the overall population, the incidence of grade 3 solicited AEs was higher in the mRNA-1273 group compared with the placebo group regardless of age. There was no apparent effect of age on the relative incidence of these AEs by vaccine group.

The incidence of SAEs reported throughout the duration of the study was comparable between treatment groups. None of the thirteen deaths reported in the phase study (6 in the mRNA 1273 vaccine group) as of 03 Dec 2020 was related to the study vaccine.

### **Pregnancy**

To be enrolled in the study, female subjects had to have a negative pregnancy test at enrollment and agree to use effective contraception until at least 3 months after the final vaccination. Details of all pregnancies in female participants are being collected from first day of dosing until study completion. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were considered SAEs. Thirteen pregnancies have been reported in Study 301 – 6 in the mRNA-1273 group and 7 in the placebo group (Table 23). As of 02 Dec 2020, 10 of the 13 pregnancies were ongoing with no reported complications. One participant (placebo group) experienced spontaneous abortion at approximately 7 gestational weeks; this SAE was considered not related to the IP.



### **3.3.3 Immunogenicity**

The immunogenicity of the COVID-19 Vaccine Moderna was studied in all 3 studies, however the results from study 301 are not available yet.

The results of Phase 1 Study 20-0003 (546 participants) showed a consistent dose response across age groups by several measures of humoral immunogenicity for both binding and neutralizing antibodies. The results from Study 101 (20-0003) showed a consistent dose response across age groups by several measures of humoral immunogenicity for both binding antibody (bAbs) and neutralizing antibody (nAbs). The advancement of the 100- $\mu$ g dose (administered as 2 injections, 28 days apart) to the Phase 2a and 3 studies was based on several observations: (i) 2 injections of 100  $\mu$ g stimulated serum bAb concentrations and titres greater than 2 injections of 25  $\mu$ g in the 18 to 55 years of age stratum; (ii) 2 injections of 100 $\mu$ g induced nAb responses (measured by PsVNA – pseudotyped lentivirus reporter single-round-of-infection neutralizing assay) similar to those measured in recipients of the 250 $\mu$ g dose in the 18 to 55 years or age subjects evaluated; and (iii) 2 injections of 100 $\mu$ g led to a lower incidence of reactogenicity than 2 injections of 250 $\mu$ g (These are published data. See dossier for references). The 50 $\mu$ g dose induced comparable humoral immune responses to the 100 $\mu$ g dose (data for the 50 $\mu$ g dose available until day 57). Also, intracellular cytokine stimulation assay was used to evaluate T-cell responses elicited by the mRNA-1273 vaccine. The 25  $\mu$ g, 100  $\mu$ g, and 250  $\mu$ g doses elicited CD4+ T-cell responses that upon stimulation by S-specific peptide pools were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. CD8+ T-cell responses to S-2P were detected at low levels after the second injection in the 100- $\mu$ g dose group. This Th1-dominant profile adds to the body of nonclinical data suggesting that mRNA-1273 is unlikely to lead to enhanced disease following natural exposure to SARS-CoV-2 (20-0003 Immunogenicity Summary Report [24 Sep 2020]).

In phase 2a (Study mRNA-1273-P201), participants who received 2 injections of either 50  $\mu$ g or 100  $\mu$ g of mRNA-1273 separated by 28 days developed both bAbs and nAbs against the SARS-CoV-2 virus, with geometric mean fold rises (GMFRs) > 20-fold (bAb as measured by the ELISA assay) and > 50-fold (nAbs as measured by the microneutralization [MN] assay), regardless of dose level. Applicant claims that data indicate that a two-dose schedule of either 50  $\mu$ g or 100  $\mu$ g of mRNA-1273 results in the rapid induction of functional antibodies against SARS-CoV-2 and support the selection of the 100  $\mu$ g dose for the Phase 3 clinical study.

No immune correlate of protection or any threshold for COVID-19 were reported.

### **3.3.4 Neutralization against SARS-CoV -2 Variants of Concern**

The emergence of SARS-CoV-2 variants with mutations in the spike protein, most recently circulating isolates from the United Kingdom (B.1.1.7) and Republic of South Africa (B.1.351), has led to lower neutralization from convalescent serum by pseudovirus neutralization (PsVN) assays and resistance to certain monoclonal antibodies. Here, using two orthogonal VSV and

lentivirus PsVN assays expressing spike variants of 20E (EU1), 20A.EU2, D614G-N439, mink cluster 5, B.1.1.7, and B.1.351 variants, applicant assessed the neutralizing capacity of sera from human subjects or non-human primates (NHPs) that received mRNA-1273. No significant impact on neutralization against the B.1.1.7 variant was detected in either case, however reduced neutralization was measured against the mutations present in B.1.351. Geometric mean titer (GMT) of human sera from clinical trial participants in VSV PsVN assay using D614G spike was 1/1852. VSV pseudoviruses with spike containing K417N-E484K-N501YD614G and full B.1.351 mutations resulted in 2.7 and 6.4-fold GMT reduction, respectively, when compared to the D614G VSV pseudovirus. Importantly, the VSV PsVN GMT of these human sera to the full B.1.351 spike variant was still 1/290, with all evaluated sera able to fully neutralize. Similarly, sera from NHPs immunized with 30 or 100µg of mRNA-1273 had VSV PsVN GMTs of ~ 1/323 or 1/404, respectively, against the full B.1.351 spike variant with a ~ 5 to 10-fold reduction compared to D614G. Individual mutations that are characteristic of the B.1.1.7 and B.1.351 variants had a similar impact on neutralization when tested in VSV or in lentivirus PsVN assays. Despite the observed decreases, the GMT of VSV PsVN titers in human vaccinee sera against the B.1.351 variant remained at ~1/300. Applicant claims that taken together, these data demonstrate reduced but still significant neutralization against the full B.1.351 variant following mRNA-1273 vaccination.

