11 March 2021
EMA/15689/2021 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

COVID-19 Vaccine Moderna

Common name: COVID-19 mRNA Vaccine (nucleoside-modified)

Procedure No. EMEA/H/C/005791/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] *Correction dated 11 March 2021 to clarify ERA statment

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AC adjudication committee

AE adverse event

AESI adverse events of special interest

ALP alkaline phosphatase

AR adverse reaction

ARDS acute respiratory distress syndrome

AST aspartate aminotransferase

bAb binding antibody

BAL bronchoalveolar lavage

BLA Biologics License Application

BWP EMA Biologics Working Party

CBER Center for Biologics Evaluation and Research

CCIT Container Closure Integrity Testing

CDC Centers for Disease Control and Prevention

CHMP Committee for Medicinal Products for Human Use

CI confidence interval

CIPC critical in-process control

CMA conditional marketing authorisation

CMV cytomegalovirus

CNS central nervous system

CoA Certificates of Analysis

COPD chronic obstructive pulmonary disease

CoV coronavirus

COVID-19 disease caused by the novel 2019 coronavirus

CPP critical process parameter

CQA Critical Quality Attributes

CSR clinical study report

CTD common technical document

DBL database lock

DMID Division of Microbiology and Infectious Diseases

DNA deoxyribonucleic acid

DSMB data safety monitoring board

DSPC 1,2-distearoyl-sn-glycero-3-phosphocholine

ECDC European Centre for Disease Prevention and Control

ECMO extracorporeal membrane oxygenation

eCRF electronic case report form

eCTD electronic common technical document

ELISA enzyme-linked immunosorbent assay

EMA European Medicines Agency

EOS eosinophil

ETF COVID-19 EMA pandemic Task Force

EU European Union

ERD enhanced respiratory disease

EUA Emergency Use Authorisation

EURD European reference date

FAS Full Analysis Set

FDA Food and Drug Administration

FD&C Federal Food, Drug, and Cosmetic

FMEA failure mode and effects analysis

GCP good clinical practice

GLP good laboratory practice

GM geometric mean

GMFR geometric mean fold-rise

GMP good manufacturing practice

GMT geometric mean titer

hMPV human metapneumovirus

HIV human immunodeficiency virus

HR hazard ratio

IA interim analysis

IA#1 interim analysis #1

IBD international birth date

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICS intracellular cytokine staining

ID50 50% inhibitory dilution

IgG immunoglobulin G

IM intramuscular

IN intranasal

IND Investigational New Drug (application)

INN international non-proprietary name

IP investigational product

IRT interactive response technology

IT intratracheally

ITT intent-to-treat

IVT *in vitro* transcription

LL lower limit

LLOQ lower limit of quantification

LOD limit of detection

LNP lipid nanoparticle

LOD limit of detection

LSS lipid stock solution

LTCF long-term care facilities

MA marketing authorisation

MAA marketing authorisation application

MAAE medically attended adverse event

MAH marketing authorisation holder

MCB master cell bank

MERS-CoV Middle East respiratory syndrome coronavirus

mITT modified intent-to-treat

MO major objection

MN microneutralisation

MN50 50% microneutralisation

mRNA messenger RNA

MRL Minimum Release Limit

MS member state

nAb neutralising antibody

NE not evaluable

NIAID National Institute of Allergy and Infectious Diseases

NHP Nonhuman primates

NP nasopharyngeal

NTP nucleoside triphosphates

OCABR Official Control Authority Batch Release

OMCL Official Medicines Control Laboratory

PaO2/FiO2 arterial oxygen partial pressure to fractional inspired oxygen

PASS post-authorisation safety study

PBMC peripheral blood mononuclear cell

PBS phosphate-buffered saline

PEG Polyethylene glycol

PEG2000-DMG 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000

Ph. Eur. Pharmacopoeia Europaea

PhV pharmacovigilance

PI product information

PIV3 parainfluenza virus type 3

PL package leaflet

PP per-protocol

PPQ process performance qualification

PRNT plaque-reduction neutralisation test

PSUR periodic safety update report

PsVNA pseudotyped lentivirus reporter single-round-of-infection neutralisation assay

PsVNT50 50% pseudotyped lentivirus reporter test

PT preferred term

QR quick response

RBD receptor binding domain

REC recommendation (EMA Post-Authorisation Measure - PAM)

RMP risk management plan

RNA ribonucleic acid

RT-PCR reverse transcription polymerase chain reaction

S-2P spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain

SAE serious adverse event

SAP statistical analysis plan

SARS-CoV severe acute respiratory syndrome coronavirus

SARS-CoV-2 2019 novel coronavirus

SM-102 heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate

SMC safety monitoring committee

SmPC summary of product characteristics

SMQ Standardised MedDRA Query

SOC system organ class

sSAP supplementary statistical analysis plan

TEAE treatment-emergent adverse event

Th1 T-helper 1

Th2 T-helper 2

Tris- HCl tris(hydroxymethyl)aminomethane-hydrochloride; VRC = Vaccine Research Centre

TSE transmissible spongiform encephalopathy

ULOQ upper limit of quantification

US United States

USP United States Pharmacopeia

UTR untranslated region

UV ultraviolet

VAED vaccine-induced enhancement of disease

VAERD vaccine-associated enhanced respiratory disease

VE vaccine efficacy

WCB working cell bank

WHO World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Moderna Biotech Spain, S. L. submitted on 30 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for COVID-19 Vaccine Moderna, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2020.

The applicant applied for the following indication: '*active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 18 years of age and older*'.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0481/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0481/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance CX-024414 (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) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
15 October 2020	EMEA/H/SA/4687/1/2020/III	Dr Anders Lignell, Dr Hans Ovelgönne

The Scientific Advice pertained to the following quality/non-clinical and clinical aspects:

- Label for the preservative-free multi-dose vial
- Manufacturing control and absence of clinical lot consistency study
- Definition of the NTPs, enzymes and linearised plasmid DNA as raw materials
- Proposal to submit batch release data only to an Official medicines control laboratory (OMCL) for fulfilment of Official control authority batch release (OCABR) requirements
- Approach to validation of process versions / scales and validation of different sites
- Potency testing of mRNA-1273
- Battery of preclinical studies conducted with mRNA-1273, supported by platform data on mRNA vaccines formulated in the same LNP formulation
- Strategy to address the theoretical concern of vaccine induced enhanced respiratory disease
- Data package to support MAA, including requirements for vaccine efficacy, and safety database
- Submission at the time of first or second interim analysis of the phase 3 study, and criteria for success
- Regulatory pathways to accelerate the availability of mRNA-1273 vaccine

Compliance with Scientific Advice

The applicant sought advice regarding the label for the preservative-free multi-dose vial, manufacturing control and absence of a clinical lot consistency study, definition of the NTPs, enzymes and linearised plasmid DNA as raw materials, the approach to validation of process versions / scales and validation of different sites, and potency testing of mRNA-1273. In the main, the advice was adopted by the applicant. Concerning the label, a statement on microbial contamination must be added in line with Guideline CPMP/QWP/159/96 corr for unpreserved sterile products. The extractable volume is tested at release; the procedures ensures that 10 doses can be withdrawn. Inclusion of additional release attributes has been recommended. Except for numerical acceptance ranges for product related impurities, this has been further discussed during the procedure and adequately addressed by the applicant. The definitions of raw /starting materials were implemented as requested. Concerning process validation and comparability the applicant followed the advice (several aspects were no longer relevant as the applicant changed the strategy). Concerning potency the applicant sufficiently justified the chosen approach for potency testing. Based on the provided data the applicant's approach was considered acceptable.

As regards the theoretical concern of COVID-19 vaccines to induce enhanced respiratory disease (ERD) the CHMP concluded that there are currently no animal models to predict the risk of ERD. The strategy proposed by the applicant to evaluate ERD in the ongoing phase 3 study by monitoring for early evidence of a potential elevated rate of COVID-19 or severe COVID-19 in the mRNA-1273 group compared to the placebo group was considered reasonable.

In addition, advice was given on the data package needed to support MAA, including requirements for vaccine efficacy, and safety database, the submission at the time of first or second interim analysis of

the phase 3 study, and criteria for success as well as regulatory pathways to accelerate the availability of mRNA-1273 vaccine.

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application:

The ETF endorsed the Scientific Advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure.

Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP in preparation of the written adoption rolling review procedures. The corresponding interim opinions were subsequently adopted by the CHMP.

For the exact steps taken at ETF, please refer to section 1.2.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Andrea Laslop

The ETF endorsed the Scientific Advice letter on	8 October 2020
The ETF agreed the request for early Rapporteur appointment on	13 October 2020
The CHMP confirmed eligibility to the centralised procedure on	15 October 2020
The ETF recommended to start the rolling review procedure on	12 November 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	15 November 2020
The procedure (Rolling Review 1) started on	16 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	2 December 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	9 December 2020
ETF discussions took place on	10 December 2020
Adoption of first Interim Opinion (Rolling Review 1) via 24 hour written procedure on	14 December 2020
The application for the marketing authorisation was formally received by the EMA on	30 November 2020
The procedure started on	1 December 2020
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: ModernaTX, Inc., One Moderna Way, Norwood, MA 02062 (USA).	4 December 2020

BWP extraordinary adobe meeting was held on	30 December 2020
An Oral Explanation was held at BWP on	30 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	31 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	31 December 2020
ETF discussions took place on	31 December 2020
BWP extraordinary meeting was held on	4 January 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary PRAC meeting on	4 January 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to COVID-19 Vaccine Moderna during an extraordinary CHMP meeting on	6 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

End of December 2019, WHO was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020 the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then the virus has spread globally and on 30 January 2020 the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

According to ECDC, histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

2.1.2. Epidemiology and risk factors

As of 27 December 2020, there have been over 80 million confirmed cases of SARS-CoV-2 infection globally with approximately 1.8 million deaths resulting from infection and subsequent coronavirus disease (COVID-19). The majority of infections result in asymptomatic or mild disease with full recovery.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities.

Increasing age is another risk factor for severe disease and death due to COVID-19. European countries that have established surveillance systems in long-term care facilities (LTCF) have reported that 5-6% of all current LTCF residents died of COVID-19, and that LTCF residents accounted for up to 72% of all COVID-19 related deaths.

Individuals with high risk of exposure to SARS-CoV-2 due to occupation include healthcare and frontline workers.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus, with a single linear RNA segment. It is enveloped and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. After infection individuals remain infectious for up to two weeks and can spread the virus even if they do not show symptoms.

The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS) presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke.

2.1.4. Clinical presentation and diagnosis

The severity of COVID-19 varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical diseases may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks. Prolonged prothrombin time and elevated C-reactive protein levels on admission to the hospital are associated with severe course of COVID-19 and with a transfer to ICU.

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone and statins, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy, (e.g. remdesivir), antibodies administered from convalescent plasma and hyperimmune immunoglobulins. These therapies have shown variable and limited impact on the severity and duration of illness, with different efficacies depending on the stage of illness and manifestations of disease.

While care for individuals with COVID-19 has improved with clinical experience, there remains an urgent and unmet medical need for a vaccine able to prevent or mitigate COVID-19 infections during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. Although a first vaccine for prevention of COVID-19 was approved recently there is still an important need for additional vaccines to meet global demands.

About the product

COVID-19 Vaccine Moderna (also referred to in this report as mRNA-1273) is a vaccine developed for prevention of COVID-19 caused by SARS-CoV-2. It is based on nucleoside-modified mRNA encoding for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. The mRNA is encapsulated in lipid nanoparticles (LNP).

The spike protein mediates attachment and entry of the virus into host cells (by binding to the angiotensin-converting enzyme 2 receptor followed by membrane fusion), making it a primary target for neutralizing antibodies that prevent infection.

Upon delivery and uptake by body cells the mRNA is translated in the cytosol and SARS-CoV-2 spike protein is generated by the host cell machinery. The spike protein is presented and elicits an adaptive humoral and cellular immune response. Neutralising antibodies are directed against it and hence it is considered a relevant target antigen for vaccine development.

COVID-19 Vaccine Moderna is administered intramuscularly in two 100 µg doses given 28 days apart. The intended indication is for 'active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals 18 years of age and older'.

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.

According to the applicant, there is a positive benefit-risk balance for in the active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals 18 years of age and older. This is based on evidence from the pivotal study P301, a Phase 3, randomised, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of COVID-19 Vaccine Moderna in individuals 18 years of age and older. The applicant stated that the available data to date from the first interim analysis indicate that its vaccine was 94.5 percent effective in preventing COVID-19, 100 percent effective in preventing severe COVID-19 and had no serious side effects, showing that the vaccine prevented mild and severe forms of COVID-19.

- It is likely that the applicant will be able to provide comprehensive data.

The applicant intends to continue the ongoing pivotal phase 3 study P301 with all participants to be followed until 24 months after the second dose to obtain long-term data and to ensure sufficient follow-up to support a standard marketing authorisation. Following the Emergency Use Authorisation granted by the FDA on 18 December 2020, the sponsor will offer to all participants in the placebo arm to receive the COVID-19 Vaccine Moderna. In all cases, it is intended to follow participants up to the original planned 24 months post-vaccination, regardless of any participants opting to crossover from placebo to active vaccination. The safety and effectiveness of COVID-19 Vaccine Moderna in patients <18 years of age have not been established for this application. 3 studies in paediatric subjects are planned as laid down in the paediatric investigation plan. An observational pregnancy outcome study is also planned in the EU. A Post-Approval Active Surveillance Safety Study to Monitor Real-World Safety of COVID-19 Vaccine Moderna will be conducted in the EU to provide additional evaluation of AESI and emerging validated safety signals in European populations. The applicant will also conduct an interventional study to evaluate safety and immunogenicity in immunocompromised subjects, and conduct non-interventional studies to provide additional evaluation of AESI and emerging validated

safety signals, and to evaluate the real-world effectiveness and long-term effectiveness of mRNA-1273 in preventing COVID-19 and severe COVID-19 disease.

- Unmet medical needs will be addressed.

According to the applicant, as there is no approved other vaccine in the EU or successful COVID-19 therapy available in the EU, an unmet medical need is existing and is likely to be addressed by this vaccine in view of the high level of protection observed in the pivotal clinical trial.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

According to the applicant, the efficacy of COVID-19 Vaccine Moderna to prevent COVID-19 was demonstrated in the first interim analysis. The observed vaccine efficacy in each subgroup as defined by age, baseline characteristics, risk for severe COVID-19 was overall consistent with the effectiveness of COVID-19 Vaccine Moderna to protect vaccinees against the disease.

2.2. Quality aspects

2.2.1. Introduction

The finished product (also referred to in this report as mRNA-1273) is presented as a dispersion for injection containing 100 µg/0.5 mL dose of single-stranded, 5' capped mRNA encoding full length SARS-CoV-2 Spike (S) protein as the active substance (referred to by the applicant as CX-024414), which is embedded in lipid nanoparticles (LNPs).

Other ingredients are: Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102), cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG), tromethamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose and water for injections. The product is available in a glass vial (type I or equivalent) sealed with a chlorobutyl rubber stopper and an aluminium seal (each vial contains sufficient volume to extract 10 doses of 0.5 mL each). Vials are packaged in a carton containing a total of ten multi-dose vials per carton.

The dossier is based on data from US manufacturing sites (mainly ModernaTX, Inc. Norwood and Lonza Biologics, Portsmouth) with appropriate comparability, transfer and validation data for EU manufacturing operations.

The CTD Module 3 dossier structure is not fully in line with EU requirements as the information on the lipid excipients and manufacture of the LNP is being placed in 3.2.S rather than 3.2.P. During the procedure, the BWP/CHMP confirmed that the mRNA (referred to by the applicant as CX-024414) should be considered as the active substance, which was accepted by the applicant. The company should undertake suitable amendment of the Module 3 CTD in line with the definition of the active substance and finished product agreed and to support filings of lifecycle activities in line with EU requirements. A corresponding recommendation has been included to this effect (REC 1.1.)

2.2.2. Active Substance

General Information

The active substance (referred to by the applicant as CX-024414) is the mRNA encoding the pre-fusion stabilizedstabilised Spike (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. The 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 applicant provided sufficient information concerning the mRNA elements (including regulatory elements within the UTRs) and the proposed mechanism of action. The RNA contains modified N1-methylpseudouridine instead of uridine to minimise the indiscriminate recognition of the mRNA by pathogen-associated molecular pattern receptors (e.g. TLRs). Figure 1 illustrates the general structure of the antigen-encoding RNA.

***Figure 1** General structure of the RNA*

Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured and controlled by Lonza, Visp, Switzerland, with appropriate GMP certification.

Moderna, Norwood, USA is listed with appropriate GMP certification for QC testing until method transfer is completed to Lonza, Visp.

At the time of authorisation, the transfer of 3 methods for the active substance from Moderna, Norwood to Lonza Visp are ongoing to conclude by end of January 2021. The Supervisory Authority, AEMPS confirmed that the GMP certificate issued to Moderna, Norwood, USA for QC testing of the finished product can cover also testing of the active substance for the interim period. A satisfactory protocol for transfer of analytical methods for the active substance has been provided.

Associates of Cape Cod, East Falmouth, MA USA, will be providing endotoxin testing until transfer is complete to Lonza, Visp by end of January 2021.

A major objection was raised regarding US sites proposed for manufacturing of the active substance, these manufacturing sites were subsequently withdrawn from the dossier.

Description of manufacturing process, characterisation and process controls

A description of the manufacturing process and process controls for the Lonza, Visp manufacturing site is provided.

The manufacturing process for CX-024414 mRNA involves several major steps. The uncapped mRNA is transcribed from linear DNA utilising an in vitro transcription (IVT) reaction followed by purification and filtration steps. Next, mRNA is enzymatically capped followed by additional purification and filtration steps. Finally, CX-214414 mRNA is filtered, dispensed and stored.

The manufacturing process of CX-024414 mRNA is described in sufficient detail. The individual process steps are appropriately controlled with appropriate process parameters; however, the information should be completed with submission of the acceptance limits for all process parameters and evidence to support the proposed hold times (**REC**). Furthermore, a clarification is requested regarding the

process control strategy (specified manufacturing process development information), including information on failure mode and effects analysis (FMEA) analysis, process characterisation studies and criticality assignment.

Control of materials

The applicant comprehensively describes the manufacture of the master cell bank (MCB) and working cell bank (WCB) of the plasmid as well as the release testing and the qualification protocol of new MCB/WCB. An adequate cell bank stability program has been outlined.

The linearised plasmid DNA is considered as the starting material. The manufacture is described in sufficient detail, covering: Origin of the DNA sequence, plasmid map, generation of the host cell line, transformation and purification of the host cell line, plasmid cell banking system and stability testing and the linearised plasmid DNA is in principle thoroughly tested. Specifications are in general appropriate for authorizationauthorisation, however, will be reviewed after a sufficient number of batches has been produced (**REC**). The omission of an in-process control test for plasmid retention and plasmid copy number is sufficiently justified. Percent covalently closed circular DNA (%cccDNA) is routinely monitored post-polishing chromatography. However, evidence regarding qualification/validation of methods used for release testing should be provided (**REC**). Furthermore, sources for all appropriate reference materials/assay controls for plasmid and linearised DNA plasmid manufacturing are requested (**REC**). The formal shelf life for the linearised plasmid DNA and stability testing is appropriate. So far, no trending or degradation has been observed. There are no materials of animal origin used in the manufacture of CX-024414 mRNA.

The nucleotide starting material specifications will be finalised with suitably tight limits for purity (and impurities and other parameters if relevant) that ensure consistent active substance quality (**REC**).

The applicant provided a conclusive description of all raw materials used. Certificates of Analysis (CoAs) were provided within the submission package and comply with pharmacopoeial requirements where appropriate. All enzymes utilised are produced in *E. coli.* Further information on the medium used for MCB and WCB manufacture is requested (**REC**). There is also a reasonable risk mitigation strategy for extractables and leachables applied to for all materials with liquid product contact used in CX-024414 process.

All materials conform with Certificates of Analysis (CoAs) or Certificates of Compliance, which includes verification of bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) certificates, as required.

The control of the critical steps of the CX-024414 manufacturing process is generally acceptable. Additional details are requested regarding the method used for quantification of residual protein (critical in-process control; **REC**).

In order to complete the characterisation of the active substance and finished product manufacturing process, the MAH should provide additional data. Further information is required as regards the overall control strategy. Hence, tabulated summaries of FMEA performed including the conclusions drawn and appropriate justifications for criticality assignment and priority assigned to characterisation studies are requested (**Specific obligation 1**). In addition, tabulated summaries of the actual settings of the investigated parameters, analytical results and the prediction profiles should be provided for all process characterisation studies (**Specific Obligation 1**).

Validation data of the process A at ModernaTX, Inc. in Norwood and the process B initial at Lonza Biologics are provided and considered acceptable. However, the validation data from the initial process B scale at Lonza Visp needs to be provided as soon as available in order to confirm the consistency of the manufacturing process (**Specific obligation 2**). The applicant has provided in the initial dossier

plans for an upscaled process, which has not been supported by validation data. If the applicant wishes to include this upscaled process (Final scale B) to the marketing authorisation a variation application should be submitted. This should include appropriate validation data for the new scale (Final scale B). The proposed lifetimes for the chromatography resins and the TFF membranes are properly justified with data from small-scale models.

The manufacturing process of CX-024414 mRNA started with a small-scale process. The process was then up-scaled to Scale A, to Initial Scale B and then to Final Scale B (to be added via variation application). Scale A batches were used in the Phase III clinical trial. The major change was from the small-scale process to the Scale A process, including the addition of two process steps for the Scale A process. No changes were made to the unit operations or sequence of unit operations from Scale A to initial Scale B processes. Initial comparability of the mRNA produced with the different process scales is considered established based on release as well as additional characterisation data. However, the applicant is asked to provide the full comparability data for the initial scale B at Lonza Visp as soon as data is available.

In order to confirm the consistency of the active substance process (Initial scale), the applicant should provide additional comparability and validation data post-marketing in the context of a specific obligation (**Specific Obligation 2**).

Characterisation

The applicant provided a detailed characterisation of the mRNA active substance including detailed information on the structural properties of the mRNA CX-024414. Additionally, data on the chromatographic profile, the thermal denaturation as well as freeze thaw degradation and their influence on protein expression have been provided.

Concerning product and process related impurities a thorough characterisation of the mRNA CX-024414 is provided.

Regarding product-related impurities, the applicant described short mRNA species that can occur because of abortive transcription or premature termination of transcription. As the majority of these short mRNAs do not contain a PolyA tail, the manufacturing process includes chromatography steps, which aim at removing these impurities to a large extent. Other short fragments are controlled by in process testing of mRNA purity. No induction of immune stimulation by uncapped mRNA can be seen and potentially stimulatory dsRNA is consistently low throughout the process scale-ups.

Additional bands are observed by an in-vitro translation assay. To further elucidate the nature of these additional bands, data should be provided. Furthermore, additional details should be provided for the *in vitro* translation method and the negative and positive controls used, since the number and intensity of unspecific bands observed still leaves some uncertainty regarding the possible translation of additional proteins/peptides. In this context additional characterisation data or a scientific justification are requested (**REC**).

Specification

The active substance specifications contain tests for: Appearance (visual), Identity RT- Sanger Sequencing), Total RNA content (UV), Purity (RP-HPLC), Product-related impurities (RP-HPLC), % 5' Capped (RP-UPLC), % PolyA tailed RNA (RP-HPLC), Residual DNA template (qPCR), pH (pharmacopoeial), Bacterial endotoxin (pharmacopoeial), Bioburden (pharmacopoeial).

The specifications provided by the applicant are considered acceptable. The lack of a specification for polyA tail length and dsRNA is in principle supported by the characterisation and the process

development data provided. However, it is emphasised that the control strategy should ensure that dsRNA levels will always be at a sufficiently low level when the manufacturing process is run within the registered process parameter ranges, considering its potentially immune-stimulatory properties. Alternatively, an appropriate release specification for dsRNA should be registered (**REC**). However, it is emphasised that these quality attributes will be tested in case of process changes or in process validation/ process performance qualification (PPQ) analysis as additional characterisation assays to support process consistency.

Analytical methods

All analytical methods used for testing of the active substance are described in the dossier. The analytical methods are described in sufficient detail and SOP numbers are provided for US and EU testing sites. However, the applicant states "Equivalent instruments and reagents may be substituted where indicated" in most method descriptions. The applicant will however follow the EU variation guideline that indicates which critical reagents can only be changed via a variation procedure. Additionally, the applicant committed to reference *Ph. Eur.* instead of USP whenever possible.

The methods are properly validated for the US testing sites with the exception of the robustness of the methods. The applicant is asked to commit to submit robustness validation data of all the methods concerned (**REC**). The transfer, verification and validation of analytical methods to perform testing for CX-024414 at Lonza AG are currently on-going. An analytical Transfer Master Protocol, which describes the transfer of test methods to Lonza AG, has been provided in the dossier. These method validation data from the EU testing site should be provided as soon as possible **(Specific obligation 2**).

The analytical transfer master protocol is provided and considered acceptable. Furthermore, information as regards the planned implementation of the Sanger Sequencing performed at Microsynth and GROUP-109205 solo VPE for in-process monitoring of mRNA concentration is requested (**REC**).

The provided batch data are acceptable. The data from the one batch provided from the EU manufacturing site meets all specifications. Additional data supporting the Lonza Visp manufacturing process should be provided as soon as available. The specifications are considered acceptable for authorisation but need to be revised when more manufacturing experience has been gained.

In order to ensure consistent product quality, the MAH should review the active substance specifications following further manufacturing experience. (**Specific obligation 3**).

The data provided relate to lots used for clinical development and manufactured at ModernaTX, Inc. Norwood and Lonza Biologics, Portsmouth. Scales A and initial scale B were used for clinical studies and the data showed good consistency and comparability of scales.

The description of the reference standard is considered acceptable and also details how future reference material will be qualified are included. The reference standard for the commercial production is derived from a PPQ lot from the Scale A process. It was thoroughly tested and characterised and will be followed up by a stability monitoring protocol. However, the respective qualification report is requested (**REC**). Implementation of a secondary reference standard (and two-tiered system) is planned as detailed in the dossier.

For the EU manufacturing site, the active substance will be stored in 20 l Mobius bags. In line with CPMP/QWP/4359/03, Mobius storage bags should be tested for extractables/leachables, a respective commitment has been provided (**REC**). Furthermore, suitability of the Mobius bags should be justified as to date no stability data with samples stored in representative storage container are available (please refer to section on stability). (**Specific Obligation 3**)

Stability

A shelf life of the active substance when stored at the intended storage condition of -20°C ± 5°C in Mobius bags was proposed by the applicant.

In relation to mRNA purity and stability, data on the degradation rate was provided and shown to demonstrate Arrhenius behaviour, with first order kinetics. The stability profiles were demonstrated to be predictable and amenable to modelling, enabling a good understanding of the chemical degradation process.

For the active substance, the stability data presented consist of data for 2 clinical lots, 3 GMP lots and one development batch. The data for GMP lots at Moderna were manufactured at the Process A scale and used appropriately validated, stability indicating assays.

The initial shelf life claim at -20°C ± 5°C is not considered acceptable based on the provided data. Furthermore, the representativeness of the container closure system used is not yet sufficiently justified, since the storage container for stability samples differs from the commercial container closure system. Hence, stability data from batches produced at Lonza Visp should be provided as soon as available (**Specific Obligation 3**).

In conclusion, based on the limited stability data presented, a reduced shelf-life at -20°C ± 5°C compared to the shelf life initially proposed can be approved for the active substance, when stored in Mobius bags.

Comparability exercise for Active Substance

Not applicable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is presented as a white to off-white, multi-dose ready-to-use dispersion for intramuscular injection. It contains an mRNA active substance (referred to by the applicant as CX-024414) that encodes for the pre-fusion stabilised spike glycoprotein of 2019-novel Coronavirus (SARS-CoV-2) encapsulated into lipid nanoparticles (LNP) dispersed in a diluent buffer at pH 7.5. The LNP are composed of four lipids which act as protectants and carriers of the mRNA. These are: heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102, a custom-manufactured, ionisable lipid), 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and cholesterol.

The finished product is supplied in a multi-dose 10R clear Type 1 borosilicate glass vial or Type 1-equivalent alkali aluminosilicate glass with a chlorobutyl rubber stopper and an aluminium seal. The vial, stopper and seal components comply with the appropriate *Ph. Eur.* monographs for primary containers and closures.

There is no manufacturing overage. Each vial contains 6.3 mL fill volume, which corresponds to 10 doses of 0.5 mL (containing 100 micrograms mRNA). There is a 1.3 mL vial overfill. During the evaluation the applicant has been requested to justify this and confirm whether it would be feasible to retrieve 11 doses. The applicant responded that the fill volume was defined using components commonly used in preparation / administration of intramuscular injections (allowing for the dead volume from BD disposable syringes 1-mL with luer lock, 20G 1.5" needles), consideration of hold-up

volume in 10R vials, the fill tolerance observed at fill finish sites and the validated extraction of 10 doses from each vial.

The composition of the finished product, including amounts per vial, function and quality standard applicable to each component, was presented.

SM-102, a novel, ionisable lipid excipient, is positively charged to drive lipid to electrostatically interact with the mRNA, when combined. Cholesterol is incorporated to provide structure and physicochemical stability to the particles. The zwitterionic "helper" lipid, DSPC, is incorporated to increase the fusogenic properties of the particles. The polyethylene glycol-lipid conjugate novel excipient, PEG2000-DMG, confers steric stabilisation to the nanoparticles.

Sucrose is added to promote product stability through freeze/thaw and long-term storage.

All excipients except the lipid excipients SM-102, DSPC and PEG2000-DMG, tromethamol hydrochloride and sodium acetate trihydrate comply to *Ph. Eur.* grade. Concerning the use of non-*Ph. Eur.* grade cholesterol also cited by the company applicant a request to only used *Ph. Eur.* cholesterol has been requested (**REC**)).

Three specifications for tromethamol hydrochloride used for the neutralising buffer are included. The applicant committed to provide a single consensus specification (**REC**).

Two different specifications have been included for the novel excipient SM-102 depending on the manufacturing site, e.g. different tests on appearance and different acceptance criteria for the test on related substances of SM-102. The applicant committed to present one aligned specification including a test on related substances with numerical limits (**REC**).

For the non-compendial excipient 1,2-distearoyl-sn-glycero-3-phosphatidylcholine (DSPC) reference is made to a United States CDER Master File. However, master files for excipients are not acceptable in the EU. The applicant committed to provide further data sufficiently describing the quality of DSPC (**REC**).

For the compendial excipient cholesterol the acceptance criterion for bacterial endotoxins included in the specification is 10 times higher (1 EU/mg) than in the *Ph. Eur.* monograph Cholesterol for parenteral use. The specification will be corrected to 0.1 EU/mg.

Novel excipients

As indicated above, the finished product contains two novel excipients, namely SM-102 and PEG2000-DMG.

SM-102

General Information

The chemical name of SM-102 is Heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino)octanoate.

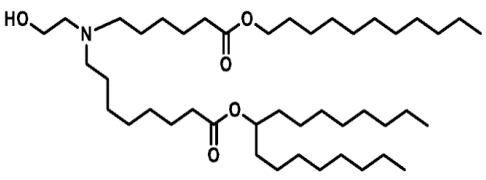


Figure 2: Structure of SM-102

Molecular Formula: $C_{44}H_{87}NO_5$, Molecular Mass: 709.7 g/mol, Molecular Weight: 710.2 g/mol.

SM-102 is very soluble in several organic solvents and practically insoluble in water.

Manufacture

The GMP manufacturing process of the novel excipient SM-102 covers synthesis and workup of Crude SM-102, reduction of Crude SM-102, and the purification. For the manufacturing process flow charts and narrative descriptions were provided including in-process controls.

The in-process control targets refer to "Report results". The applicant committed to include numerical values **(REC)**.

Information on the manufacturers, synthesis and specifications for both starting materials of SM-102 is presented in the dossier. The specifications for partly contain "Report results" as acceptance criteria. The applicant committed to include numerical values **(REC)**.

Manufacturing process development of the novel excipient SM-102 contains the development history including process optimisations. Differences between SM-102 manufacturers are also discussed. It can be concluded that all sites produce comparable quality of SM-102. Nevertheless, CQAs, CPPs and critical attributes of the materials used for the manufacture of SM-102 are missing. The applicant will provide those post-marketing **(REC)**.

Characterisation

The structure of the novel excipient SM-102 has been adequately characterised by means of IR-, ^{1}H-NMR and ^{13}C-NMR and mass spectrometry as well as elemental analysis.

The information provided on potential impurities in SM-102 comprise product related substances and process related impurities (elemental impurities, residuals solvents, peroxides, water content and inorganic impurities). The applicant will provide an evaluation of mutagenic impurities based on ICH M7 **(REC)**.

Control of SM-102

The specification for the excipient SM-102 comprises in principle all necessary tests to control its quality.

However, the specification for the test on related substances should be revised to include specified identified impurities with suitable limits. The applicant will revise the specification accordingly **(REC)**.

The assay limits in the specification of SM-102 are rather wide. A commitment has been provided to tighten the limits as more experience is gained **(REC)**.

A test on benzene, which might be present in e.g. toluene or acetone should be performed on the final excipient or on a suitable intermediate if not otherwise justified. The applicant committed to present a risk assessment for the presence of benzene in SM-102 **(REC)**.

The in-house test procedures for SM-102 and the respective validations are not sufficiently described. The applicant will provide detailed procedure descriptions and validation reports **(REC)**.

Batch analysis data have been provided for 18 batches. The results are consistent across batches. The applicant will clarify which batches were included in toxicological and clinical studies **(REC)**.

Reference Standards or Materials

The SM-102 reference standard is used for identification and assay. Information on the primary standard is provided.

Container Closure System

The applicant committed to revise this section to only include one container closure system instead of the currently used two depending on the manufacturing site. The SM-102 primary packaging information will be amended. All components are fully compliant with current international food contact regulations such as (EU) No 10/2011. The applicant will provide specifications for the foil pouches in which the glass containers are packaged and sealed (functional secondary packaging for SM-102) **(REC)**.

Stability

The stability programme for the excipient SM-102 currently covers 8 batches. Data are available for 36 months (2 batches) and 24 months (1 batch) at long-term conditions of -20°C ± 5°C and for 12 months (1 batch), 24 months (1 batch) and 36 months (1 batch) at 5°C ± 3°C. At 25°C /60% no stability data are currently available.

Further data are available for 9 months (1 batch) and 6 months (1 batch) at long-term conditions of -20°C ± 5°C and for 9 months (1 batch), and 6 months (1 batch) at 5°C ± 3°C. At 25°C /60% no stability data are currently available.

The provided data support the proposed re-test periods. The applicant will provide a post-approval stability protocol, which is currently missing. The applicant will provide results from forced degradation studies **(REC)**.

A.3.2 PEG2000-DMG

General Information

1,2-Dimyristoyl-rac-glycero-3-methylpolyoxyethylene (PEG2000-DMG) is a novel excipient.

The structure is shown in Figure 6.

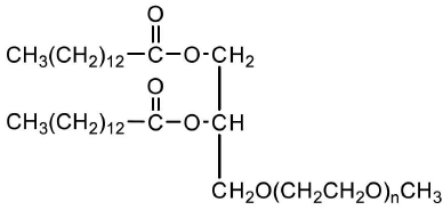


Figure 3: Structure of PEG2000-DMG

PEG2000-DMG is a white to off white powder soluble in water and most of organic solvents.

Manufacture

The manufacturing process consists of the following steps: reaction of the starting materials, concentration, purification vacuum drying, and packaging.

The manufacturing process description is not very detailed, however, considered acceptable. Details on the lyophilisation step of the manufacturing process are missing and will be provided post-approval **(REC)**.

Justifications for the selection of the starting materials will be provided post-approval. Specifications have been provided. Information on the additional supplier(s) of one of the starting materials will be provided post-approval. A description of the analytical methods to control the starting materials will be provided post-approval **(REC)**. Information on the suppliers of all raw materials is provided and specifications have been provided.

Appropriate CPPs have been defined.

In-process testing has been described, however, information on analytical methods used for in-process testing is missing and will be provided post-approval **(REC)**.

Information provided on manufacturing development history, CQA risk assessment and control strategy has been provided needs however to be adapted (**REC**).

Characterisation

The spectroscopic studies performed to investigate the molecular structure DMG-PEG2000 are: Infrared Absorption Spectroscopy, ^{1}H-NMR Spectroscopy, ^{13}C-NMR Spectroscopy and Mass Spectroscopy. Exemplary spectra including an interpretation of the results have been provided.

The polydispersity was analysed by GPC Information on the impurity profile has been provided. That information is not sufficient since reporting of impurities in the batch analysis data is not consistent with the current characterisation data (see below). Potential presence of mutagenic impurities in PEG2000-DMG should be evaluated and the results will be provided post-approval **(REC)**.

Control of PEG2000-DMG

The following attributes have been included in the specification of the novel excipient PEG2000-DMG: appearance, identification by NMR, average molecular weight by TOF-MS, purity by RP-HPLC, moisture by Karl Fischer, residual solvents by GC, bacterial endotoxins, bioburden, residual heavy metals. The specification is currently not acceptable. Polydispersity should be included in the specification for PEG2000-DMG post-approval. Numerical limits for specified and unspecified impurities will be included in the PEG2000-DMG specification post-approval. The current reporting of impurities is not acceptable. Characterisation data for impurities which are reported under 'content of unknown' should be provided post-approval **(REC)**.

Analytical methods have been adequately described. However, in the description of the HPLC purity method information on the reporting threshold is missing and should be provided post-approval. Validation data for the analytical methods to control DMG-PEG2000 are missing and should be provided post-approval **(REC)**.

Batch analysis data for five batches have been provided. All results comply with the specifications. More detailed information on these batches will be provided post-approval (**REC**).

Reference Standards or Materials

Sufficient information has been provided for reference standards or materials.

Container Closure System

The container closure system has been described. Information and specifications on the material used for the storage of PEG2000-DMG is missing and will be provided post-approval **(REC)**.