### **3.4 Risk Management Plan**

#### **3.4.1 Product description**

Acceptable

#### **3.4.2 Non clinical information**

Acceptable

### 3.4.3 Clinical information

a. Important identified risks:

<b>M</b>	<b>WHO</b>	<b>Comments</b>
Anaphylaxis	Anaphylaxis	Anaphylaxis is known to be possible with any injectable vaccine. Anaphylaxis can be upgraded to an identified risk based on the outcome of the assessment of the clinical data of ongoing studies or post-marketing information. A minimum period of 15-minutes of observation is recommended for each vaccinee after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions

b. Important potential risks:

<b>M</b>	<b>WHO</b>	<b>Comments</b>
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. Although available data have not identified VAED as a concern for mRNA-1273, the risk of VAED cannot be ruled out. VAED may be potentially serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention.
	Programmatic errors	It may be necessary to minimize this situation in advance under real use conditions. It will be monitored via routine pharmacovigilance activities and will be presented in each PBRER/PSUR

c. Missing information:

<b>M</b>	<b>WHO</b>	<b>Comments</b>
Use in pregnancy and while breast-feeding	Use during pregnancy and while breastfeeding	Pregnant and lactating women not included in the clinical trials
Use in immunocompromised subjects	Use in immunocompromised patients	This population was excluded from the clinical trials.
Use in frail subjects with unstable health conditions and co-morbidities (e.g.	Use in frail subjects with unstable health conditions and co-morbidities (e.g.	No safety data are available for frail individuals with unstable comorbidities

chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	
Interaction with other vaccines	Interaction with other vaccines	The safety, immunogenicity, and efficacy of this vaccine when co-administered with other vaccines (e.g. influenza) has not been evaluated.
	Interchangeability or sequential use with other vaccines	The evidence to support interchangeability or sequential use mRNA-1273 with other COVID-19 vaccines is still not available.
	Use in pediatric population <18 years of age	No efficacy data are available from participants ages <18 years and younger.
Use in subjects with autoimmune or inflammatory disorders	Use in patients with autoimmune or inflammatory disorders	There is limited information on the safety of mRNA-1273 in individuals with autoimmune or inflammatory disorders and a theoretical concern that the vaccine may exacerbate their underlying disease.
Long-term safety	Long-term safety	Long-term safety profile of mRNA-1273 is currently limited and it is recognized that further follow-up for all vaccines is required. Additional activities will be needed to obtain such information.
	Impact of the emergence of variants on vaccine efficacy/effectiveness and safety	Moderna should provide to WHO any data on new emerging variants particularly from vaccine breakthrough cases as soon as available, irrespective of source.

### 3.4.4 Pharmacovigilance Plan

Routine pharmacovigilance activities: Acceptable in general, adverse reaction reporting, and signal detection are in accordance with national and international Good Pharmacovigilance (GPV) guidelines.

The monitoring of adverse events (AEs) of interest should consider facial paralysis, Guillain-Barre Syndrome and neurological disorders, reactogenicity following vaccination and all serious adverse events, as included in routine pharmacovigilance in the submitted RMP.

This vaccine is available in several countries. The Center for Disease Control (CDC), USA, had conducted a descriptive analyses of safety data from the first month of vaccination (December 14, 2020–January 13, 2021). In this analysis they found that anaphylaxis was within a similar range

reported as for other vaccines, such as influenza or herpes zoster, although they described at least three limitations<sup>8</sup>:

- VAERS analyses are based on passive surveillance, and reporting biases are possible.
- Long-term Care Facility (LTCF) residents might have been undercounted because the search strategy for identifying LTCF residents relied primarily on vaccination facility documentation.
- V-safe is a voluntary self-enrollment program requiring smartphone access, and all vaccination locations might not have offered equal access to v-safe enrollment materials to vaccine recipients; therefore, information from v-safe might not be representative or generalizable.

A general concern exists about the low rate of collection of AEs in LMICs and the limited information from the clinical trials, because of the lack of adequate pharmacovigilance systems

Considering the limitation of reporting and the access to the tools to ensure the implementation of reporting, routine pharmacovigilance activities should be implemented in all WHO regions. The spontaneous reporting needs preferably be harmonized in most of the countries, as well as using the VigiBase platform.