Stability

Stability data for three batches stored at long-term and accelerated conditions have been provided. No negative trends but a certain variability in the results for purity have been observed in the stability studies. From the information provided with the specification it is concluded that the shelf-life (re-test period) is acceptable.

Pharmaceutical development

The applicant has sufficiently described the formulation development, mainly referring to similar platforms and scientific publications. This includes the choice of the four lipids, the molar ratio of the

single lipids and the manner in which the mRNA is encapsulated leading to a mRNA-loaded LNP intermediate which is further processed to produce the finished product.

As indicated above, the finished product comprises four lipids: SM-102, DSPC, cholesterol, and PEG-lipid. SM-102 is a proprietary ionisable lipid that was selected by the applicant out of a panel of lipids because of its vaccine potency and tolerability and biodegradability. The applicant has optimised lipid ratios for his purpose.

There are only minor differences between the early clinical formulations used in phase I and II studies and the formulation of the phase III finished product batches. In Phase I and II studies, a target concentration of 0.5 mg/mL mRNA was prepared and a range of doses tested. After selection of the final dose, a target concentration of 0.20 mg/mL mRNA was developed for Phase III and commercial batches as a ready-to-use solution. Slight variations in the sodium acetate content and the distribution of tromethamol in the Dilution Buffer (tromethamol base and tromethamol HCl) were caused by the dilution step of the Phase I and II batches. In addition, the lipid concentrations were slightly modified during manufacture for Phase III.

The suitability of the formulation composition has been studied in a number of developmental stability studies at the intended long-term storage conditions as well as shorter term accelerated studies to enable manufacturing of the finished product. The data available to date demonstrate that there is no change in mRNA purity and LNP biophysical qualities when stored at -70°C. In contrast, mRNA chemical degradation is observed at -20°C, 5°C, and 25°C in a temperature-dependent manner. The proposed storage of finished product at -20°C is nevertheless acceptable, since only slight degradation is observed at -20°C as shown by preliminary stability data.

Since the finished product is presented in multi-dose vials, the applicant has analysed the effect of several preservatives on the biophysical parameters 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 justify the development of the vaccine without preservatives, since a microbiological challenge hold time study demonstrated no microbial growth for at least 12 hours at room temperature after inoculation of low levels of selected microorganisms.

Physicochemical properties (density, viscosity, surface tension, osmolality, glass transition temperature) of mRNA-loaded LNP intermediate and the finished product solutions have been shown at different temperatures.

Manufacturing process development

The manufacturing process development includes processes of different scales at different manufacturing sites, which have been sufficiently described.

As indicated above, the manufacturing process for the finished product comprises several stages.

The manufacturing process development of each of these has been provided. Changes to the specification and of the analytical procedures between the different processes have been presented.

The LNP are comprised of four lipid components (cholesterol, SM-102, DSPC and PEG2000-DMG).

mRNA-loaded LNP intermediate

The product consists of an mRNA-lipid complex dispersion that contains the mRNA (CX-024414) that encodes for the pre-fusion stabilised Spike protein of 2019-novel Coronavirus (SARS-CoV-2).

Comprehensive development data have been provided. Changes made during development have been described. They included scale-up, addition of a bulk freezing step, change of some equipment and

revision of the lipid molar ratios to allow for harmonisation with the platform process. The overall lipid content remained unchanged.

The Initial Scale B process has been transferred to the site registered for EU manufacture Lonza, Visp. Changes were made to materials for regional availability, operations and equipment to maintain aseptic processing aligned with facility fit, and equipment availability.

In accordance with ICH Q9, a FMEA was performed with respect to the manufacturing process. A science-based approach was used to identify Critical Quality Attributes (CQAs), CPPs and CIPCs to inform process design studies, and to establish the manufacturing control strategy. Characterisation data supporting the PARs for the CPPs and non-critical process parameters are included. The small-scale model used for the characterisation studies is described and evaluated demonstrating that the small-scale model is representative for the scaled process.

The PARs defined in the development section are in general appropriately transferred to the commercial manufacturing process description. Some clarifications and amendments are needed for the manufacturing process description (**REC**). Some clarifications and amendments were needed for the manufacturing process description. Respective information and/or commitments have been provided.

The proposed CQAs of the LNP are appearance, mRNA identity, total RNA content, purity and product-related impurities, % RNA encapsulation, particle size, lipids identification, lipids content, lipids purity, pH, osmolality, bacterial endotoxins and bioburden. The CPPs for the mRNA-1273 LNP manufacturing process have been described. No CIPCs were identified for the mRNA-1273 LNP manufacturing process.

A risk assessment concerning potential extractables and leachables from manufacturing components and container closure systems has been performed according to the applicant. However, no details are available on possible extractables. The applicant will provide respective data (**REC**).

Comparability

Analytical comparability data were generated with one Phase 3 clinical lot and three PPQ lots manufactured by the development site, ModernaTX in Norwood, US (not being registered for manufacture of product for the European market) at development scale. Additional data have been generated with commercial scale batches. Samples were analysed in a side-by-side format whenever possible.

The following attributes have been investigated in the analytical comparability studies: LNP size distribution, LNP size distribution, sub-visible particles (SVP) counts and morphology, LNP surface characterisation, LNP charge, LNP charge distribution, LNP structure, LNP density, LNP surface characterisation and protein expression by *in vitro* protein expression.

Extended characterisation data have also been provided for the first GMP batch manufactured at Lonza AG, CH. With results to date it is demonstrated that the pre-change and post-change manufacturing processes and quality attributes were comparable.

Differences to batches manufactured by Moderna, TX observed in the extended characterisation exercise and release testing of the first GMP batch manufactured at Lonza AG, CH for several attributes related to particle size and particle size distribution will be further be evaluated (**REC**).

The applicant committed to provide comparability results including extended characterisation data using the full panel of characterisation methods from all PPQ batches manufactured by Lonza AG, CH demonstrating that the commercial product manufactured at the Lonza, Visp site is representative of the material used in the clinical trials. (**Specific Obligation 2**).

Forced degradation will be evaluated in the next comparability phase. Results from forced degradation studies should be submitted when available (**REC**).

Finished product

Comprehensive development data on the finished product have been provided. Changes made during development have been described. Changes were related to scale up required for commercial supply.

The proposed CQAs for the finished product are: appearance, mRNA identity, total RNA content, purity and product-related impurities, % RNA encapsulation, *in vitro* translation, lipid identity, lipid content, lipid impurities, mean particle size and polydispersity, pH, osmolality, particulate matter, container content, bacterial endotoxin, and sterility.

CQAs, CPPs, and CIPCs have been defined based on risk assessments, process characterisation studies, and knowledge gained from manufacturing experience and an appropriate control strategy has been established, in accordance with ICH Q9. The applicant committed to provide the underlying process risk assessment (**Specific obligation 1**). The approach to define a cumulative time out of refrigeration (room temperature) and at 2°C - 8°C is acceptable; however, it should be noted that increasing process time negatively impacts RNA purity.

Characterisation studies have been performed in order to demonstrate that the quality attributes of the final product are highly similar across processes.

Comparability

Analytical comparability data were generated with four Phase 1/Phase 2 and six Phase III pilot scale A batches from Moderna, TX; three pilot scale A PPQ batches from Catalent intended for clinical/emergency use authorisation/commercial use outside EU, and one scale B batch from Rovi, Spain (EU finished product manufacturer intended for commercial use). A similar approach to comparability was used across manufacturing processes. Comparability between the processes has been shown by a) comparison of the processes and description of the changes, b) extended characterisation (physico-chemical properties, particle size, and impurities) of Phase 1/2 and Phase 3 clinical lots and PPQ lots up to Scale A and c) batch release results. Further Scale A to Scale B comparability will be based on description and justification of process changes including sites, scales, raw materials, process equipment and evaluation of process performance with respect to CPPs and IPCs as well as statistical evaluation of comparability of release testing results. Extended analytical characterisation testing is not performed at the level of the finished product as part of comparability studies as finished product characteristics are the same as for mRNA-loaded LNP intermediate. Nonetheless, results are available for one commercial scale B lot manufactured at the finished product manufacturing site for the EU market (Rovi, Spain) therefore, although there is sufficient comparability information to justify approval in this pandemic, no final conclusion can be drawn with regard to Scale A to Scale B comparability. The final validation report including an assessment of comparability is requested (**Specific obligation 2**).

Container closure system

A standard container closure system has been chosen that is suitable for the intended purpose. It is composed of glass vials and rubber stoppers. Both components are compliant with *Ph. Eur.* requirements. The sterilisation cycles used for sterilisation of vials and stoppers are not described and has been requested (**REC**). For the container closure components, vendor-generated extractables data were used for an initial quantitative toxicological assessment. The assigned safety concern threshold for some stopper oligomers is exceeded in the estimated amount per dose. However, a product-specific leachable study indicated no reportable organic compounds over the analytical evaluation threshold.

Compatibility

Compatibility testing that establishes the clinical in-use period for the finished product under refrigerated and ambient conditions was performed (see stability section). Materials of contact planned for clinical dosing (e.g., needles, syringes, vials) were used to determine material compatibility and clinical in-use stability. Hold times in the syringe of 0 and 8 hours were assessed under ambient conditions (room temperature) and 5°C with clinical material from early phase trials containing 0.1 mg/mL or 0.5 mg/mL mRNA concentration. Results showed no notable change to attributes of the finished product. Stability was demonstrated for clinical in-use for up to 8 hours at either ambient temperature or at 5°C.

Additional in-use studies were performed for the commercial dosage strength of 0.20 mg/mL. The product solution was held in the vial at room temperature for either 1 hour or 7 hours after thaw. Dosing syringes were prepared from the vial after 1 hour and then again after 7 hours upon completion of a 1-hour thaw at room temperature. The syringes were then held for 0, 4, 8, and 12 hours at room temperature and refrigerated conditions. Clinical in-use stability was demonstrated for dosage strengths of 0.20 mg/mL for 6 hours after first puncture in the vial followed by 8 hours in the syringe at either ambient temperature or at storage between 2°C to 8°C (see stability section).

Microbiological attributes

The finished product is manufactured by a conventional aseptic process using sterilising filtration. Prefiltration bioburden is monitored as part of the manufacturing process. The microbiological quality attributes are monitored by testing for sterility and endotoxins at release. Sterility is also monitored annually as part of the stability testing program. The microbiological suitability of the selected primary container closure system has been demonstrated through container closure integrity (CCI) testing studies. Results from container closure integrity testing demonstrate that the chosen container is suitable for storage and provides adequate protection.

The finished product does not include a preservative. As discussed above the lipid nanoparticle-based product is not compatible with common preservatives.

A microbial challenge hold time study, also known as growth promotion study was performed with a range of different microorganisms to assess the impact of low levels of microbial contamination from initial needle puncture/vial entry for the finished product. The level inoculum levels were representative of contamination that may occur in an in-use situation when multiple doses are withdrawn from the same vial. The results showed that growth of the inoculated microorganisms is hindered for up to 24 hours at 20°C – 25°C. Hence, the proposed 6 hours in-use period from initial needle puncture described in the product information is supported.

Manufacture of the product and process controls

mRNA-loaded LNP intermediate

Valid GMP certificates for the registered manufacturing sites have been provided.

The LNP manufacturing process comprises lipid stock solution (LSS) preparation, nanoprecipitation mixing, tangential flow filtration (TFF), dilution and cryoprotectant addition, clarification, fill, and freezing and storage.

The manufacturing process will be validated using a concurrent validation approach. This is acceptable in view of the pandemic and the data provided. Process validation and comparability data will have to be provided (**Specific obligation 2**). Upscaling of the manufacturing process should be included by variation post-authorisation.

Reprocessing is not performed for any unit operation.

CPPs and their PARs and IPCs for the LNP manufacturing process have been defined Process intermediate hold conditions have been described and justified. Some clarifications and amendments were needed for the manufacturing process description. Respective information and/or commitments have been provided (**REC**).

Microbial controls have been adequately described.

For the manufacturing process of the LNP at the development manufacturing site (Moderna, TX) protocols for PPQ have been provided Reports are available covering three PPQ batches each of the proposed manufacturing scales. Altogether, the manufacturing process at Moderna, TX met acceptance criteria and expected outcomes.

A comprehensive PPQ protocol for the proposed manufacturing site Lonza, Visp, Switzerland for the EU market at the proposed commercial batch size is available. The pre-PPQ batch is executed in order to verify and evaluate the transferred process and check the readiness of the process at manufacturing scale prior to validation. Acceptable test results have been provided for that batch. This will be followed by three PPQ batches at the commercial production scale. Validation results in accordance with the PPQ protocols for the EU site Lonza, Visp, Switzerland are expected. This results in a specific obligation (**Specific obligation 2**).

For the manufacturing process of mRNA-1273 LNP at Moderna, TX (not being registered for manufacture of product for the European market) protocols for process performance qualification have been provided Reports are available. Altogether, the manufacturing process for the scales presented met acceptance criteria and expected outcomes.

A comprehensive PPQ protocol for the proposed EU manufacturing site Lonza, Visp, Switzerland for the registered commercial batch size of mRNA-1273 LNP is available. However, some clarification was needed, which has been provided.

The pre-PPQ batch has been executed at Lonza, Visp in order to verify and evaluate the transferred process and check the readiness of the process at manufacturing scale prior to validation. The test results for that batch have provided. This will be followed by three PPQ batches at the commercial production scale.

Validation results in accordance with the PPQ protocols for Lonza, Visp, Switzerland are required (**Specific obligation 2**). A brief description of the shipping process of mRNA-1273 LNP to the finished product manufacturer should be included in the dossier (**REC**).

Finished product

Sites responsible for manufacturing and testing of the finished product (from mRNA-loaded LNP intermediate to finished product) have been described Valid EU GMP certificates have been provided.

At the time of authorisation, the transfer of the identity and *in vitro* translation tests from Moderna, TX (not being registered for manufacture of product for the European market) to Rovi Pharma Industrial are ongoing to conclude by end of January 2021. The development site was inspected by AEMPS and it was found to be GMP compliant. A time-limited exemption allowing reliance on batch control testing conducted in the registered site that is located in a third country for these two QC tests is being applied. (see Annex II of the opinion).

The nominal manufacturing batch size for the finished product has been defined.

Manufacturing process:

The manufacturing of the finished product (from mRNA-loaded LNP intermediate) consists of dilution of the mRNA-loaded LNP intermediate with a formulation buffer followed by 0.2 µm sterile filtration, filling, stoppering, capping inspection, labelling and packaging.

The total process duration is defined.

Reprocessing is not performed during the production of the finished product.

The manufacturing process including controlled process parameters and in-process controls has been described in sufficient detail. All single-use material used in the finished product manufacturing process has been indicated. The control of critical steps and intermediates has been sufficiently described. CQA and CPP and IPCs have been defined.

The microbial control strategy is in principle acceptable; however, the full data set supporting the hold times is pending (**Specific obligation 2**).

Process performance qualification has been performed for three Scale A batches manufactured at the Catalent, US site (not being registered for manufacture of product for the European market). For the relevant process steps, IPCs and process parameters have been monitored with consistent results. Process qualification also includes aseptic manufacturing steps in the filling line which is adequately controlled by regular media fills.

For the Rovi site, which is the finished product manufacturing site (from bulk mRNA-loaded LNP intermediate to finished product) for the EU CMA, the PPQ is ongoing; only one batch has been manufactured to date. An adequate PPQ protocol has been submitted. The available data indicate that the manufacturing process performs reliably and delivers product of adequate quality; however, the full data set including at least 3 representative lots and including a justification of the hold times, justified from a microbiological perspective, is required (**Specific obligation 2**). The applicant committed towill provide a brief summary of the shipping validation of the finished product (**REC**).

A process validation scheme for the finished product has been provided. It includes supplemental studies (i.e. Container Closure Integrity Testing (CCIT) qualification, filter validation, etc.). Results for CCI qualification studies, acceptable data for the first process validation batch and the Bacterial Challenge Filter Validation Study have been provided.

A concurrent validation approach will be used due to the urgent need for this product in the pandemic situation and in light of the validation data already submitted this is accepted.

Control of excipients

Lipid SM-102 is a novel excipient, not previously used in an approved finished product within EU. 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) is a non-compendial excipient sufficiently controlled by an in-house specification.

Cholesterol is controlled according to the *Ph. Eur.* monograph 0993 with additional tests for residual solvents and microbial contamination. However, the applicant is also referring to a non-compendial cholesterol. This should be clarified post-approval (**REC**).

1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG),,) is a novel excipient, not previously used in an approved finished product within EU. The other excipients (tromethamol, acetic acid, sodium acetate trihydrate, sucrose and water for injections) are controlled according to respective *Ph. Eur.* monograph or by in-house specifications (tromethamine hydrochloride).

Product specification

mRNA-loaded LNP intermediate

The following attributes have been included in the specification for mRNA-1273 LNP: appearance, mRNA identity by reverse transcription/Sanger sequencing, total RNA content by anion exchange chromatography, purity and product-related impurities by RP-HPLC, % RNA encapsulation by absorbance assay, mean particle size and polydispersity by DLS, lipid identity by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid impurities by UPLC-CAD (% individual impurities and sum of impurities), pH, osmolality, bacterial endotoxins (*Ph. Eur.* 2.6.14, kinetic chromogenic method) and bioburden (*Ph. Eur.* 2.6.12).

A justification for each specification attribute has been provided. batches from Moderna, TX have been used to justify the acceptance criteria.

As indicated above, the applicant has committed to providing an updated LNP and finished product appearance testing description including the characterisation test of potentially occurring visible particles (**Specific Obligation 1**)

Following the request from the CHMP, the applicant added numerical specification limits for product-related impurities in the specification for mRNA-loaded LNP intermediate.

As mentioned earlier, a commitment to tighten the specifications when more batch analysis data from routine manufacturing are available has been provided. The applicant should establish final specifications for LNP and the finished product no later than 30-06-2021 (**Specific Obligation 3**).

The mRNA-loaded LNP intermediate has been characterised with the following techniques: mRNA encapsulation (absorbance assay) sub-micron LNP size distributions, size distributions), sub-visible particles size distribution, sub-visible particle concentration, surface characterisation, surface charge, and *in vitro* protein expression. The employed techniques are state-of-the-art methods to characterise lipid nanoparticles and it can be concluded that the lipid nanoparticles have been comprehensively characterised.

Lipid impurities and degradants are monitored and quantified to ensure impurity levels are well-controlled.

Characterisation of mRNA-loaded LNP intermediate identified the presence of product variants and degradants derived from CX-024414 mRNA covalently linking to LNP lipid impurities and degradants. These lipid-RNA species render mRNA inactive and thus affect the potency of the product.

The lipid-RNA species have been isolated for characterisation. By multiple orthogonal analyses the lipid-RNA species are analytically indistinguishable from unmodified mRNA and are not RNA aggregates. Stability studies under frozen liquid and accelerated conditions have monitored these impurities. The characterisation of these impurities is well described.

It was confirmed that lipid modification is significant enough prevent protein expression from the particular mRNA molecule on which it resides.