Signal detection is proposed; Moderna plans to prepare a Summary Monthly Safety Report to submit to EMA in complement to the submission of routine periodic reports (Periodic Benefit-Risk Evaluation Reports). These monthly safety reports should be submitted to WHO containing the following:

1. Interval and cumulative number of reports (serious and non-serious), overall and by age groups and in special populations (e.g., pregnant women);
2. Total number of adverse event reports by country, WHO regions and globally;
3. Exposure data stratified by country including any available data on age groups, race, ethnicity, on indigenous populations and remote communities;
4. Changes to reference safety information in the interval;
5. Ongoing and closed signals in the interval;
6. List of adverse events of special interest including the Safety Platform for Emergency vACcines (SPEAC) list and RMP safety concerns (including the additional missing information): reports – numbers and relevant cases, including time-to-onset and observed/expected analyses;
7. Fatal reports – numbers and relevant cases, including observed/expected analyses;
8. Vaccination failure / lack of efficacy (including confirmed and suspected cases) reports and vaccination errors (categories according to preferred terms);

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<sup>8</sup> Gee J, Marquez P, Su J, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:283–288. DOI: [http://dx.doi.org/10.15585/mmwr.mm7008e3external icon](http://dx.doi.org/10.15585/mmwr.mm7008e3external%20icon)

9. Potential interaction with other vaccines/concomitant treatments-number and relevant cases;
10. Summary outcomes of some of the routine pharmacovigilance activities (as presented in the European Union (EU) RMP Part III and applied in the WHO context) for the purpose of rapid signal detection and communication activities. Summary of all ongoing registries and studies in the six-month scheduled PBRERs, unless a safety signal is identified that requires immediate regulatory action; and
11. Overall risk/benefit assessment.

For traceability, the applicant will create Traceability and Vaccination Reminder cards, printed cards to vaccinators, that may be completed at the time of vaccination when necessary for individual members states (only EU). The card will be also accessible electronically and through a QR code, on the applicant's website. The applicant is requested to implement appropriate methods to ensure adequate traceability in all regions. To date, unclear is whether these traceability enhancements will be applied to shipments through COVAX / outside the EU.

In addition, the applicant is requested to monitor and evaluate the impact of emerging SARS-CoV-2 variants of concern (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of COVID-19 vaccine Moderna and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

Moderna has considered non-interventional and interventional studies as additional pharmacovigilance activities, eight studies to identify and characterize the risks of the product. Four studies are interventional, including the three ongoing clinical trials and a study in immunocompromised subjects and four studies are noninterventional by design, including 3 for safety and 1 on effectiveness.

The additional pharmacovigilance activities described in the EU RMP are intended for implementation in the European Economic Area (EEA) US, and Canada only, six of them in the EU, one in EEA, and one in EEA, US and Canada. No additional pharmacovigilance activities are planned for other WHO regions.

The applicant proposes the following studies in post authorization development plan:

1. Phase I, Open Label, Dose Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults (ongoing report date 1 November 2022 in US). Safety concern addressed anaphylaxis and long-term safety data.
2. 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  $\geq 18$  Years Interventional (ongoing report date 18 November 2021 in US). Safety concern addressed anaphylaxis and long-term safety data.
3. 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 (ongoing report date 31 December 2021 in US). Safety concern



addressed anaphylaxis, Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) and long-term safety.

4. Study of the Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in immunocompromised Adults (planned report date 31 January 2023 in US and at least one site in Canada). Post-Authorization Safety of SARSCoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in Health Verity (planned report date 30 June 2023 in US).
5. Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S (planned report date 30 June 2025 in US).
6. Post-authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (planned report date 31 December 2023 in EU).
7. Moderna mRNA-1273 Observational pregnancy outcome study (planned report date 30 June 2024 in EU, Canada, US).

Use while breastfeeding is categorized as missing information. The applicant stated that this will be evaluated in the EU PASS. As the protocol does not clearly indicate how breastfeeding will be evaluated, the applicant should clarify how this missing information will be studied.

#### **3.4.5 Risk minimization activities**

The routine risk minimization activities are sufficient to manage the safety concerns of the medicinal product. Large scale mass vaccination may potentially introduce the risk of medication errors related to storage, handling, dosing, and administration errors associated with a multi-dose vial, and confusion with other COVID-19 vaccines. These potential medication errors are mitigated through the information in the SmPC. The applicant should implement these in all WHO regions and ensure the feasibility to measure these in all countries.

The applicant is encouraged to consider developing educational materials aimed at minimizing the risk of immunization errors (for example printed posters / guides), in addition to providing information in the SmPC in all WHO regions.

#### **Conclusion**

The RMP submitted by the applicant is adequate but does not address specific considerations related to LMIC. The applicant is therefore requested to generate the necessary information about safety and effectiveness in the different WHO regions for the purpose of EUL. These recommendations should be integrated in an updated version of the RMP specifically for WHO.

## 4 Outcome of review

### 4.1 Quality

Outcome of WHO review on programmatic aspects and suitability for LMICs highlighted the absence of VVM and preservative, the vaccine being only available in a multidose presentation. Nevertheless, the applicant provided assurance that temperature during shipping from manufacturer to country storage facilities was strictly and closely monitored. Absence of contamination of opened vials for up to 24 hours after opening at room temperature is provided as well. These matters were then considered as non-critical for the overall quality of the vaccine within its use in LMIC settings.