Several actions have been undertaken to optimise the manufacturing processes of the lipid component SM-102 and mRNA-1273 LNP leading to a significant reduction in potential lipid-RNA species. The applicant should provide a comprehensive summary of the investigations and process changes related to lipid-RNA species. The control strategy for lipid-RNA species its implementation and plans for further improvement should be justified in more detail. Furthermore, the applicant should commit to update the relevant Module 3 manufacturing development sections with this information (**REC**).

It should be demonstrated that the detection wavelength is suitable for the quantification of lipid-RNA species. UV spectra for impurity-enriched fractions should be provided post-approval (**REC**).

Analytical methods

All analytical methods are well described and the respective SOPs have been provided.

All analytical methods have been validated in accordance with ICH Q2. Validation summaries and detailed validation reports from Moderna, TX have been provided. The quality of these reports is high with the exception that robustness is addressed with the acceptance criterion 'Intermediate precision criteria are met' what is not acceptable. Additional data should be provided post-approval.

Analytical method transfer protocols for the LNP from Moderna Tx to Lonza, Visp (EU testing site) have been submitted. Final validation reports from Lonza, Visp should be provided once available (**REC**).

Batch analysis

Batch analysis data for several batches manufactured at Moderna, TX have been provided. All results comply with the specifications applicable at the time of release. Moving forward, mRNA-1273 LNP will be tested in accordance with the validated methods.

Batch analysis data and a CoA for Lot Lonza, Visp, EU commercial site has been provided.

Reference standard

For the Ultra-High-Performance Liquid Chromatography with Charged Aerosol Detection (UPLC-CAD) method for lipid identification, lipid content and lipid impurity a lipid reference standard is used.

Finished product

The proposed finished product release specification includes tests for appearance (visual), mRNA identity by reverse transcription/Sanger sequencing, total RNA content by anion exchange chromatography, purity and product-related impurities by RP-HPLC, % RNA encapsulation by absorbance assay, *in vitro* translation (methionine labelling), lipid identity by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid content by UPLC-CAD (SM-102, cholesterol, DSPC, PEG2000-DMG), lipid impurities by UPLC-CAD (% individual impurities and sum of impurities), mean particle size and polydispersity by DLS, pH, osmolality, particulate matter, container content (USP), bacterial endotoxin (*Ph. Eur.* 2.6.14, kinetic chromogenic method) and sterility (*Ph. Eur.* 2.6.1). Reference is made to the FP stability section - mRNA-1273 LNP, for end of shelf-life specifications.

For the appearance test, the presence of product-related particles is covered by the specification, although there have never been observed visible particles in the finished product to date. As indicated above, the applicant committed to provide an updated LNP and finished product appearance testing description including the characterisation test of potentially occurring visible particles as described earlier in the report (**Specific Obligation 1**).

The presence of the 5´Cap structure and the polyA tail is controlled at release of CX-024414 mRNA; omission of these tests at finished product release has been sufficiently justified.

Specifications are set relatively wide for a variety of release tests, although batch release data demonstrate very consistent results which would allow for tighter limits. Following a request from the CHMP, the applicant tightened the specification limit for %RNA encapsulation addressing the CHMP concern since the included non-clinical data demonstrates strongly reduced protein expression for lots with only that value of RNA encapsulation. For the in-vitro translation test the proposed specification for a MW was also deemed too wide and was tightened.

The applicant was also requested to add numerical specification limits for the product-related impurities and not only report them as proposed. This was satisfactorily addressed by the applicant. These limits may be further revised when batch analysis data become available (**Specific Obligation 3**).

The originally proposed specification limit for RNA purity was deemed not acceptable. The first finished product batches (which include the clinical batches) had a purity higher than the originally proposed limit. The one finished product lot manufactured at Rovi also had higher purity. This was raised as a MO together with the shelf life claim and total process duration. The applicant has analysed the influence of the process duration on RNA purity. The influence of the process duration on finished product CQA has been analysed. During the procedure, the applicant provided phase III clinical data to support the end-of-shelf life limit of RNA purity. This data included efficacy data from a limited number of subjects receiving vaccine with lower purity (at least one of the two doses). The presented data did not show an association between breakthrough cases of COVID-19 from clinical trials and RNA purity level (within the ranges under discussion). In the Phase II study, comparable neutralising antibody responses were observed for subjects receiving effective doses of 40 and 79 µg. In addition, in the non-clinical setting, lots with low purity were shown to be as effective as lot with higher purity. Considering the totality of data, the proposed lower purity limit is considered to be scientifically justified. Under consideration of the well-defined degradation kinetics, the applicant proposes now higher release specification of purity that would ensure acceptable RNA purity throughout the shelf life.

As indicated above, a commitment to tighten the specifications when more batch analysis data from routine manufacturing are available has been provided. The applicant should review the specifications for CX-024414, LNP, and the finished product no later than 30-06-2021 (**Specific Obligation 3**).

The applicant has committed to perform a risk assessment with respect to the potential presence of elemental impurities in the finished product in line with ICH Q3D (**REC**).

The applicant provided a preliminary risk evaluation regarding potential nitrosamine contaminations in the finished product, which is considered acceptable, but should be complemented with a quantitative risk assessment, especially focusing on nanoparticle constituents. (**REC**).

Analytical methods

The analytical methods used for control of the final product have been described and most validation reports for the Rovi site are part of the CMA dossier. Several requests related to the method descriptions and validations have been adequately addressed. The applicant is performing a dye ingress test for CCI verification during the stability, in lieu of sterility testing. The applicant has committed to provide a description of this CCI test and its validation by 31-03-2021 (**Specific Obligation 2**). For the in-vitro translation assay and the identity test, validation reports are missing for Rovi and should be provided (respective reports are available for the testing site ModernaTX used during the temporary exemption-ref. to Annex II.A). The applicant has will provide them no later than 31-01-2021 (**REC**). Non-compendial methods have been validated using appropriate validation parameters.

Batch analysis

Batch analysis results have been presented for Scale A batches from the Moderna, TX site used for phase III clinical trials, for Scale A batches PPQ batches manufactured at the Catalent, US site and for 5 Scale B batch from Catalent US site and for 1 Scale B batch from Rovi. All batches meet the pre-defined specifications and the respective CoAs are included in the dossier. Release data for the remaining PPQ lots from Rovi should be provided (**Specific Obligation 2**).

Reference standard

The CX-024414 reference material is described in the active substance (CX-024414) section and will serve as the reference material for mRNA-1273 finished product testing for the total RNA content method by AEX-HPLC, the % purity method by RP-HPLC (system suitability) and the *in vitro* translation assay/methionine labelling assay (positive control).

For the Ultra-High-Performance Liquid Chromatography with Charged Aerosol Detection (UPLC-CAD) method for lipid identification, lipid content and lipid impurity a lipid reference standard is used.

Stability of the product

mRNA-loaded LNP intermediate

The mRNA-loaded LNP intermediate stability program was executed according to ICH Q1A (R2) and ICH Q5C.

Stability samples manufactured per the commercial process were stored in containers made of the same materials as the commercial closure system. Samples were stored at -60°C to -90°C (long term conditions) for up to 4 months and 5°C ± 3°C (accelerated conditions) for 1 month.

Samples were tested using suitable stability-indicating assays for appearance, total RNA content, purity, product-related impurities, % RNA encapsulation, lipid identity, lipid content, lipid impurities, mean particle size, polydispersity, pH, osmolality, bacterial endotoxin and residual solvent (ethanol).

Up to now, all results are within specifications.

Data have been generated from one development lot, one clinical lot and three PPQ lots All lots were manufactured at ModernaTX, Inc. Additional stability data will be provided post-approval.

The applicant will include all PPQ batches manufactured by Lonza AG, CH into the stability programme. Section 3.2.S.7.2 'Post-approval stability protocol and stability commitments' will be updated post-approval (**REC**).

Stability studies in support of mRNA-loaded LNP intermediate freeze-thaw cycling were performed using the development lot. The results show that the mRNA-1273 LNP biophysical attributes (particle size, polydispersity, encapsulation) are not impacted by the different freeze-thaw processes (room temperature or 2°C to 8°C) or 5 cycles of freeze-thaw.

The proposed shelf-life is considered acceptable.

Finished product

A finished product shelf-life of 7 months at -20°C including a period of 30 days at 2°C - 8°C (protected from light) plus 12 hours at 8°C to 25°C (see product information for specific details) is proposed.

The finished product stability program was executed according to ICH Q1A (R2) and ICH Q5C.

Data from mRNA-1273 Phase 1, Phase 2, engineering and Phase 3 and commercial supplies were provided. The mRNA-1273 development studies include lots representative of the GMP scales manufactured at ModernaTX, Inc. (Norwood, MA). Samples were stored in a container made of the same materials as the commercial closure system.

Samples were stored at -60°C to -90°C for up 6 months, -20°C ± 5°C (intended long-term condition) for up to 6 months, 2°C - 8°C (intended short-term condition) for up to 5 months, 25°C ± 2°C (accelerated condition) for up to 72h.

Samples were tested using suitable stability-indicating assays for appearance, RNA identification, total RNA content, purity, product-related impurities, % RNA encapsulation, lipid identity, lipid content, lipid

impurities, mean particle size, polydispersity, pH, *in vitro* translation, osmolality, particulate matter, bacterial endotoxin and bioburden. However, not all tests are performed at every time point.

Stability data up to 6 months for two developmental lots and up to 4 months for clinical/PPQ lots at different temperatures is available to date. These batches represent Scale A lots manufactured at Moderna and Catalent in the US. No stability data from Rovi, EU batches are available so far. As stated by the applicant, RNA purity in the finished product is clearly temperature sensitive and represents the most important stability-indicating parameter. In addition, the parameters product-related impurities and particle size are also impacted. For all stability lots, results showed no change of these parameters when stored at -70°C for up to 6 months. For lots stored at -20°C, a slight decrease in RNA purity and an increase in process-derived impurities and an increase in particle size can be observed over time; all results were within the specification. At higher storage temperatures, RNA degradation is accelerated, as expected. At 2°C - 8°C after 4 weeks a clear reduction of purity (together with increase of product-related impurities and increase of particle size) is measured, A statistical model aligned with the WHO 2006 guidance document, Guidelines on Stability Evaluation of Vaccines, is being applied for the finished product The degradation rates and associated variance estimates were used to calculate an internal Minimum Release Limit (MRL) for purity. This limit supports up to 7 months of storage at -15°C to -25°C that can include up to 1 month of storage of the unopened vial at 2°C to 8°C (protected from light), plus 12 hours at 8°C to 25°C. Reference is made to the approved product information for precise details of the respective storage periods and permitted in-use storage.

The applicant first proposed a staggered shelf life approach, which defined the shelf-life dependent on the RNA purity at release and whether lots were being tested before or after packaging. This approach was not considered practical nor in line with EU expectations and was withdrawn by the applicant in response to a major objection. A preliminary shelf life of 7 months at -20°C including a period of 30 days at 2°C - 8°C plus in-use time of up to 12 hours at RT was subsequently proposed and justified by the available stability data. A post-approval stability protocol and stability commitment has been provided. This should also include final photostability results. Nevertheless, the applicant should provide periodic updates on the stability data and completion of the study should be provided for the PPQ lots from Rovi stored at -20°C followed by a period at 2°C - 8°C. (**Specific Obligation 3**).

Stability studies in support of finished product freeze-thaw cycling were also performed. The freeze-thaw cycling was repeated up to five times. All results were within the specification and indicate that the final product is relatively stable with regard to repeated freeze-thaw steps support five freeze/thaw cycles. Repeated freeze-thaw of vials upon marketing is however, not permitted in the approved product information.

Upon request from CHMP, preliminary results from a photostability study performed in accordance with ICH Q1B were presented. Final results will be submitted to the Agency. The presented data show that the mRNA is sensitive to excessive light exposure but can be handled under normal room lighting conditions without affecting product quality for at least 2 days of normal light exposure at 25°C. A precautionary statement regarding light exposure has been included in the SmPC.

In-use stability studies were also performed. The finished product (vial) was held at room temperature for either 1 hour or 7 hours after thaw. Dosing syringes were prepared from the vial after 1 hour and then again after 7 hours upon completion of a 1-hour thaw at room temperature. The syringes were then held for 0, 4, 8, and 12 hours at room temperature and refrigerated conditions. All attributes remained within the acceptance criteria when held in a vial for up to 7 hours at room temperature after first puncture, followed by storage in a syringe for up to 12 hours supporting the approved in-use stability instructions of up to for 6 hours at 2 to 25ºC, in the product information.

Clinical in-use stability was also demonstrated for 6 hours after first puncture of the vial followed by 8 hours in the syringe at either ambient temperature or at storage between 2°C to 8°C. The data

support the chemical and physical in-use stability for 6 hours at 2 to 25ºC after first puncture claimed in the product information.

A finished product shelf-life of 7 months at -20°C including a period of 30 days at 2°C - 8°C (protected from light), plus 12 hours at 8°C to 25°C (see product information for specific details) is accepted.

Adventitious agents

Section 3.2.A.2 should be updated to include information as regards control of sterility and a statement as regards compliance with EMEA/410/01 Rev.3 requirements. The applicant has committed to do so no later than 31-03-2021 (**REC**).

There are no materials of animal or human origin used in the manufacture of the active substance or finished product.

The manufacturing process description for active substance and finished product also documents the microbial control strategy- see Microbiological attributes section under Description of the product and Pharmaceutical Development - Manufacturing process development- (mRNA-1273 LNP).

GMO

Not applicable.

Regional information

Process validation schemes for LNP (Lonza, Visp) and the finished product (Rovi, Spain) have been provided the dossier. A concurrent validation approach will be used for initial Scale B process and Scale B due to the urgent need for this product. The rationale for this approach is documented. This concurrent approach requires interim reports to be documented for each individual validation run. An overall report per site will be compiled that summarizessummarises all evaluations and contains a comparability assessment of the data of all batches manufactured. Finally, a concluding report linked to this plan will be written that summarises all findings from the different validation reports.

2.2.4. Discussion on chemical, pharmaceutical aspects and biological aspects

During the procedure, a number of issues were highlighted relating to: GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release, the comparability between clinical and commercial material, and the absence of data on finished product manufactured at the commercial site.

These issues were classified as Major Objections (MOs) in order to ensure completion of the data set by the applicant at appropriate time points. Further MOs were raised regarding the potential presence of visible particles in the mRNA-loaded LNP intermediate and final product and regarding the proposed RNA purity at release and at the end of shelf life. EU GMP certificates for the manufacturing and testing sites were subsequently obtained. This MO was therefore resolved.

Data have been submitted by the applicant during the procedure in relation to the Major Objections, while a number of specific obligations (SOs) are identified as necessary in order to complete the quality documentation. Further information is provided below on the resolution of the major objections and the rational for accepting a number of open issues to be addressed as specific obligations post-marketing. Several other issues are further highlighted as Recommendations to be addressed by the applicant post-approval.

The CTD Module 3 dossier structure currently describes the mRNA, the lipid excipients and the lipid nanoparticles in 3.2.S. During the procedure, the BWP confirmed that the mRNA (referred to by the applicant as CX-024414) should be considered as the active substance as per Directive 2001/83/EC and this was accepted by the applicant. Although the current dossier structure would require adjustment to meet EU CTD requirements, there are no associated risks for GMP or product quality at the time of authorisation. In order to bring the current dossier structure in line with EU CTD requirements the company should update the Module 3 CTD structure in line with the agreed active substance and finished product definitions (**REC 1.1**).

In addition, it should be ensured that, in accordance with Annex I of Directive 2001/83/EC and Article 16 of Regulation (EC) No 726/2004, the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and controls (including the specifications) shall be designed to ensure product consistency and a product quality of at least shown to be safe and efficacious in clinical trials and shall introduce any subsequent changes to their manufacturing process and controls as needed.

Active substance

The major part of the dossier is of acceptable quality. However, certain information and data requirements remain to be provided, due to the very short time frame of product development. These data will be submitted in the closing sequence or further addressed in specific obligations and other post-approval measures (recommendations). Information on the manufacturing process and process controls for the manufacturing sites Lonza, Visp, and Rovi is provided.

Biological characterisation of the active substance was provided and certain points need to be addressed post-approval. Since these outstanding data form the basis of the determination of comparability for scale-up and transfer of manufacturing processes for the active substance, additional data are requested as **Specific Obligation 1**.

Several active substance processes have been used during the development; from personalised vaccine unit to Process Scale A (clinical trial material) and initial Scale B. The major change was from PVU process to the Scale A process, including the addition of two tangential flow filtration unit operations for the Scale A process. No changes were made to the unit operations or sequence of unit operations from Scale A to initial Scale B processes. Major Objections in relation to insufficient validation data for the active substance manufacturing process (initial scale B) resulted in **Specific Obligation 2**.

In the initial Rolling Review submission, PPQ data from the Scale A and initial Scale B from the US manufacturing sites was provided. In a second submission data from one batch manufactured at Lonza, Visp included. The data from the EU manufacturing batch showed a good comparability to the PPQ lots from the US sites. The complete PPQ/validation of Lonza, Visp will be provided post-approval via a **Specific Obligation 2**.

The proposed specification for active substance is acceptable with respect to the attributes chosen for routine release testing in the context of the pandemic situation. However, the active substance specifications acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability.

Although the stability data were limited, the applicant has demonstrated a good understanding of the mode and rate of degradation. and the data available justify the current shelf life. To supplement the knowledge on stability, further data are requested as **Specific Obligation 3**.

The proposed initial shelf life for the active substance is 6 months at the recommended storage temperature of -20°C.

Finished product

The finished product is a multi-dose (10-dose) ready-to-use dispersion for intramuscular injection of mRNA embedded in lipid nanoparticles (LNP).

The formulation development studies of the mRNA containing lipid nanoparticles have been sufficiently described.

The development of the manufacturing process is sufficiently described, and critical process parameters are defined.

The manufacturing process includes lipid nanoparticle fabrication followed by fill and finish (at Rovi). The processes have been acceptably described.

Comparability between the commercial finished product and the clinical finished product has been sufficiently demonstrated for a CMA for the attributes tested. Limited data on the intermediate and finished product batches manufactured at the commercial facility Lonza, Visp and Rovi (EU market) were presented, since so far only one PPQ batch of the intermediates and the final product has been produced.

Although initial information has been provided to support comparability of LNP intermediate, the applicant should provide comparability results including extended characterisation data using the full panel of characterisation methods from all PPQ batches manufactured by Lonza AG, CH demonstrating that the commercial product manufactured at the Lonza, Visp site is representative of the material used in the clinical trials. (**Specific Obligation2**).

For the finished product, results are available for one scale B lot manufactured at the finished product manufacturing site for the EU market (Rovi, Spain) therefore, although there is sufficient comparability information to justify approval in this pandemic, no final conclusion can be drawn with regard to Scale A to Scale B comparability. The final validation report including an assessment of comparability is therefore requested in a specific obligation (**Specific Obligation 2**).

Process validation (PPQ) for commercial scale batches were initiated, and a summary report from one PPQ validation batch was provided. The reported results were comparable to the PPQ batches from the US sites. Further data was requested in order to conclude on the consistency of finished product manufacturing, to assure comparability between the commercial product with the product produced at the US sites that was also used in clinical trials, and to support the claimed finished product shelf-life and storage conditions. A process validation plan for PPQ lots has been provided. A concurrent validation approach will be used due to the urgent need for this product and the pandemic situation. The rationale for this approach has been documented.

An overall PPQ report, which also includes comparability data, will be submitted when data from three consecutive batches manufactured at Lonza, Visp and Rovi will be available. In summary, an acceptable validation program has been established and an interim report from one PPQ validation batch was provided, therefore the information on process validation is considered acceptable subject to a specific obligation for submission of the remaining data (**Specific Obligation 2**).

The specification document for finished product includes a comprehensive panel of relevant tests along with corresponding acceptance criteria. Several issues in relation to the acceptance criteria in the finished product specifications were raised in the 1st Quality data submission, i.e. the LNP size, polydispersity, RNA encapsulation, *in-vitro* expression. In addition, open questions regarding the regarding the clinical justification of the proposed minimum acceptable RNA purity were discussed in

an oral explanation. during the evaluation. Whilst finished product specifications were subsequently amended and overall found to be acceptable, the acceptance limits should be re-assessed, and revised as appropriate, as further data becomes available (**Specific Obligation 3**). In addition, the applicant should provide an updated appearance testing description for LNP and finished product including the characterisation test of potentially occurring visible particles since these have not been clinically qualified (**Specific Obligation 2**).

The proposed initial shelf life for the finished product of shelf life of 7 months at -20°C including a period of 30 days at 2°C - 8°C is found acceptable, but should be confirmed by further stability data from lots manufactured at the Rovi site (**Specific Obligation 3**).

The applicant is performing a dye ingress test for cCCI verification during the stability, in lieu of sterility testing. The applicant has committed to provide a description of this CCI test and its validation (**Specific Obligation 2**).

Two novel excipients are included in the LNP. Limited information is provided for both the lipid SM-102 and the PEGylated lipid PEG200-DMG. Although this is sufficiently supportive for conditional marketing authorisation, in order to assure comprehensive control throughout the lifecycle of the finished product and to ensure batch-to-batch consistency, further information needs to be submitted regarding the synthetic process and control strategy in line with raised recommendations (**Specific Obligation 1**).

2.2.5. Impact on the benefit-risk assessment:

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine manufactured at Scale A. The commercial batches are produced using an up-scale process (initial Scale B for the active substance, Scale B for the finished product), and the comparability of these processes rely on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

The characterisation and control of active substance and finished product are acceptable in relation to critical quality attributes and impurities.

The control strategy for active substance and finished product is essential to guarantee acceptable quality and ensure batch-to-batch consistency of the finished product. Regarding the proposed control strategy, questions were raised with regards to the acceptance criteria for some tests. However, the data provided so far, including specifications and in-process controls, assure an overall consistent good quality of the product and the potential risks founded on data not yet available are considered to be very low. Therefore, control of the active substance and finished product is considered acceptable.

While some of the characterisation data still need to be completed, the characterisation of the active substance and finished product are considered acceptable subject to specific obligation, and the proposed specifications for RNA purity and is considered scientifically justified and acceptable subject to specific obligation.

2.2.6. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be sufficiently consistent and acceptable subject to specific obligations.

In general, physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in an acceptable way. While some of the characterisation data still need to be completed, the results of tests carried out indicate consistency of product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product is expected to have a satisfactory clinical performance.

The submitted information indicate that currently manufactured product batches are of a quality that is appropriate and sufficiently comparable to that of clinical development batches. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product a number of issues are expected to be addressed though fulfilment of specific obligations, within defined time frames.

The CHMP has identified the following specific obligations to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. The specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed below.

In accordance with Article 16 of regulation (EC) No 726/2004, the MAH shall inform the Agency of any information which might influence the quality of the medicinal product concerned, such as any necessary tightening of the finished product specifications earlier than July 2021. This is also related to the general obligation to vary the terms of the marketing authorisation to take into account the technical and scientific progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

To complete the quality documentation in the framework of the conditional marketing authorisation, the applicant should fulfil the following **specific obligations** (SOs) post-approval.

- SO1: In order to complete the characterisation of the active substance and finished product manufacturing processes, the applicant should provide additional data. no later than 01-02-2021.
- SO2: In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the applicant should provide additional comparability and validation data. no later than 30-04-2021. Interim reports will be provided monthly prior to this date.
- SO3: In order to ensure consistent product quality, the applicant should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience. no later than 30-06-2021.

As regards SO1 the following data are requested in order to complete the characterisation of the active substance and finished product manufacturing processes

(i) A tabulated summary of FMEA performed for the CX-024414 (mRNA) active substance including the conclusions drawn and appropriate justifications for criticality assignment and (de) prioritisation of characterisation studies should be provided no later than 15-01-2021.

(ii) Tabulated summaries of the actual settings of the investigated parameters, analytical results, and the prediction profiles should be provided for all process characterisation studies of CX-024414 (mRNA) active substance no later than 15-01-2021.

(iii) The applicant should provide the updated LNP and finished product appearance testing description including the characterisation test of potentially occurring visible particles no later than 01-02-2021.

(iv) A summary of the process risk assessment that forms the basis for process characterisation and the control strategy for the finished product should be submitted as committed by the applicant by 15-01-2021.

As regards SO2 the following data are requested in order to confirm the consistency of the active substance and finished product, manufacturing process (initial and final scales), the applicant should provide additional comparability and validation data.

(v) The applicant should provide additional data to confirm that the initial Scale B CX-024414 (mRNA) active substance and initial Scale B for LNP intermediate processes are properly validated at Lonza, Visp.

(vi) Process and batch data from at least 3 representative batches should be provided for the CX-024414 (mRNA) active substance (initial Scale B process at Lonza, Visp. The final PPQ report for initial Scale B willshould be submitted no later than 30-04-2021. Batch data will be submitted monthly before final PPQ.

(vii) The applicant should provide comprehensive comparability data on CX-024414 (mRNA) active substance and LNP from initial Scale B process at Lonza, Visp demonstrating that the commercial product manufactured at the Lonza, Visp site is representative of the material used in the clinical trials no later than 30-04-2021

(viii) The applicant should provide additional data to confirm finished product process validation. Process and batch data from at least 3 representative finished product batches should be provided for the scale B process at Rovi, Spain. A justification of the hold times, from a microbiological perspective, should be included. A process validation data summary report will be submitted no later than 01-02-2021.

(ix) The applicant should provide comprehensive comparability data demonstrating that the commercial finished product manufactured at the Rovi site is representative of the material used in the clinical trials. A final validation report including an assessment of comparability should be provided no later than 01-02-2021.

(x) The applicant should submit the description of the container closure integrity (CCI) test used as part of stability testing and its validation information by 31-03-2021.

As regards SO3, additional information on stability of the active substance and finished product should be provided and a review of the active substance and finished product specifications should be conducted following further manufacturing experience.

(xi) An update on all ongoing stability studies on CX-024414 (mRNA) active substance should be provided when data through 3 months is available from the three PPQ batches (initial Scale B CX-024414) manufactured at Lonza, Visp in Mobius bags no later than 31-05-2021.

(xii) The applicant should review the specifications for CX-024414 (mRNA) active substance: appearance, purity, product-related impurities, % 5'capped, % PolyA tailed RNA, residual DNA template; LNP: appearance, lipid impurities, purity, product-related impurities, % RNA encapsulation, particle size, polydispersity, osmolality; no later than 30-06-2021.

(xiii) The applicant should review the specifications for the finished product: appearance, RNA content, purity, product –related impurities, % RNA encapsulation, *in vitro* translation, lipid content, lipid impurities, particle size, polydispersity, osmolality no later than 30-06-2021.

(xiv) Periodic updates on the stability data (e.g. upon availability of data for 3 m + 4 weeks at 2°C – 8°C, 6 m + 4 weeks at 2°C – 8°C and 12 m and completion of the study) should be provided for the PPQ lots from Rovi. For the first Rovi lot, 3 months at -20°C + 4 weeks at 2°C – 8°C by 31.05.2021; 12 months of data to support overall program (basis of US data) at -20°C + 4 weeks at 2°C – 8°C by 28.02.2021. The applicant will provide quarterly stability updates starting on 01-04-2021. Completion of study by 01-04-2021.

2.2.7. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends additional points for investigation, as listed in Annex I of this document.

Note: The active substance is the mRNA CX-024414. However, in the submitted dossier, the information on the LNP have not been provided in the correct section of the dossier. An update of the current dossier structure should be provided (see **REC1.1)**. The references in the list of recommendations relate to the current structure of the dossier. It is recommended (**REC1.1**), that all information pertaining to the LNP should be moved in adequate sections of 3.2.P.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical immunogenicity and protective activity of mRNA-1273 have been evaluated in young mice (Balb/c, Balb/cJ, C57BL/6, and B6C3F1/J), aged mice (Balb/c), Syrian golden hamsters, and rhesus macaques. The potential of mRNA-1273-associated enhancement of the respiratory disease was also addressed in these animal models. The animal models that were used are considered suitable for the assessment of the immunogenicity, efficacy and safety of mRNA-1273.

No studies on the secondary pharmacodynamics, safety pharmacology, and pharmacodynamics drug interactions have been performed, which is in accordance with applicable guidelines.

Regarding the test item, mRNA-1273 is a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 encodes for the full-length S protein of SARS-CoV-2, modified to introduce 2 proline residues in order to stabilise the S protein in a prefusion conformation (S-2P). The mRNA is encapsulated in LNPs through a modified ethanol-drop nanoprecipitation process.

Table 1 – Overview of non-clinical development

Study Title	**Study Number**	**Test System**
Pharmacology Studies		
Vaccination and protein re-stimulation in young BALB/c mice with enhanced respiratory disease endpoint monitoring[a]	MOD-3937	BALB/c mice F only
Evaluation of immunogenicity and determination of titres dynamic range of mRNA-1273 (SARS-CoV-2)[a]	MOD-3938/ MOD-3940	BALB/c mice F only
Immunogenicity and protection from SARS-CoV-2 challenge of mice immunized with mRNA-1273[a]	VRC01	BALB/cJ, C57BL/6J, and B6C3F1/J mice
Efficacy of mRNA-1273 and enhanced disease in aged BALB/c mice[a]	VRC02	BALB/c mice, >12 months age
Study Title	**Study Number**	**Test System**

Evaluation of immunogenicity and efficacy of mRNA-1273 in the Syrian golden hamster model[a]	UTMB01[b]	Syrian golden hamster M and F
Immunogenicity and protective efficacy of mRNA-1273 in rhesus macaques[a]	VRC04	Rhesus macaques
Evaluation of immunogenicity and efficacy from expanded dose range of mRNA-1273 in rhesus macaques[a]	VRC07	Rhesus macaques
Biodistribution Study		
A single dose intramuscular injection tissue distribution study of mRNA-1647 in male Sprague-Dawley rats[c]	5002121 Amendment 1	Sprague Dawley rat, M only
Repeat-dose Toxicology Studies		
Zika: A 1-month (3 doses) intramuscular injection toxicity study of mRNA-1706 in Sprague-Dawley rats with a 2-week recovery period[d, e]	5002045	Sprague Dawley rat, M and F
A 1-month (3 doses) intramuscular injection toxicity study of mRNA-1706 in Sprague-Dawley rats followed by a 2-week recovery period [d, e]	5002231	Sprague Dawley rat, M and F
A 1-month (3 doses) study of mRNA-1653 by intramuscular injection in Sprague-Dawley Rat with a 2-week recovery period [f,e]	5002033	Sprague Dawley rat, M and F
A 1-month (3 doses) intramuscular injection toxicity study of mRNA-1893 in Sprague-Dawley rats followed by a 2-week recovery period [g, e]	5002400	Sprague Dawley rat, M and F
A 6-week (4 doses) intramuscular injection toxicity study of mRNA-1647 in Sprague-Dawley rats followed by a 2-week recovery period [c, e]	5002034	Sprague Dawley rat, M and F
A 6-week (4 doses) intramuscular injection toxicity study of mRNA-1443 in Sprague-Dawley rats followed by a 2-week recovery period [i, e]	5002158	Sprague Dawley rat, M and F
Other Toxicity Study		
A non-GLP repeat-dose immunogenicity and toxicity study of mRNA-1273 by intramuscular injection in Sprague Dawley rats [a]	2308-123	Sprague Dawley rat, M and F
Genotoxicity Studies		
SM-102 bacterial reverse mutation test in *Salmonella typhimurium* and *Escherichia coli* [e]	9601567	*S. typhimurium* and *E. coli* strains, *in vitro*
SM-102 *in vitro* mammalian cell micronucleus test in human peripheral blood lymphocytes[e]	9601568	Human peripheral blood lymphocytes
Zika mRNA: mammalian erythrocyte micronucleus test in rat [d, e]	9800399	Sprague Dawley rat, M and F
NPI luciferase mRNA in SM-102-containing lipid nanoparticles: *in vivo* mammalian bone marrow erythrocyte micronucleus assay in the rat	AF87FU.125012 NGLPICH.BTL	Sprague Dawley rat, M and F

Abbreviations: CMV = cytomegalovirus; eCTD = electronic common technical document; ERD = enhanced respiratory disease; F = female; GLP = Good Laboratory Practice; M = male; mRNA = messenger RNA; SM-102 = heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate; Tris- HCl = tris(hydroxymethyl)aminomethane-hydrochloride; VRC = Vaccine Research Centre.

Notes

a mRNA-1273 contains a single mRNA sequence that encodes for the full-length SARS-CoV-2 S-2P combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 20 mM Tris, 87 mg/mL sucrose, 10.7 mM sodium acetate, pH 7.5.

b This study was designed by the Sponsor and conducted by the University of Texas Medical Branch.

c mRNA-1647 contains 6 mRNAs which encode the full-length CMV gB and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex. The 6 mRNAs are formulated at a target mass ratio of

1:1:1:1:1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.
d mRNA-1706 contains a single mRNA sequence that encodes the prME structural proteins of Zika virus combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 20 mM Tris, 8% sucrose, pH 7.4.
e A Good-Laboratory Practice study.
f mRNA-1653 contains 2 distinct mRNA sequences that encode the full-length membrane-bound fusion proteins of hMPV and PIV3. The 2 mRNAs are formulated at a target mass ratio of 1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 7% PG, 1 mM DTPA, pH 7.4.
g mRNA-1893 contains a single mRNA sequence that encodes the prME structural proteins of Zika virus in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 100 mM Tris, 7% PG, 1 mM DTPA, pH 7.5.
h mRNA-1443 contains a single mRNA sequence that encodes for a phosphorylation mutant of the CMV pp65 protein (i.e., deletion of amino acids 435-438) combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.
i NPI luciferase mRNA is combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 25 mM Tris, 123 g/L sucrose, 1 mM DTPA, pH 7.5.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Immunogenicity studies

In rodents (mice, hamsters) and nonhuman primates (NHPs), mRNA-1273 elicited robust humoral immune responses in a dose-dependent manner, following intramuscular administrations. This is evidenced for the S-2P-binding IgG responses measured in Enzyme-Linked-Immunosorbent Assays (ELISAs), and equally also for the neutralising antibodies when assayed using either homotypic SARS-CoV-2 pseudovirus or live virus plaque reduction neutralisation test. The induced antibodies were shown to be specific for the Receptor-Binding-Domain and S1_N Terminal Domain of the Spike protein in mRNA-1273-vaccinated mice and NHPs. The post-boost binding and neutralising antibody titres induced by the mRNA-1273 prime-boost schedule were generally higher than the post-prime titres induced on the prime-only schedule across the tested species (rodents, NHPs) and regardless of strains and age of mice tested.

In two studies in young Balb/c mice, a strong positive correlation between S-2P-binding IgG titres and neutralising antibody titres induced by mRNA-1273 was observed. In general, a higher dose of mRNA-1273 was required for induction of detectable neutralising titres in mice and NHPs than for induction of detectable binding IgG response.

To assess the potential risk for Vaccine-induced Enhancement of Disease (VAED) for mRNA-1273, the type of T helper responses (Th1 vs Th2) was evaluated in mRNA-1273 immunised mice and NHPs, based on IgG subclasses measured by ELISA (IgG2a, IgG1, IgG2a/IgG1, young and aged Balb/c mice), and/or T-cell cytokines (e.g. IFN-g, IL-2, TNF-a; IL-4, IL-5, IL-10, IL-13, etc) measured by intracellular cytokine straining (ICS) and FACS (in young Balb/c mice, in NHPs). In mice, high IgG1 subclass with low or no IgG2a (Balb/c) is associated with a Th2 response, whereas a balanced IgG2a/IgG1 ratio is indicative of a Th1-directed response. The vaccine was shown to elicit a balanced IgG2a/IgG1 ratio in the immunised young and aged Balb/c mice, which is indicative of a Th1-skewed response. Consistent with this, vaccination of young mice with mRNA-1273 drove a Th1-directed CD4+ T cell response to both S1 and S2 overlapping peptide pools that encompass the entire S protein of the SARS-CoV-2, characterised by IFN-g/IL-2/TNF-a-producing T cells. Robust Th1-directed CD8+ T cell response to S1 peptide pool (but not S2 peptide pool) was also evident in vaccinated young mice. Overall, the frequency of S-derived peptides-specific CD4+ and CD8+ Th2 cytokine secreting cells (e.g. IL-4, IL-5, IL-13) were lower than Th1-directed T cells in mRNA-1273-vaccinated mice.

In NHPs, mRNA-1273 was shown to induce substantial Th1-directed CD4+ T cells as well as IL-21-producing follicular helper (Tfh) cell response to the SARS-CoV-2 S1 peptide pool, in a dose-dependent

manner. There was no evidence of a Th2-directed CD4+ T cell response induced in the vaccinated NHPs. No analysis on S1-specific CD8+ T cells was performed in these NHP studies.

Challenge studies

The protective activity of mRNA-1273 was evaluated in challenge-protection studies in young and aged Balb/c mice, hamsters and NHPs. Three weeks post-boost, hamsters were challenged i.n. with 10^5 PFU of wild-type SARS-CoV-2 virus. Four weeks post-boost (5 weeks for young mice), aged and young mice were challenged with mouse adapted SARS-CoV-2 virus (i.n. 10^3 PFU in aged mice; i.n. 10^5 PFU in young mice), and NHPs with wild-type SARS-CoV-2 (i.t. and i.n., $7.6x10^5$ PFU).

A clear dose-dependent protection was demonstrated in all animal challenge studies.

In aged mice, 1 µg dose of mRNA-1273 on prime-boost schedule completely protected mice from virus replication in the lungs at Days 2 and 4 post-challenge and prevented body weight loss at Day 4 post-challenge. Full protection against lung inflammation and lung haemorrhage was also evident. The 0.1 µg dose conferred partial protection, consistent with a lower immune response compared to the 1 µg dose group.

In young mice, 1 or 10 µg dose of mRNA-1273 conferred complete protection from virus replication in the lungs at Day 2 post-challenge, with 0.1 µg dose conferring partial protection. In this model, a clear effect on lung histopathology was evident even for the 0.1 µg and 0.01 µg doses.