### 4.2 Clinical

This clinical assessment raised a limited number of queries and comments from the reviewers on clinical submitted evidence and issues related to the RMP. These have either been considered addressed by Moderna to the EMA CHMP list of questions or have been incorporated into the recommendations listed below and in the conclusion section of this document. The available data may be not be generalizable to populations in low and middle-income countries (LMIC) who have profiles that can impact on the efficacy of this vaccine (for example, ethnicity, concomitant infections and malnutrition)".

The TAG recommends that an EUL may be granted by WHO to COVID-19 Vaccine Moderna, provided that Moderna commits to meet the following conditions post-EUL:

1. The applicant should submit to WHO further interim analyses and the final clinical study reports of the ongoing studies (Study 101, 201 and 301) once they are completed.
2. Once available any relevant data coming from post EUL effectiveness studies should be shared with WHO, as this might change the benefit/risk profile of the vaccine.
3. The applicant is urged to continue the ongoing randomized controlled clinical trials as originally randomized and blinded for as long as possible, as randomized controlled trials remain the best way to collect unbiased data about the vaccine.
4. The RMP should also include/address the following:
  - Safety specifications:
    - Potential risks: add *programmatic error*
    - Missing information: add *use in paediatric population <18 years of age, and impact of the emergence of variants on vaccine efficacy/effectiveness and safety.*
    - *Interaction with other vaccines and interchangeability* should be considered separately from each other.
  - Pharmacovigilance plan
    - *The applicant is requested to submit the monthly reports mentioned in the RMP and the PSUR every 6 months. Moderna is requested to ensure that they receive available data from all routine pharmacovigilance activities in all WHO regions.*

- *The applicant is requested to conduct additional pharmacovigilance activities (non-interventional and interventional studies as those intended for implementation in the US, the EEA and Canada) in other WHO regions.*
- *A summary of the protocol should be part of an updated version of the RMP.*
- Risk minimization activities
  - *A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.*

In addition, in light of the recent evidence of vaccine escape of some emerging SARS-Cov-2 variants of concern, the applicant is requested to closely monitor and evaluate the impact of these emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of COVID-19 vaccine Moderna and to discuss with WHO in case of plans to make changes to the vaccine to address this issue. Although cross-neutralization data suggest that antibodies induced by the vaccine can still neutralize these variants, it may not reflect efficacy against infection by these variants in the absence of an established correlate of protection. Moderna should monitor vaccine effectiveness linked to emerging variants of concern based on long-term follow up on clinical trials 101, 201 and 301 and by collecting sequence data in primary data collection observational study from the places that the vaccine will be introduced, including in LMIC. In addition, Moderna should monitor emerging mutations in public data bases and should be supportive of establishment of international efforts for monitoring of emerging variants.

## **5 Technical considerations**

### **5.1 Vaccine characteristics**

#### **Qualitative and Quantitative composition**

COVID-19 mRNA Vaccine Moderna dispersion for injection

This is a multidose vial which contains 10 doses of 0.5 mL.

One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles).

Single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

*List of excipients*

Lipid SM-102 Cholesterol  
1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)  
1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG)  
Tromethamol  
Tromethamol hydrochloride  
Acetic acid  
Sodium acetate trihydrate Sucrose

*Pharmaceutical Form*

Dispersion for injection  
White to off white dispersion (pH: 7.0 – 8.0).

## **5.2 Special precautions for storage and handling proposed by the applicant**

### **Shelf life**

*Unopened vial:*

The vaccine can be stored 7 months at -25°C to -15°C.

The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days.

Once thawed the vaccine should not be re-frozen.

The unopened vaccine may be stored at 8°C to 25°C up to 12 hours after removal from refrigerated conditions.

Comment:

This sentence above should be deleted as this is not suitable with programmatic aspects for LMIC and is not aligned with WHO multidose vial policy.

*Punctured Vial:*

Chemical and physical in-use stability has been demonstrated for 6 hours at 2°C to 25°C after initial puncture.

The vaccine does not contain any preservation. Each individual vial should be used in one single vaccination session or within six hours of opening at specified temperature, whichever comes first, in line with the WHO Multi-Dose Vial Policy (MDVP).

Comment:

The section should be updated as follows:

“Storage After First Opening (puncture) of the Vaccine Vial

The vaccine contains no preservatives.

In-use stability of the vaccine has been demonstrated for 6 hours at 2°C to 8°C. The product should preferably be used immediately after first puncture of the vial; however, it can be stored between 2°C to 8°C for a maximum of 6 hours otherwise discarded at the end of the

immunization session, which ever come first, in compliance with the WHO Multidose Vial Policy.”

### **Special precautions for storage**

Store in a freezer frozen between -25°C to -15°C.

Store in the original carton to protect from light.

Do not store on dry ice or below -40°C.

For storage conditions after thawing and first opening.

### **Nature and contents of container**

5 ml dispersion in a vial (type 1 or type 1 equivalent glass) with a stopper (chlorobutyl rubber) and a flip-off plastic cap with seal (aluminium seal).

Each vial contains 10 doses of 0.5mL.

Pack size: 10 multidose vials

### **Special precautions for disposal and other handling**

The vaccine should be prepared and administered by a trained healthcare professional using aseptic techniques to ensure sterility of the dispersion.

The vaccine comes ready to use once thawed.

Do not shake or dilute. Swirl the vial gently after thawing and before each withdrawal.

COVID-19 Vaccine Moderna vials are multidose.

Ten (10) doses (of 0.5 mL each) can be withdrawn from each vial.

An additional overfill is included in each vial to ensure that 10 doses of 0.5 mL can be delivered.

## **5.3 Indication, warnings and contraindications**

### **Therapeutic indications**

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 use of this vaccine should be in accordance with official recommendations.

### **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## **Special warnings and precautions for use**

### Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

### Hypersensitivity and anaphylaxis

Anaphylaxis has been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. The second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine Moderna.

### Anxiety-related reactions

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

### Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

### Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

### *Immunocompromised individuals*

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COVID-19 Vaccine Moderna may be lower in immunosuppressed individuals.

### *Duration of protection*

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

### *Limitations of vaccine effectiveness*

Individuals may not be fully protected until 14 days after their second dose. As with all vaccines, vaccination with COVID-19 Vaccine Moderna may not protect all vaccine recipients.

## **5.4 Posology and method of administration**

### Posology

#### *Individuals 18 years of age and older*

COVID-19 Vaccine Moderna is administered as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose (see sections 4.4 and 5.1).

No data are available on the interchangeability of COVID-19 Vaccine Moderna with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of COVID-19 Vaccine Moderna should receive the second dose of COVID-19 Vaccine Moderna to complete the vaccination course.

#### *Paediatric population*

The safety and efficacy of COVID-19 Vaccine Moderna in children and adolescents less than 18 years of age have not yet been established. No data are available.

#### *Elderly population*

No dosage adjustment is required in elderly individuals  $\geq 65$  years of age.

### Method of administration

The vaccine should be administered intramuscularly. The preferred site is the deltoid muscle of the upper arm.

Do not administer this vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products. For precautions to be taken before administering the vaccine, For instructions regarding thawing, handling and disposal of the vaccine, see section 5.2.

## **5.5 Fertility, pregnancy and lactation**

### Pregnancy

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.

### Breast-feeding

At present not enough data is available whether COVID-19 Vaccine Moderna is excreted in human milk.

## **5.6 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

Concomitant administration of COVID-19 Vaccine Moderna with other vaccines has not been studied.

## **5.7 Effects on ability to drive and use machines**

COVID-19 Vaccine Moderna has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under ‘undesirable effect’ below may temporarily affect the ability to drive or use machines

## **5.8 Safety profile**

### Summary of the safety profile

The safety of COVID-19 Vaccine Moderna was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of COVID-19 Vaccine Moderna (n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older.

The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

Overall, there was a higher incidence of some adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1.

### Tabulated list of adverse reactions from clinical studies

The safety profile presented below is based on data generated in a placebo- controlled clinical study on 30,351 adults  $\geq$  18 years of age.

Adverse reactions reported are listed according to the following frequency convention:

Very common ( $\geq$ 1/10)

Common ( $\geq$ 1/100 to <1/10)

Uncommon ( $\geq$ 1/1,000 to <1/100)



Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Lymphadenopathy*
Immune system disorders	Not known	Anaphylaxis Hypersensitivity
Nervous system disorders	Very common	Headache
	Rare	Acute peripheral facial paralysis**
Gastrointestinal disorders	Very common	Nausea/vomiting
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Fatigue Chills Pyrexia Injection site swelling
	Common	Injection site erythema, Injection site urticaria, Injection site rash
	Uncommon	Injection site pruritus
	Rare	Facial swelling***

\*Lymphadenopathy was captured as axillary lymphadenopathy on the same side as the injection site.

\*\*Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the COVID-19 Vaccine Moderna group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2.

\*\*\*There were two serious adverse events of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination

The reactogenicity and safety profile in 343 subjects receiving COVID-19 Vaccine Moderna, that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. This allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V and include batch/Lot number if available.

## **5.9 Overdose**

No case of overdose has been reported.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is recommended.

### **Pharmacodynamic properties**

#### *Clinical efficacy*

The primary efficacy analysis population (referred to as the Per Protocol Set or PPS), included 28,207 subjects who received either COVID-19 Vaccine Moderna (n=14,134) or placebo (n=14,073) and had a negative baseline SARS-CoV-2 status. The PPS study population included 47.4% female, 52.6% male, 79.5% White, 9.7% African American, 4.6% Asian, and 6.2% other. 19.7% of participants identified as Hispanic or Latino. The median age of subjects was 53 years (range 18-94).

Among all subjects in the PPS, no cases of severe COVID-19 were reported in the vaccine group compared with 30 of 185 (16%) cases reported in the placebo group. Of the 30 participants with severe disease, 9 were hospitalised, 2 of which were admitted to an intensive care unit. The majority of the remaining severe cases fulfilled only the oxygen saturation (SpO<sub>2</sub>) criterion for severe disease ( $\leq 93\%$  on room air).

The vaccine efficacy of COVID-19 Vaccine Moderna to prevent COVID-19, regardless of prior SARS-CoV-2 infection (determined by baseline serology and nasopharyngeal swab sample testing) from 14 days after Dose 2 was 93.6% (95% confidence interval 88.5, 96.4%).