In hamsters, mRNA-1273 was shown to protect animals from body weight loss and viral infection, respectively, by Day 6 and Day 4 post-challenge. The protected animals, receiving 1, 5, and 25 µg of mRNA-1273 on a prime/boost schedule, displayed mean viral titres below the limit of detection in the lungs and nasal turbinate at Day 4 post-challenge, and all but one in the 1 µg prime-boost group had no detectable viral replication (sgRNA) in the lungs by Day 4 post-challenge. Consistent with these findings, the lung pathological changes were generally milder in the vaccinated hamsters compared to the control animals.

In nonhuman primates, IM administration of mRNA-1273 at 30 µg dose on a prime-boost schedule or 100 µg dose on a prime-only schedule conferred complete protection from virus replication in the lungs at Day 2 post-challenge. The 2.5 µg prime-boost dose provided partial protection, consistent with suboptimal immune responses. Although breakthrough virus replication in the lungs was detected in this low dose group of animals, the lung histopathological analyses did not reveal enhanced lung inflammation compared to control animals. In another study, 100 µg of mRNA-1273 on a prime-boost schedule completely protected animals from virus replication in the lungs at Day 4 post-challenge. This protective effect was further substantiated by post-challenge assessments of the bronchoalveolar lavage (BAL) IgG and cytokines/chemokines, post-challenge neutralising titres, or lung histopathology data. Breakthrough virus replication in the lungs was detected at Day 2 post-challenge in both 10 µg and 100 µg dose groups in this study, however, lung histopathology analyses in these breakthrough animals did not reveal enhanced lung inflammation compared to control animals.

The aggregate data of challenge-protection studies do not indicate a sign of disease enhancement risk for mRNA-1273, when compared to controls including PBS group. Specifically, all challenge-protection studies conducted in mice, hamsters and NHPs did not show increased infiltrate of the eosinophils in the lung of the vaccinated animals.

Efforts have been made to explore a surrogate of protection in challenge protection studies using 2-3 dose levels of mRNA-1273, in order to achieve full and partial protection. However, no clear conclusion could be made at this moment.

Safety pharmacology programme

No dedicated safety pharmacology studies with mRNA-1273 were conducted. This is considered acceptable in light of the lack of signals on vital organ functions from the completed GLP repeat-dose toxicity studies and clinical studies submitted with mRNA-1273, as recommended by applicable vaccines guidelines (e.g. WHO Guidelines on Nonclinical Evaluation of Vaccines).

2.3.3. Pharmacokinetics

No dedicated ADME studies with mRNA-1273 were conducted, which is acceptable as generally nonclinical PK studies are not relevant to support the development and licensure of vaccine for infectious diseases. However, distribution studies should be conducted in the case of new formulations or novel excipients used.

Accordingly, the biodistribution of the vaccine platform was evaluated with mRNA-1647 in a non-GLP, single-dose, intramuscular injection study in Sprague Dawley rats. The objectives of this study were to determine the tissue distribution and pharmacokinetic characteristics of mRNA-1647 constructs following IM administration.

mRNA-1647 contains 6 mRNAs, which encode the full length CMV glycoprotein B (gB), and the pentameric glycoprotein H (gH)/glycoprotein L (gL)/UL128/UL130/UL131A glycoprotein complex (Pentamer). The 6 mRNA are formulated at a target mass ratio of 1:1:1:1:1:1 in the Sponsor's standard proprietary SM-102–containing LNPs. It is biologically plausible that the distribution of the mRNA vaccine is determined by the lipid nanoparticle content, whereas the influence of the mRNA itself is considered very limited. Therefore, it is acceptable that the biodistribution study was performed with the same lipid nanoparticles containing another mRNA (i.e. mRNA-1647).

The amount of the LNPs in the test material differed slightly in particle size from the final vaccine formulation of mRNA-1273. Even though it is not straightforward to understand the impact that the different particle size might have on mRNA tissue distribution, if any, nevertheless the liver distribution is not affected because the average diameter of endothelial fenestrae in the liver sinusoids in the test system (Sprague–Dawley rats) is 161 nm. The observed biodistribution with smaller LNP particle size should thus represent a worst-case scenario.

A qualified multiplex branched DNA (bDNA) assay was used for determination of mRNA in various tissues in the biodistribution study conducted with mRNA-1647. The LLOQ of the method were set at 0.05 ng/mL for the gB mRNA and UL130 mRNA, and 0.01 ng/mL for the gH, gL, UL128 and UL131A mRNAs. Following single IM injection at 100 µg mRNA-1647, subgroups of 5 rats were sequentially sacrificed pre-dose and 2, 8, 24, 48, 72, and 120 hours after dosing, for quantitation of 6 mRNA constructs in blood and a pre-specified set of organs/tissues.

Concentrations of mRNA-1647 were quantifiable in the majority of tissues examined at the first time point collected (2 hours post-dose) and peak concentrations were reached between 2- and 24-hours post-dose in tissues with exposures above that of plasma. Besides injection site [muscle] and lymph nodes [proximal and distal], increased mRNA concentrations (compared to plasma levels) were found in the spleen and eye. Both tissues were examined in the frame of the toxicological studies conducted with mRNA-1273 final vaccine formulation. Low levels of mRNA could be detected in all examined tissues except the kidney. This included heart, lung, testis and also brain tissues, indicating that the mRNA/LNP platform crossed the blood/brain barrier, although to very low levels (2-4% of the plasma level). Liver distribution of mRNA-1647 is also evident in this study, consistent with the literature reports that liver is a common target organ of LNPs.

The $T_{1/2}$ of mRNA-1647 was reliably estimated in muscle (site of injection), proximal popliteal and axillary distal lymph nodes and spleen with average $T_{1/2}$ values for all vaccine components of 14.9, 34.8, 31.1 and 63.0 hours, respectively. mRNA-1647 was rapidly cleared from plasma during the first 24 hours with the $T_{1/2}$ estimated in a range of 2.7 - 3.8 hours. The mean concentrations of all vaccine components became undetectable after 24 hours, except for gH, which was detectable up to the last time point of 120 hours but which was also detectable in 2 pre-dose plasma samples. The mRNA constructs were not measurable after maximum 3 days in tissues other than the muscle, lymph nodes, and spleen (~25 hours in brain).

Reference with regards to the mRNA biodistribution is made to the respective adverse findings observed in rat spleens in toxicological studies. No adverse findings were detected in the ophthalmological examinations or the brain/CNS.

No dedicated studies on absorption, metabolism, and excretion for mRNA-1273 have been submitted. This is generally acceptable with regards to the nature of the vaccine product.

2.3.4. Toxicology

The applicant submitted product specific and non-product specific studies; the latter studies were conducted with mRNA vaccine candidates that are based on the same LNP-technology as applied in mRNA-1273.

Repeat dose toxicity

The following seven repeated dose toxicity studies were submitted:

- Study 2308-123: Non-GLP compliant study examining the repeated dose toxicology of mRNA-1273;

- Study 5002045: GLP-compliant study examining the repeated dose toxicology of mRNA-1706, a LNP product containing mRNA that encodes the pre-membrane and envelope structural proteins of Zika virus;

- Study 5002231: GLP-compliant study examining the repeated dose toxicology of mRNA-1706, an LNP product containing mRNA that encodes encoding the prME structural proteins of Zika virus;

- Study 5002033: GLP-compliant study examining the repeated dose toxicology of mRNA-1653, a mRNA vaccine product containing 2 distinct mRNA sequences that encode the full-length membrane-bound fusion proteins of human metapneumovirus and parainfluenza virus type 3;

- Study 5002400: GLP-compliant study examining the repeated dose toxicology of mRNA-1893, a LNP-mRNA vaccine candidate that encodes the prME structural proteins of Zika virus;

- Study 5002034: GLP-compliant study examining the repeated dose toxicology of mRNA-1647, a LNP product containing an equal fraction of 6 mRNAs which encode the full-length cytomegalovirus glycoprotein B (gB) and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex;

- Study 5002158: GLP-compliant study examining the repeated dose toxicology of mRNA-1443, a LNP product containing a single mRNA sequence that encodes for a phosphorylation mutant of the CMV phosphoprotein 65 protein.

In all studies the control group was treated with Phosphate-buffered Saline (PBS).

The product-specific Study 2308-123 was not conducted in GLP-compliance, and exhibits major procedural/methodological limitations. In principle these aspects would render this study inadequate for evaluating the repeated dose toxicity of mRNA-1273 to the extent recommended in relevant guidance on non-clinical development of vaccine products. However, as no clear differences in toxicity

are observed between study 2308-123 and the repeated dose toxicity studies conducted with other LNP-mRNA products, the latter studies are considered sufficient to support clinical development and MAA.

The six submitted non-product-specific (but LNP-specific) repeated dose toxicity studies were conducted in GLP-compliance and meet the recommended criteria set out by relevant guidelines. Considering that the translated antigens of the evaluated mRNA-products are expected to elicit similar immunologic reactions, and considering that all these products are based on the same LNP technology, the extent of the submitted repeated dose toxicity programme is deemed acceptable. In the light of this statement, the GLP and procedural/methodological limitations of study 2308-123 are accepted.

In all studies, at least 2 - 4 doses of the product were applied to male and female Sprague Dawely rats (n = 5 per group and sex in Study 2308-123, n = 10 per group and sex in the other studies) by intramuscular administration, dosing ranged from 9 to 150 µg mRNA/dose. Apart from study 2308-123 in which only in-life endpoints, haematology and binding antibodies were analysed, clinical endpoints, ophthalmology examinations, clinical pathology parameters (haematology, coagulation, and clinical chemistry), post-mortem examinations (necropsy, histo(path)ology), neutralising antibodies and cytokine analysis (usually different interleukins, interferon gamma, acute-phase proteins) were generally assessed in the remaining studies. Reversibility of effects was generally studied after a two weeks recovery period.

In general, the repeated dose toxicology of the tested products proved to be quite similar among the studies, supporting that observed toxicities were not product specific, but rather caused by the immunologic responses towards the translated antigens, and potentially by a contribution of the novel LNP formulation. Test article-related adverse effects were observed at all tested concentrations, dose-dependency was frequently observed.

The following test-article related observations were generally noted in the submitted rat toxicity:

Test article-related in-life observations observed at ≥9 µg/dose included reversible or reversing erythema and oedema at the injection site and transient increase in body temperature at 6 hours post-dose returning to baseline 24 hours post-dose.

Haematology changes included increase in white blood cells, neutrophils, and eosinophils and decreased lymphocytes; coagulation changes included increase in fibrinogen and activated partial thromboplastin time; and clinical chemistry changes included decrease in albumin, increase in globulin, and a corresponding decrease in albumin/globulin ratio. Clinical pathology changes generally reversed or were reversing by the end of the 2-week recovery period.

Test article-related transient cytokine increases were observed at ≥9µg/dose at 6 hours post-dose including IFN-γ-induced protein-10, monocyte chemoattractant protein, and macrophage inflammatory protein 1 α. Cytokine changes were generally reversing by the end of the 2-week recovery period.

Post-mortem test article-related and generally dose-dependent changes in organ weights and macroscopic and microscopic findings were observed at ≥9 µg/dose. Organ weight increases were observed in the spleen, liver, and adrenal gland. Organ weight changes were generally reversing by the end of the 2-week recovery period. Macroscopic changes included skin thickening at the injection site and enlarged lymph nodes. Injection site changes completely recovered, and lymph node changes were recovering by the end of the 2-week recovery period. Microscopic changes included mixed cell inflammation at the injection site; increased cellularity and mixed cell inflammation in the inguinal, iliac, and popliteal lymph nodes; decreased cellularity in the splenic periartiolar lymphoid sheath; increased myeloid cellularity in the bone marrow; and hepatocyte vacuolation and Kupffer cell hypertrophy in the liver. Microscopic changes were generally reversing by the end of the 2-week recovery period.

Genotoxicity

mRNA-1273 contains natural nucleosides and lipid nanoparticles. The applicant submitted genotoxicity data to evaluate the genotoxic potential of the novel excipient SM-102 as well as the final vaccine formulation. The other lipid components contained in the final formulation, i.e. PEG2000-DMG, DSPC and cholesterol, were not separately tested but are contained in the formulation tested in the *in vivo* genotoxicity studies, which is acceptable. DSPC and cholesterol do not raise any concern in terms of genotoxic potential.

SM-102 was tested for its genotoxic potential in study 9601567 in a bacterial reverse mutation test in *Salmonella typhimurium* and *Escherichia coli*. Results did not indicate any evidence of genotoxic activity in this *in vitro* mutagenicity assay. SM-102 did not show any evidence of genotoxic activity in the conducted *in vitro* mammalian cell micronucleus test in human peripheral blood lymphocytes (Study 9601567). No cytotoxicity was observed in this assay. Both assays were performed in compliance with GLP.

In *in vivo* genotoxicity testing, NPI luciferase mRNA in SM-102-containing LNPs was determined to be negative (non-clastogenic) after a single dose of 0.32/6.0, 1.07/20, or 3.21/60 mg/kg NPI luciferase mRNA/SM-102 in Sprague Dawley rats. A statistically significant decrease in PCEs (polychromatic erythrocyte) was observed in the low dose 0.32/6.0 mg/kg NPI luciferase mRNA/SM-102 in the male group only (male and female were tested in separate groups) at the 48-hour time point. This effect did not show dose dependency and after 24 hours was no longer evident.

Increases in cytokines IL-6, MCP-1, MIP-1α, and IP-10 were observed in this study 6 hours after IV administration of 1.07/20 mg/kg and 3.21/60 mg/kg NPI luciferase mRNA/SM-102, respectively. Reference in this regard is made to the nonclinical pharmacology section, dealing with cytokine release after the intramuscular administration of clinically relevant doses of mRNA-1273 to NHP.

Another GLP-compliant *in vivo* micronucleus study in rat was performed with mRNA-1706 in SM-102-containing lipid nanoparticles using IV administration. In this study statistically significant increases in micronucleated erythrocytes were reported in both sexes. A strong increase in Molecular initiating event (MIE) was observed 48 hours after the final administration in the highest dose group in male rats (mRNA-1706: 4.0/5.2 mg/kg; SM-102: 54.1 mg/kg). No clear dose-response relationship was reported.

With regards to the positive findings observed in *in vivo* micronucleus assays, ICH S2(R1) states that in this case 'all the toxicological data should be evaluated to determine whether a non-genotoxic effect could be the cause or a contributing factor'. In the toxicological studies conducted in rat, various non-genotoxic effects that could impact on the increase of micronucleated erythrocytes in this species were observed: hyperthermia, disturbance of erythropoiesis (lower reticulocyte count, higher red blood cell distribution width) and increase and inflammation of the spleen, which could affect clearance of micronucleated cells from the blood.

Carcinogenicity

No carcinogenicity studies were submitted. This is scientifically acceptable and in line with relevant guidelines on non-clinical development of vaccine candidates. The components of the vaccine formulation are lipids and natural nucleosides that are not expected to have carcinogenic potential.

Reproduction Toxicity

A GLP-compliant reproductive and developmental toxicology (DART) study with mRNA-1273 has been conducted in female Sprague Dawley CD rats.

IM administrations of mRNA-1273 to female SD 1 rats at the human clinical dose, twice before mating and twice during gestation, was associated with non-adverse effects including thin fur cover, swollen hindlimbs and limited usage of the hindlimb. However, 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 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.

In this study, no vaccine dose was administered during the 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. The overall pregnancy index was numerically lower in mRNA-1273 vaccinated female rats (84.1%), compared to control animals (93.2%), but remains within the Test Facility's historical control range (low range being 75%).

Apart from that, no consistent adversities were observed in the male and female reproductive tracts of Sprague Dawley rats during macroscopic and microscopic investigation in the frame of the submitted repeated dose toxicity studies.

Local Tolerance

No stand-alone local tolerance studies were submitted. This is acceptable and in line with relevant guidance on non-clinical vaccine development since local tolerance was evaluated in repeated dose toxicity studies.

In these studies, administration of LNP-mRNA products proved to induce local irritancy and inflammation. These effects can be related to an immunologic response towards the administered mRNA-1273 at and in the vicinity of the injection site, the former being the desired pharmacological mode of action of mRNA-1273. However, the observed local inflammatory response towards LNP-mRNA injection in rats was not only noted in the direct vicinity of the injection site, but also in adjacent tissues and/or organs. For example, subcutaneous tissue, the dermis, epidermis, skeletal muscle (with myofiber degradation), perineurial tissue surrounding the sciatic nerve, and draining lymph nodes in proximity to the injection site were commonly affected by inflammation after LNP-mRNA administration.

2.3.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100), due to their nature vaccines and lipids are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this Application for Marketing Authorisation, which is considered acceptable.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The nonclinical proof-of-concept studies included evaluation of immunogenicity and protective activity of mRNA-1273 in young and aged mice, Syrian golden hamsters and nonhuman primate (rhesus macaques). The potential risk for VAED in these animal models was also assessed.

In each animal model, IM administration of mRNA-1273 at clinically relevant dose(s) elicited robust SARS-CoV-2 S-2P-binding and neutralising antibody titres. 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 nonhuman primates. 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.

In challenge protection studies, the immunised animals were challenged with mouse adapted SARS-CoV-2 virus (IN, 10^3 PFU for aged mice, 10^5 PFU for young mice) or wild-type SARS-CoV-2 virus (IT and IN, $7.6x10^5$ PFU for nonhuman primates; IN, 10^5 PFU for hamsters). In aged mice, 1 µg dose of mRNA-1273 on prime-boost schedule completely protected mice from virus replication in the lungs, at Days 2 and 4 post-challenge, as well as preventing body weight loss at Day 4 post-challenge. Full protection against lung inflammation was also evidenced. The 0.1 µg dose conferred partial protection, consistent with a lower immune response compared to the 1 µg dose group. In young mice, 1 or 10 µg dose of mRNA-1273 conferred complete protection from virus replication in the lungs at Day 2 post-challenge, with 0.1 µg dose conferring partial protection. In this model, a clear effect on lung histopathology was evidenced even for the 0.1 µg and 0.01 µg doses. In hamsters, mRNA-1273 administration at 1, 5, or 25µg on a prime-boost schedule conferred clear protection from body weight loss and viral infection in the lungs and nasal turbinate, generally consistent with the lung pathological changes.

Regarding challenge-protection studies in nonhuman primates, IM administration of mRNA-1273 at 30 µg dose on a prime-boost schedule or 100 µg dose on a prime-only schedule, in one study, conferred complete protection from virus replication in the lungs, at Day 2 post-challenge. The 2.5 µg prime-boost dose provided partial protection, consistent with suboptimal immune responses. In another study, 100 µg of mRNA-1273 on a prime-boost schedule completely protected animals from virus replication in the lungs at Day 4 post-challenge. Breakthrough virus replication in the lungs was detected in some mRNA-1273 vaccinated animals, however, lung histopathology analyses of these animals did not reveal a sign of enhanced lung inflammation or of disease enhancement risk of mRNA-1273.

In conclusion, robust proof-of concept data have been submitted and the potential risk of mRNA-1273-associated disease enhancement has been appropriately addressed and no risk identified.

Biodistribution

The evaluation of mRNA-1273 tissue distribution was based on a rat biodistribution study using a similar mRNA-based vaccine encoding CMV antigens (mRNA-1647). The non-GLP status and no inclusion of female rats do not qualify this study as pivotal, which is not considered critical, given the general acceptance of platform approach for evaluating the toxicology profile of mRNA-1273.

Following single IM injection at 100 µg mRNA-1647, the plasma and tissue pharmacokinetics and tissue distribution were assessed in blood and a pre-specified set of organs/tissues for a period of 120 hours. A qualified branched DNA (bDNA) multiplex method was used.

As expected, 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 distributes. For these highly exposed 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.

In summary, the data are useful for understanding the tissue distribution pattern of mRNA-1273. Only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the

mRNA constructs did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen.

Distribution, metabolism, and PK of the novel lipid component SM-102 have not been extensively studied in dedicated studies. However, data with SM-86, a close structural analogue, have been generated. These data show consistent biodistribution compared to the mRNA administered with the LNP. Furthermore, efficient metabolisation via ester hydrolysis and rapid elimination of the remaining aliphatic acid head group via biliary and renal clearance were reported. Quantitative Whole-Body Autoradiography (QWBA) confirmed the biodistribution of SM-86 and revealed no persistence of the lipid component in any tissue beyond 168 hours. Because of the reported structural similarity between SM-86 and SM-102, it is assumed that SM-102 will distribute similarly and will be efficiently and rapidly metabolised and eliminated via biliary and renal routes.

SM-102 pharmacokinetics after IV administration of similar PEG2000-DMG containing LNPs were determined to be very similar to those parameters observed for SM-86. Altogether, these data do not suggest accumulation of SM-102 upon repeated dosing.

Toxicology

During the assessment of the submitted toxicology studies of mRNA-1273, the following observations were made from the repeated dose toxicity:

Alterations in erythropoiesis such as a decrease in mean reticulocyte count and increase in red cell distribution width were observed in most of the submitted rat repeated dose toxicity studies. Furthermore, in the mRNA-1273-specific study 2308-123, a decrease of RBC mass (erythrocytes, haemoglobin, and/or haematocrit) were noted. Such alterations can – in principle – be correlated to infections and associated inflammations, and therefore can presumable be related to inflammatory responses after LNP-mRNA product administrations in rats. The potential clinical relevance is not known however these findings were reversible.

Among the submitted rat toxicity studies, hepatic alterations (increased liver weights, hepatocytic vacuolation, hypertrophy of Kupffer-cells, centrilobular degeneration characterised by presence of mixed inflammatory cell in sinusoids with single cell necrosis or degeneration of hepatocytes) and corresponding changes in clinical chemistry (statistically significant increases in AST, ALP, triglyceride, cholesterol, bilirubin, urea nitrogen) were frequently -but not consistently- observed. It is possible that the inconsistent changes observed in the liver of rats are not a direct result of LNP-mRNA administration, but rather secondary to the systemic inflammation observed following LNP-mRNA administration.

Throughout the repeated dose toxicity studies, increases in eosinophil counts (up to 6.5-fold compared to the control groups) were consistently observed in the haematology samples taken after the last booster administrations. The absolute eosinophil counts observed in LNP-mRNA studies reached values that would be classified as eosinophilia in patients: in humans, eosinophilia starts when absolute EOS counts exceed 450-500 cells µL-1 (Ramirez et al. 2018). In study 5002034, the mean female EOS count of the highest dose group (100 µg mRNA/dose) was 451 cells µL-1, with the highest individual EOS count being 1020 cells µL-1 in animal No. 4507. Increased eosinophil counts can be correlated with diseases such as IgE-mediated type-1 allergy, in which peripheral eosinophils are increased as a consequence of the late-phase allergic reaction, and asthma. The observed eosinophil increase in rat LNP-mRNA studies could therefore be potentially clinically relevant. Considering these aspects, this finding is included in the SmPC under 5.3, however, it is noted that its toxicological potential to humans is low.

Decreasing lymphocyte counts (up to more than a factor of 4 relative to control groups) were consistently observed after LNP-mRNA vaccine administration throughout the submitted rat toxicity

studies. Furthermore, histological investigations demonstrated test-article related minimal to mild decreased lymphoid cellularity and/or single cell necrosis of lymphocytes in the spleen (periarteriolar sheath), mesenteric lymph nodes (paracortex) and in the thymus (cortexin) in some of the submitted studies. Based on available literature, these findings are presumably caused by test-article related severe stress, originating from the intense inflammatory response after mRNA-1273 administration to rats.

Throughout the rat repeated dose toxicity studies, increases in activated partial thromboplastin time (APTT, up to ~30%) and fibrinogen (up to ~2.5-fold) were consistently observed. These haemostatic alterations could potentially be clinically relevant and were therefore mentioned in section 5.3 of the SmPC. However, the toxicological potential of these rat findings is low for humans.

A significant increase of plasma potassium (up to 20%) was observed in most of the submitted repeated dose toxicity rat studies. However, the observed increases in plasma potassium levels in the submitted rat GLP repeated dose toxicity studies are consistent with biologic variability in rats, and were reversed or were reversing after recovery, and were not considered test-item related by the study director and/or clinical pathologist. Furthermore, the magnitude of the observed alterations is not of relevance in susceptible patients suffering from hyperkalaemia and/or cardiac morbidities.

In different rat toxicity studies, splenic alterations and/or splenic toxicity were consistently observed. These alterations ranged from splenomegaly (significant weight increases were frequently observed throughout all test-article groups), decreased cellularity of the periarteriolar lymphoid sheath, increased cellularity of macrophages (e.g. in red pulp), neutrophilic infiltration in the red pulp, single cell necrosis of lymphocytes in the spleen (periarteriolar sheath), and increased extramedullary haematopoiesis. Furthermore, LNP-mRNA accumulation in the spleen was observed in the submitted PK rat study 5002121. The observed spleen changes were minimal and caused by a transient systemic inflammatory response to LNP administration and/or to the expected compensatory response. Furthermore all the splenic changes fully resolved or were resolving following a 2-week recovery period. Because of these aspects, it is considered that the observed spleen findings could only bear limited relevance for humans.

In different rat repeated dose toxicity studies, statistically significant adrenal gland alterations were observed, which ranged from increased organ weights to dose-dependent minimal cortical hypertrophy. As these findings generally resolved after recovery and were only inconsistently observed among the submitted rat toxicity studies, no concern arises from this finding.

Generally, local inflammatory response towards LNP-mRNA injection in rat repeated dose toxicity studies was not only observed in the direct vicinity of the injection site, but also in adjacent tissues and/or organs. For example, subcutaneous tissue, the dermis, epidermis, skeletal muscle (with myofiber degradation), perineurial tissue surrounding the sciatic nerve, and draining lymph nodes in proximity to the injection site were commonly affected by inflammation after LNP-mRNA administration. The observed spread of inflammation into adjacent tissues of the injection site 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 concentration of drug product at the site of injection in rats compared to humans. Considering this aspect, the applicant calculated a safety margin of ~ 375. Therefore, it is considered that these severe local inflammations bear no clinical relevance.

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 two times only, and a low dose containing around 1 mg SM-102 per dose will be administered at the proposed posology. 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. Taking all these data together, a relevant genotoxic risk is thus not expected for mRNA-1273.

A GLP-compliant reproductive and developmental toxicology (DART) study with mRNA-1273 has been conducted in female Sprague Dawley CD rats.

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.

In this study, 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. 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%). In summary, no mRNA-1273 related effect on pregnancy is expected from these data.

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.

2.3.7. Conclusion on the non-clinical aspects

No major non-clinical issues are identified in this application. A range of other concerns identified have been properly addressed by the applicant.

The CHMP is of the view that non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

2.4. Clinical aspects

2.4.1. Introduction

A dose-ranging Phase 1 safety and immunogenicity study (20-0003); a dose-confirmation Phase 2a safety and immunogenicity study (mRNA-1273-P201); and a pivotal Phase 3 efficacy, safety, and immunogenicity study (mRNA-1273-P301) are ongoing (see the below tabular overview of clinical studies). No clinical studies with mRNA-1273 have been completed at the time this report was written.

- **GCP**

The applicant claimed that the clinical trials included in the application were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In addition, to seek further reassurance of the GCP compliance of the studies included in this dossier, in the context of the COVID-19 pandemic and under the framework of the EMA-FDA GCP initiative, EMA gathered additional information from the USA Regulatory Authority, US-Food and Drug

Administration (US-FDA) and shared the outcome of the GCP inspections performed by US-FDA with the CHMP, in order for this information to be considered in the assessment:

- Establishment Inspection Reports from GCP inspections performed by US-FDA of nine investigator sites in USA for study mRNA-1273-P301 "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".

Based on the review of clinical data, the above-mentioned reports and the general advisory input from the COVID-19 EMA pandemic Task Force (ETF), a GCP inspection of the clinical trials included in this dossier was not considered necessary by the CHMP.

- **Tabular overview of clinical studies**

Table 2 Overview of ongoing clinical studies

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot*
20-0003 (USA)/ Ongoing	• Immunogenicity of mRNA-1273 measured by IgG bAb levels to SARS-CoV-2 spike protein and the receptor binding domain (secondary) • Immunogenicity of mRNA-1273 measured by nAb levels against SARS-CoV-2 pseudovirus and wild-type virus (exploratory) • The SARS-CoV-2 protein-specific T-cell responses in a subset of participants (exploratory)	Safety and reactogenicity of 4 dose levels of mRNA-1273 vaccine: • Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination (primary) • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination (primary) • Frequency of SAEs, NOCMCs, and MAAEs from Day 1 to Day 394 (primary)	**Age Groups:** 18 to 55 (n=75), 56 to 70 (n=40), ≥71 (n=40) **mRNA-1273 Dose Groups:** 10 µg (n=15)[a], 25 µg (n=35), 50 µg (n=35), 100 µg (n=35), 250 µg (n=35)[b]	Phase 1, open-label, dose ranging	10, 25, 50, 100, or 250 µg mRNA-1273 2 IM injections, 28 days apart	Immunogenicity: Day 119[c] Safety: 07 Oct 2020

Abbreviations: AE = adverse event; AR = adverse reaction; IM = intramuscular; MAAE = medically attended adverse event; NOCMC = new onset of chronic medical condition; SAE = serious adverse event.

a In Study DMID 20-0003, Cohort 13 (10 µg, 18-55 years, n=15) was not enrolled.

b In Study DMID 20-0003, dosing at the 250-µg level was discontinued after Cohort 3 (18-55 years, n=15) and prior to enrolment in Cohorts 6 (56-70 years, n=10) and 9 (≥71 years, n=10).

c Day 57 post-vaccination for participants who received the 50-µg dose.

* Additional data will be provided as it accumulates.

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot*
mRNA-1273-P201 (USA)/ Ongoing	• Immunogenicity of 2 dose levels of mRNA-1273 as assessed by the level of specific binding antibody (primary) • Immunogenicity of 2 dose levels of mRNA-1273 as assessed by the titer of neutralising antibody (secondary)	Safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine: • Solicited local and systemic ARs through 7 days after each injection (primary) • Unsolicited AEs through 28 days after each injection (primary) • MAAEs through the entire study period (primary) • SAEs throughout the entire study period (primary) • Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only; ≥55 years of age) (primary) • Vital sign measurements and physical examination findings (primary)	**Age Groups:** **Cohort 1**: ≥18 to <55 (n=300) **Cohort 2**: ≥55 (n=300) **Dose Groups:** Placebo (n=200) mRNA-1273 dose groups: 50 µg (n=200), 100 µg (n=200)	Phase 2a, randomised, observer-blind, and placebo-controlled	50 or 100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart	Immunogenicity: Day 57 Safety Day 57

*Additional data will be provided as it accumulates.

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot*
mRNA-1273-P301 (USA)/ Ongoing	• Efficacy of mRNA-1273 to prevent COVID-19 (primary) • Efficacy of mRNA-1273 to prevent severe COVID-19 (secondary) • Efficacy of mRNA-1273 to prevent COVID-19 regardless of prior SARS-CoV-2 infection (secondary) • Efficacy of mRNA-1273 to prevent SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity (secondary)	Safety and reactogenicity of mRNA-1273 vaccine: • Solicited local and systemic ARs through 7 days after each injection (primary) • Unsolicited AEs through 28 days after each injection (primary) • MAAEs or AEs leading to withdrawal through the entire study period (primary) • SAEs throughout the entire study period (primary) • Pregnancies and perinatal outcomes (primary)	**Age Groups:** 18+ (n=30000) **Dose Groups:** Placebo (n=15000) mRNA-1273 100 µg (n=15000) **Stratification:** 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	Phase 3, randomised, stratified, observer-blind, placebo-controlled	100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart	**Data snapshot 1** date: 11 Nov 2020 (data cut-off: IA1 efficacy 07 Nov 2020 Safety set 11 Nov 2020) **Data snapshot 2** date: 25 Nov 2020 (data cut-off: final efficacy analysis 21 Nov 2020 safety set 25 Nov 2020) Immunogenicity: Not yet included in application

* Additional data will be provided as it accumulates.

2.4.2. Clinical Pharmacology

For vaccines, pharmacokinetics is not applicable, and pharmacodynamics relates to investigation of immunogenicity. Immunogenicity was evaluated by assessing changes from baseline in SARS-CoV-2-specific binding antibodies (bAb) levels and neutralising antibody (nAb) titres.

Mechanism of action

COVID-19 Vaccine Moderna contains mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation. After intramuscular injection, cells at the injection site and the draining lymph nodes take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into viral protein. The mRNA delivery system is based on the principle and observation that cells *in vivo* can take up mRNA, translate it, and express viral protein antigen(s) in the desired conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is non-replicating, and is expressed transiently mainly by dendritic cells and subcapsular sinus macrophages. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The expressed, membrane-bound spike protein of SARS-CoV-2 is then recognised by immune cells as a foreign antigen. This elicits both T-cell and B-cell responses to generate functional neutralising antibodies, which may contribute to protection against COVID-19.

Immunogenicity studies

The immunogenicity data available so far were generated from one phase 1 and one 2a study conducted in the USA. No immunogenicity data from Phase 3 are available for assessment at the time this report was written. No study reports are yet available for this application. Immunogenicity data were mainly presented in listings, tables and figures.

Assays

Across the Phase 1, 2, and 3 studies, ELISA is being used to measure vaccine-induced binding IgG antibodies to the SARS-CoV-2 spike protein and, in some cases, to specific domains of the protein, (i.e., the RBD of the spike protein). Multiple assays are being used to measure the titres of nAbs. In Study 20-0003, vaccine-induced neutralising activity was assessed by PsVNA (performed at the NIAID Vaccine Research Center, USA) and by live wild-type SARS-CoV-2 virus PRNT assay (performed at the Vanderbilt University Medical Center, USA). These experimental assays were developed using a fit-for-purpose approach.

Assays used in later phases followed more typical qualification and validation paths. A qualified MN assay (performed by Battelle) and qualified ELISAs (performed by PPD) were used to test samples from Study mRNA-1273-P201. A panel of validated assays will be used to assess immunogenicity in Study mRNA-1273-P301.

In addition, in Study 20-0003, convalescent sera obtained from 41 patients who recovered from SARS-CoV-2 infection were used during assay development to generate a relative benchmark (based on levels elicited by natural infection).

To address concerns about the theoretical risk of enhanced disease after injection with mRNA-1273, an additional series of *in vitro* studies were performed using peripheral blood mononuclear cells isolated from participants in Study 20-0003. The induction of a Th2-directed response has been linked to ERD, as seen in vaccines for other respiratory virus infections, in particular, formalin-inactivated respiratory syncytial virus vaccine (Kim et al 1969; Haynes et al 2020). In animal models of vaccine-induced immunity against other coronaviruses, specifically MERS and SARS-CoV-1, a Th1-directed immune response has been correlated with a lack of ERD immunopathology (Grifoni et al 2020; Peng et al 2020; Sekine et al 2020; Weiskopf et al 2020). Activated CD4+ T cells can be segregated into Th1- and Th2-directed responses based on the production of specific cytokines; therefore, ICS assays were used to evaluate CD4+ and CD8+ T-cell responses elicited by the mRNA-1273 vaccine in clinical samples.

An assessment of the assay qualification parameters and assay conduct led to the conclusion that the main assays used in the phase 2 study are acceptable (ELISA for determination of binding antibodies, the pseudovirus neutralisation assay and the cytokine stimulation assay). Formal qualification reports are requested to be submitted as part of the final clinical study report, which is the subject of a specific obligation.

Phase 1 (study 20-003)

This study is a phase 1, open-label, dose-ranging study of the safety and immunogenicity of mRNA-1273 in healthy adults (3 age cohorts: 18-54 yrs, 55-70 yrs, ≥71 yrs).

Table 3 – Overview of Study 20-003

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot
20-0003 (US)/ Ongoing	• Immunogenicity of mRNA-1273 measured by IgG bAb levels to SARS-CoV-2 spike protein and the receptor binding domain (secondary) • Immunogenicity of mRNA-1273 measured by nAb levels against SARS-CoV-2 pseudovirus and wild-type virus (exploratory) • The SARS-CoV-2 protein-specific T-cell responses in a subset of participants (exploratory)	Safety and reactogenicity of 4 dose levels of mRNA-1273 vaccine: • Frequency and grade of each solicited local and systemic reactogenicity AE during a 7-day follow-up period post each vaccination (primary) • Frequency and grade of any unsolicited AEs during the 28-day follow-up period post each vaccination (primary) • Frequency of SAEs, NOCMCs, and MAAEs from Day 1 to Day 394 (primary)	**Age Groups:** 18 to 55 (n=75), 56 to 70 (n=40), ≥71 (n=40) **mRNA-1273 Dose Groups:** 10 µg (n=15)[b], 25 µg (n=35), 50 µg (n=35), 100 µg (n=35), 250 µg (n=35)[c]	Phase 1, open-label, dose ranging	10, 25, 50, 100, or 250 µg mRNA-1273 2 IM injections, 28 days apart	Immunogenicity: Day 119[d] Safety: 07 Oct 2020

Abbreviations: AE = adverse event; AR = adverse reaction; IM = intramuscular; MAAE = medically attended adverse event; NOCMC = new onset of chronic medical condition; SAE = serious adverse event.

[a] A second analysis with data snapshot 25 Nov 2020 will be submitted to the EUA application when at least 151 cases have been adjudicated as meeting the case definition for the primary endpoint and at least 2 months of median safety and efficacy follow-up data have accumulated.