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

#### *Elderly population*

COVID-19 Vaccine Moderna was assessed in individuals 18 years of age and older, including 3,768 subjects 65 years of age and older. The efficacy of COVID-19 Vaccine Moderna was consistent between elderly ( $\geq 65$  years) and younger adult subjects (18-64 years).

#### *Pediatric population*

No data is available in children under 18 years of age.

### **Pharmacokinetic properties**

Not applicable.

## **Pharmaceutical Particulars**

### *Incompatibilities*

This medicinal product must not be mixed with other medicinal products or diluted.

## **6 Monitoring of performance of the vaccine in the field**

The Applicant proposes eight studies to further evaluate safety and effectiveness, and to address missing information in the post marketing setting. There are four interventional studies and four non-interventional studies. Seven of these studies have safety as outcome, four will generate immunogenicity data, and interesting only one is specifically stated to generate effectiveness data. All these studies will be conducted in Europe or USA.

None of the studies submitted in this application were conducted in LMIC. Therefore, the applicant should propose studies in countries representative of LMIC.

### **6.1 Vaccine efficacy/effectiveness and safety Monitoring**

In addition to the collection and monitoring of spontaneous reports and signal detection from healthcare professionals and vaccinees, Moderna has proposed the following studies in post authorization development plan:

1. Phase I, Open Label, Dose Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults (ongoing report date 1 November 2022 in US). Safety concern addressed anaphylaxis and long-term safety data.
2. 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  $\geq 18$  Years Interventional (ongoing report date 18 November 2021 in US). Safety concern addressed anaphylaxis and long-term safety data.
3. 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 (ongoing report date 31 December 2021 in US). Safety concern addressed anaphylaxis, Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD) and long-term safety.
4. Study of the Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in immunocompromised Adults (planned report date 31 January 2023 in US).
5. Post-Authorization Safety of SARSCoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in Health Verity (planned report date 30 June 2023 in US).

6. Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S (planned report date 30 June 2025 in US).
7. Post-authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (planned report date 31 December 2023 in EU).
8. Moderna mRNA-1273 Observational pregnancy outcome study (planned report date 30 June 2024 in EU, Canada, US).

## **6.2 Programmatic aspects**

### Vaccine vial monitor

No VVM was claimed by the applicant (see next paragraph).

### Programmatic suitability

Self-assessment against PSPQ criteria has been provided by the applicant and one mandatory and one critical criterion are not compliant as follows:

- **MANDATORY:** Though required, the multidose vaccine is not preserved. The applicant has analysed the effect of several preservatives (m-cresol, phenol, and methylparaben) on the biophysical parameters like RNA encapsulation, polydispersity and particle size. Results showed an increase of particle size and polydispersity index and a decrease in % RNA encapsulation in the presence of these preservatives. The effects were enhanced after freezing. These results demonstrate the incompatibility of the drug product with common anti-microbial preservatives due to their ability to partition into membranes and analogously, the nanoparticle. Additionally, in-use stability was demonstrated with a microbial hold time challenge study over a 24-hour timeframe. Results demonstrated that growth of inoculated microorganisms is hindered for up to 24 hours at room temperature;
- **CRITICAL:** As stated above, no VVM is claimed by the applicant as the candidate vaccine does not meet VVM2 profile. During shipment, temperature is controlled on three levels. A primary control is done via Sensitech temperature data loggers for temperature control and monitoring. These data loggers are placed on the pallet or in v-Q-Tec containers. Secondary and tertiary controls are done in the truck, which is equipped with bi-temperature, double-deck equipment, ADR, and qualified with active temperature control from -25°C to -15°C according to GDP standards. The alarm is programmed with the following thresholds:
  - high limit (-15°C)
  - low limit (-50°C)
  - triggered when temperature exceeds set limits.

Data sampling interval is set to 5 minutes and the startup delay to 0 minutes. The alarm is single exposure. Temperatures are read by the recipient at reception of the delivery. In case of any excursion outside recommended temperature and time parameters, the recipient should contact a Moderna QA specialist by using a specific email address.

### International shipping

Procedure and validation for international shipping are provided and meet requirements of WHO guidelines for the international shipment of vaccines.

## **7 SAGE recommendations**

The Strategic Advisory Group of Experts on Immunization (SAGE) issues recommendations for use on vaccines of public health importance, including investigational products considered for use during a public health emergency. A SAGE working group on COVID-19 vaccination was set up in spring 2020 to develop the basis for recommendations once vaccines become authorized. Based on advice provided by SAGE, the initial use of vaccine is prioritized for health workers with high and very high risk of exposure and older adults, with the intention of preserving the most essential services and reducing mortality and morbidity from disease. Below is their recommendation:

### **Goal and strategy for the use of the Moderna mRNA-1273 vaccine against COVID-19**

The COVID-19 pandemic has caused significant morbidity and mortality throughout the world, as well as major social, educational and economic disruptions. There is an urgent global need for effective and safe vaccines and to make them available at scale and equitably across all countries.

The mRNA-1273 vaccine against COVID-19 developed by Moderna (Moderna COVID-19 vaccine) has been shown to have an efficacy of 94.1%, based on a median follow-up of two months. High efficacy was maintained across all age groups (above 18 years) and was not affected by sex or ethnicity. The data reviewed by WHO at this time support the conclusion that the known and potential benefits of mRNA-1273 outweigh the known and potential risks. As sufficient vaccine supply will not be immediately available to immunize all who could benefit from it, countries are recommended to use the WHO Prioritization Roadmap [4] and the WHO Values Framework (5) as guidance for their prioritization of target groups. When vaccine supplies are very limited (stage I in the WHO Prioritization Roadmap), in settings with community transmission, the Roadmap recommends that priority be given initially to health workers at high risk and older people with and without comorbidities. Protecting high-risk health workers has a threefold purpose: (i) to protect the individual health workers; (ii) to protect critical essential services during the COVID-19 pandemic, and (iii) to prevent onward transmission to vulnerable people. Protecting older people will have the greatest public health impact in terms of reducing the number of deaths. As more vaccine becomes available, additional priority groups should be vaccinated as outlined in the WHO Prioritization Roadmap [4], taking into account national epidemiological data and other relevant considerations.

Further details of the SAGE recommendation are seen in the following link:

<https://www.who.int/publications/i/item/interim-recommendations-for-use-of-the-moderna-mrna-1273-vaccine-against-covid-19>

## **8 Regulatory oversight**

The EMA is the regulatory body that has granted the conditional marketing authorization to COVID-19 Vaccine Moderna on 6<sup>th</sup> January 2021. WHO has followed up the assessment procedure and rely on EMA's decisions. Therefore, EMA is the regulatory agency of record for this vaccine as per the WHO EUL procedure. The WHO Vaccine Prequalification Team will continue to rely on the regulatory oversight of EMA and will continue fostering participation of WHO experts in EMA's regulatory process.

## **9 Benefit/Risk Assessment**

According to WHO, the COVID-19 pandemic has caused, as of 24 April 2021, over 141 million cases of the disease and over 3.1 million deaths<sup>9</sup>. COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population and has become a major cause of morbidity and mortality given the inexistence of a vaccine and of proved specific treatment. SARS-CoV-2 transmission continues to occur with an increasing rate. Hopes that herd immunity be achieved by natural infection have not been borne out because a large proportion of the population remains seronegative, which supports the hypothesis that they are susceptible to the virus. This scenario has been complicated by the recognition of new SARS-CoV-2 variants, whose increased transmissibility and evidence of immune escape mutations has caused concern. The development of effective and safe vaccines and their deployment worldwide may decrease the spread of the disease and its morbidity and mortality.

The primary efficacy objective of Study 301 was met, with the VE of mRNA-1273 to prevent symptomatic COVID-19 disease observed to be 94.1% after the prespecified endpoint of more than 151 cases accrued. The vaccine was also observed to be efficacious in preventing severe COVID-19 and in preventing COVID-19 regardless of prior SARS-CoV-2 infection in key secondary analyses of efficacy. The population in Study 301 included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID 19. In an exploratory subgroup analysis, the estimates of efficacy of mRNA-1273 against symptomatic COVID-19 disease were comparable across the demographic groups analyzed.

The immunogenicity of mRNA-1273 was evaluated in Studies 101 and 201 and is supportive of the efficacy of the vaccine to prevent COVID-19 as demonstrated in the pivotal Phase 3 study. In Study 101, doses of 100 µg or higher generated the highest titers of bAb or nAb, and the 100 µg dose was observed to have a better tolerability profile than the 250 µg dose in subjects 18-55 years of age. Together, this was the basis for selecting the 100 µg dose for use in the pivotal Phase 3 study. The antibody levels after 2 injections of mRNA-1273 exceeded those in convalescent sera. Similar responses were observed among all groups for the 100-µg dose and responses were detected in all participants through Day 119. Day 119 responses declined relative to Day 57 but

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<sup>9</sup> <https://covid19.who.int/>

remained comparable to responses in convalescent serum. The immunogenicity results from the 100 µg dose group in Study 201 confirmed the robust immunogenicity results observed in the Phase 1 study.

The safety assessment of mRNA-1273 is largely based on data from the pivotal Phase 3 study using 11 Nov 2020 and 25 Nov 2020 data snapshots. Solicited local and systemic ARs were more common in participants who received mRNA-1273 compared with placebo, and systemic ARs were more common after the second injection. The majority of these reactions occurred within the first 1 to 2 days after administration of mRNA-1273 and persisted for a median of 2 to 3 days or less. The overall incidences of unsolicited AEs reported up to 28 days after vaccination and SAEs reported throughout the entire study were similar in participants who received mRNA-1273 or placebo. A total of 13 deaths occurred in Study 301, including a single death due to COVID-19 in the placebo group, with 6 deaths occurring in the mRNA-1273 group and 7 deaths occurring in the placebo group. None were considered related to study vaccine. Causes of death were not unexpected given the population enrolled in the study. There were fewer cases of severe COVID-19 or COVID-19 in participants who received mRNA-1273 compared with placebo, and thus no evidence of vaccine-associated ERD has been observed. There was no notable difference in the incidence of solicited AEs based on SARSCoV-2 serology at baseline.

Overall, there is an urgent public health need for rapid development of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease. Based on the results from the pivotal Phase 3 study, mRNA-1273 prevents COVID-19 and severe COVID-19 with an observed VE of 94.1% and 100%, respectively. The efficacy of mRNA-1273 to prevent COVID-19 and severe COVID-19 demonstrated in the trial at the time of our primary analysis also mitigates concern about the risk of enhanced disease during the 28-day period following two injections of vaccine. The clinical benefit of mRNA-1273 was consistent in older and younger adults, with or without risk factors for complications of COVID-19, in males and females, and in participants who were White as compared to those from communities of color. The results from the pivotal efficacy trial are supported by the substantial immune response observed in the Phase 1 and 2 trials that was consistent across age groups and persisted over 3 months after the second injection of mRNA-1273. mRNA-1273 produced a robust immune response both in terms of bAbs and nAbs and induced CD4<sup>+</sup> T-cells with a Th-1 dominant phenotype.

After the administration of mRNA-1273 to more than 15,693 adults across all 3 clinical studies to date, there have been no emergent safety concerns, and the AE profile has been observed to be largely characterized by mild to moderate reactogenicity of a median duration of 2-3 days.

Vaccination with mRNA-1273 results in transient local injection site and systemic reactions. The incidence of unsolicited AEs and AEs leading to discontinuation of study vaccine were similar between the treatment groups. Less common but clinically significant AEs, such as SAE and deaths, were reported at similar rates for placebo and vaccine recipients. The overall safety profile observed in the Phase 3 trial was generally consistent with the safety profile observed to date in the Phase 1 and 2 studies.

In conclusion, the data presented in this submission show that mRNA-1273 administered as two 100 µg injections 28 days apart is an effective vaccine with an acceptable safety profile for the prevention of symptomatic COVID-19 in adults 18 years of age and older. Considering the ongoing public health emergency due to SARS-CoV-2, the lack of approved preventative vaccines, as well as the available safety and efficacy data from the three clinical studies presented herein, it is considered that the known and potential benefits of the product outweigh the known and potential risks for mRNA-1273.

## **10 Conclusion**

Considering the public health need to halt COVID-19 morbidity and mortality and to continue immunizing the world's population to the largest extent possible, the introduction of new vaccines that would protect the population from disease and, whenever possible, from SARS-CoV-2 infection is needed.

Based on assessment of the available evidence, the TAG is of the opinion that sufficient data is available on COVID-19 vaccine Moderna for an EUL recommendation, subject to the post-listing commitments as indicated in the below sections.

Should new evidence become available that change the benefit-risk assessment (e.g. as a result of the new variants) the EUL recommendation could be reconsidered.

### **10.1 Quality (CMC) perspective**

Based on the outcome of the review of the quality data provided by the applicant, the listing for emergency use of the Covid-19 Vaccine Moderna can be granted. However, the following specific information must be provided as post-listing commitments:

1. Agreement to modify the shelf life section of the product insert to the WHO agreed version, dated 29 April 2021;
2. Clarification on the commitment to providing a Lot Summary Protocol (and samples where applicable) to the NRA of any importing country requesting these;
3. Assurance that all CHMP obligations will be implemented and conveyed to WHO as they become available. Furthermore, progress on all CHMP recommendations should also be conveyed to WHO;
4. Clarification on the requirements whether containers have to be returned to Moderna once the vaccines are delivered in the country (reverse-cold chain logistics) and if yes, what will be the chain of custody for these containers;
5. Update on change in production scale or addition of new manufacturing sites, if applicable.



## 10.2 Clinical perspective

From the clinical point of review the TAG recommended that an EUL may be granted by WHO to COVID-19 Vaccine Moderna provided that Moderna Biotech commits to provide the following requested information post-EUL as soon as such information becomes available:

1. The applicant should submit to WHO further interim analyses and the final clinical study reports of the ongoing studies (study 101, study 201 and study 301) once they are completed.
2. Once available any relevant data coming from post EUL effectiveness studies should be shared with WHO, as this might change the benefit/risk profile of the vaccine.
3. The applicant should investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy
4. of the vaccine against disease caused by emerging SARS-CoV-2 variants of concern (such as B.1.1.7, B.1.351 and P.1). This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant.
5. The applicant is urged to encourage participants, especially those not prioritized for vaccine access, to remain in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine.
6. The RMP should include/address the following:
  - Safety specifications:
    - Potential risks: text should be aligned with the table in section 3.4.3 and add *programmatic error*.
    - Missing information: text should be aligned with the table in section 3.4.3 and add *use in paediatric population <18 years of age, and impact of the emergence of variants on vaccine efficacy/effectiveness and safety*.
    - *Interaction with other vaccines and interchangeability* should be considered separately from each other.
  - Pharmacovigilance plan
    - *The applicant is requested to submit the monthly reports mentioned in the RMP and the PSUR every 6 months. Moderna is requested to ensure that they receive available data from all routine pharmacovigilance activities in all WHO regions.*
    - *The applicant is requested to conduct additional pharmacovigilance activities (non-interventional and interventional studies as those intended for implementation in the US, the EEA and Canada) in other WHO regions, representative of LMIC.*
    - *A summary of the protocols planned should be part of an updated version of the RMP.*
  - Risk minimization activities
    - *A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.*