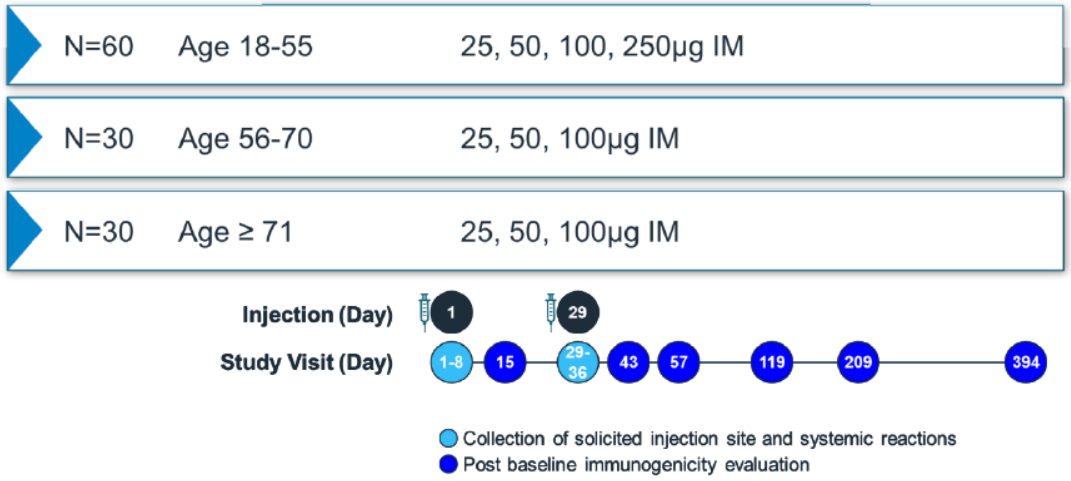
[b] In Study DMID 20-0003, Cohort 13 (10 µg, 18-55 years, n=15) was not enrolled.

[c] In Study DMID 20-0003, 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).

[d] Day 57 post-vaccination for participants who received the 50-µg dose.

* Additional data will be provided as it accumulates.

Figure 4 - Study 101 Design



In the phase 1 study 120 participants were enrolled and assigned to different treatment groups as depicted in the table below.

Cohort	Sample Size	Age	First and Second Dose
1	15	18-55	25 µg mRNA-1273
2	15	18-55	100 µg mRNA-1273
3	15	18-55	250 µg mRNA-1273
4	10	56-70	25 µg mRNA-1273
5	10	56-70	100 µg mRNA-1273
7	10	≥71	25 µg mRNA-1273
8	10	≥71	100 µg mRNA-1273
10	15	18-55	50 µg mRNA-1273
11	10	56-70	50 µg mRNA-1273
12	10	≥71	50 µg mRNA-1273

Note: Cohorts 6, 9, and 13 were not enrolled as decided by the study team and therefore are not included.

Report Date: 26OCT2020
Data Cutoff Date: 07OCT2020

Assays used

- IgG ELISA to the SARS-CoV-2 S (spike) protein and receptor binding domain (RBD);
- Neutralisation assay using a SARS-CoV-2 pseudovirus (pseudovirus neutralisation assay; PsVNA);
- Neutralisation assay using a live wild-type SARS-CoV-2 (plaque reduction neutralisation test; PRNT); strain: SARS-CoV-2/human/USA/USA-WA1/2020 (GenBank: MN985325.1);
- Neutralisation assay using a live wild-type SARS-CoV-2 (focus reduction neutralisation test; FRNT-mNG); strain: SARS-CoV-2/human/USA/USA-WA1/2020 (GenBank: MN985325.1);
- Intracellular cytokine stimulation assay (T cell response).

Results

Binding and neutralising antibody responses (secondary and exploratory objectives, respectively)

Kinetics of antibody titres binding to SARS-CoV-2 S protein in sera of subjects vaccinated with mRNA-1273 are shown in **Figure 5**. The spike seen after day 29 coincides with the evaluation after the second vaccination.

Figure 5 – Serum IgG ELISA Area Under the Curve (AUC) values by time points and vaccination group – S-2P

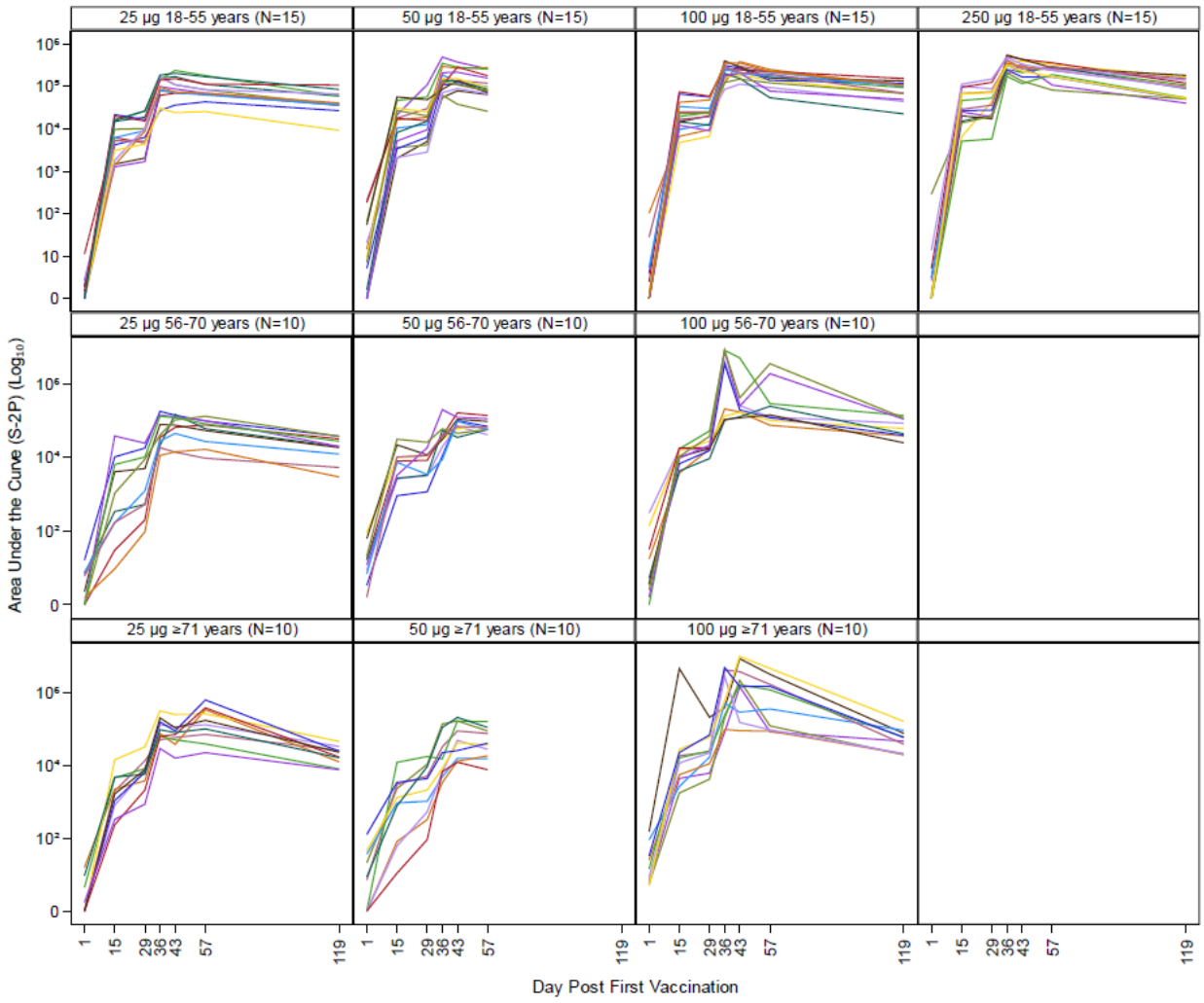


***Table* 4** below shows GMT results across age strata for the relevant 100 µg mRNA-1273 dose.

Table 4– Serum IgG ELISA Endpoint Titre Geometric Mean Results with 95% confidence intervals by time point and vaccination group in Study 20-003 – Spike stabilised antigen (S-2P) – All age group 100 µg mRNA-1273

Time Point	Statistic	100 µg mRNA-1273 18-55 years (N=15)	100 µg mRNA-1273 56-70 years (N=10)	100 µg mRNA-1273 ≥71 years (N=10)	Convalescent Sera
Day 1 (Pre-Vaccination 1)	n	15	10	10	41
	GMT	131	655	953	138,901
	95% CI	65, 266	270, 1591	493, 1842	82876, 232799
Day 29 Post Vaccination 1 (Pre-Vaccination 2)	n	15	10	10	NA
	GMT	109209	115831	203365	NA
	95% CI	79051, 150874	73288, 183069	97384, 424686	NA
Day 43 Post Vaccination 1 (14 Days Post Vaccination 2)	n	14	9	10	NA
	GMT	811119	1305996	8091439	NA
	95% CI	656336, 1002404	581138, 2934971	2546249, 25712881	NA
Day 57 Post Vaccination 1 (28 Days Post Vaccination 2)	n	14	9	10	NA
	GMT	782719	1183066	3638522	NA
	95% CI	619310, 989244	379698, 3686201	1316233, 10058130	NA
Day 119 Post Vaccination 1 (90 Days Post Vaccination 2)	n	15	9	10	NA
	GMT	413971	366252	195272	NA
	95% CI	322891, 530744	213031, 629675	117647, 324112	NA

Abbreviations: GMT = geometric mean titer; n = number of participants with results available at time point; N = number of participants; NA = not available.

Kinetics of pseudovirus neutralisation titres in sera of subjects dosed with mRNA-1273 are shown in **Figure 6** (across age strata and dose levels). The spike seen after day 29 coincides with the evaluation after the second vaccination.

Figure 6 – Pseudovirus Neutralisation Assay titres by time point and vaccination group - ID50

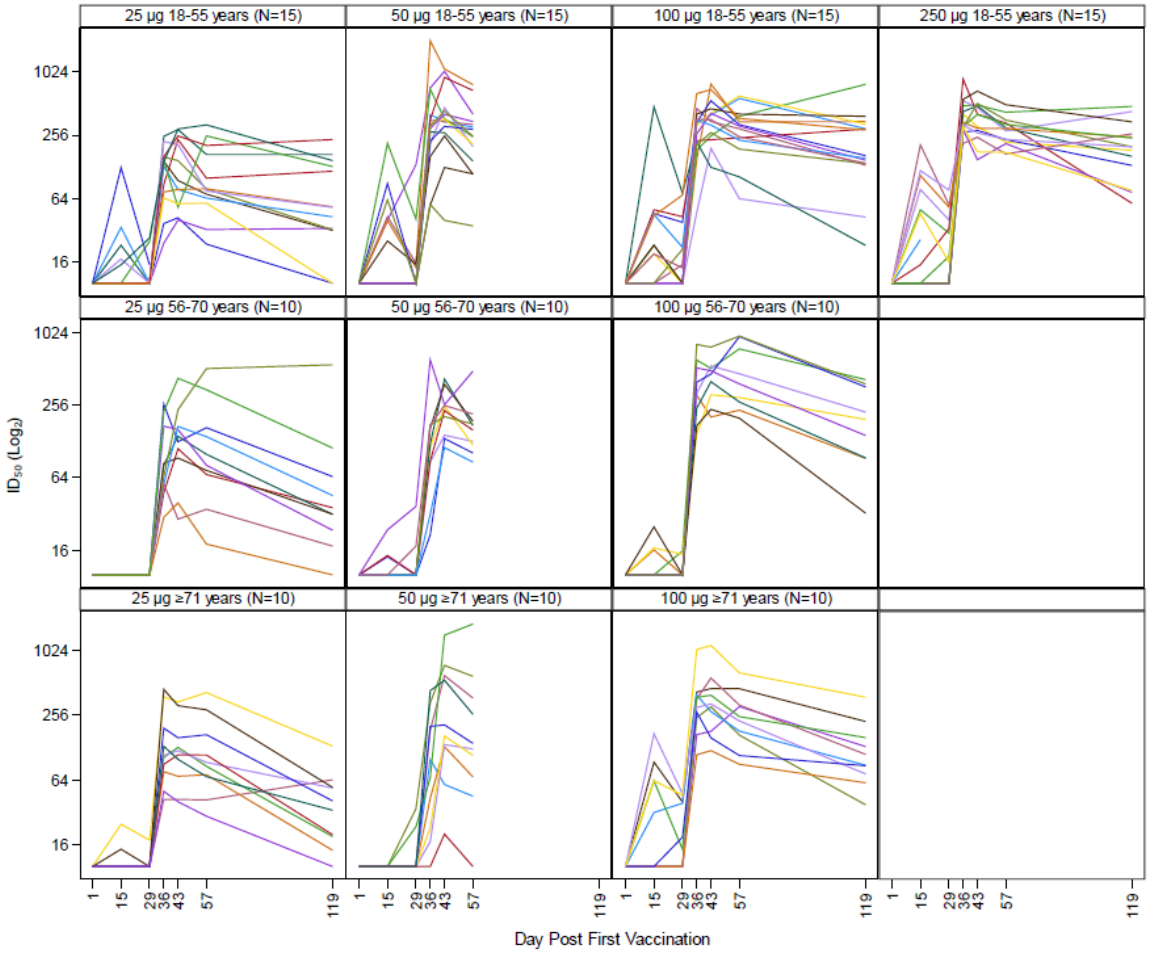
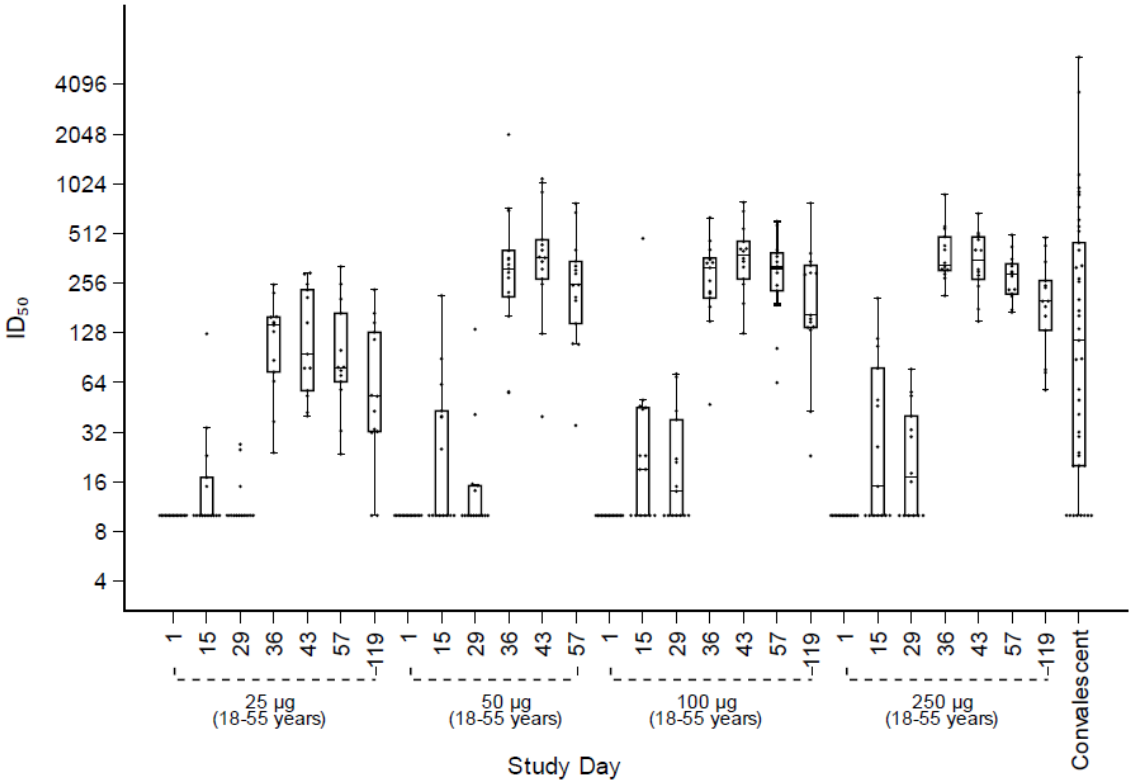


Figure 7 below shows pseudovirus neutralisation assay titres distribution by time point and dose level for the 18-55 YOA cohort. Similar kinetics (for the evaluated 50 and 100 µg mRNA-1273-dose) were seen for the other cohorts.

Figure 7– Pseudovirus Neutralisation assay titres distribution by time point and treatment group – ID50 – Age 18-55



Note: Boxes and horizontal bars denote interquartile range (IQR) and median ID_{50}, respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median +/- 1.5 x IQR. The convalescent sera panel includes specimens from 41 individuals.

Plaque reduction neutralisation and focus reduction neutralisation (assays employing live virus) across age cohorts are shown in the figures below (for the 100 µg mRNA-1273 dose).

Figure 8 - Plaque Reduction Neutralisation Test titres distribution by time point and treatment group – PRNT80

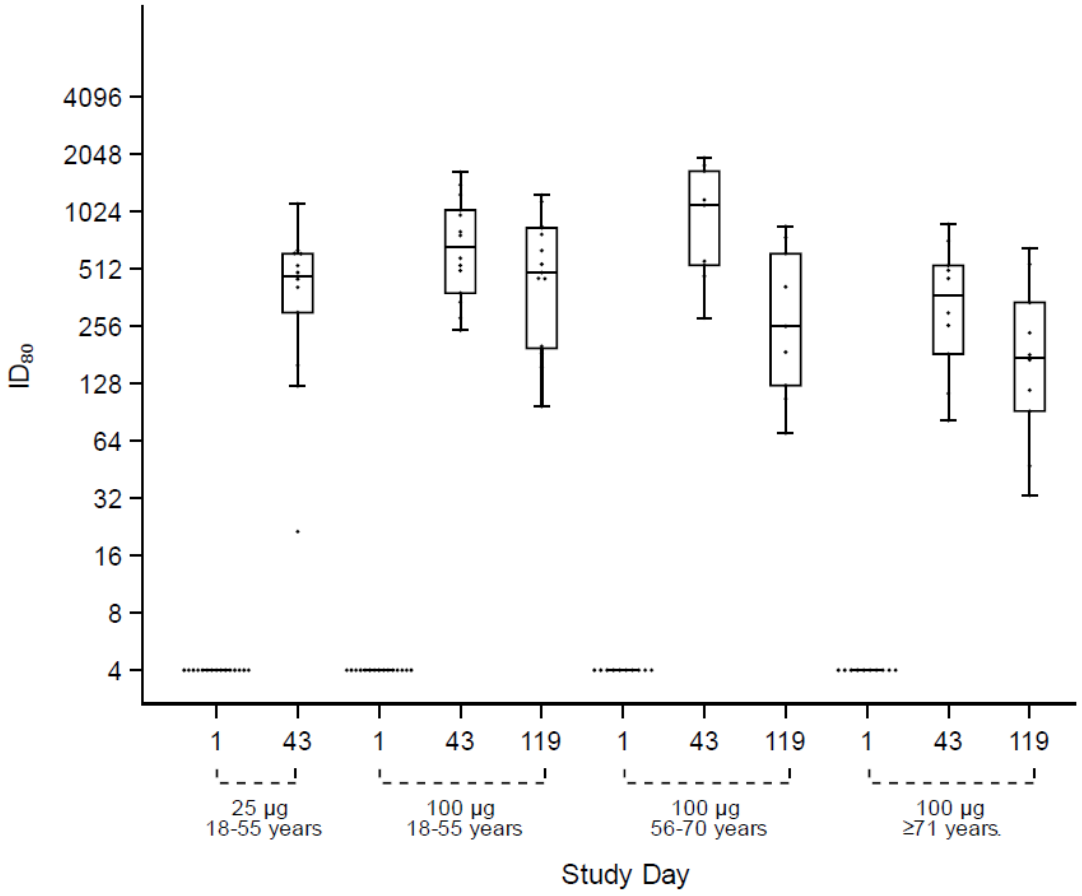
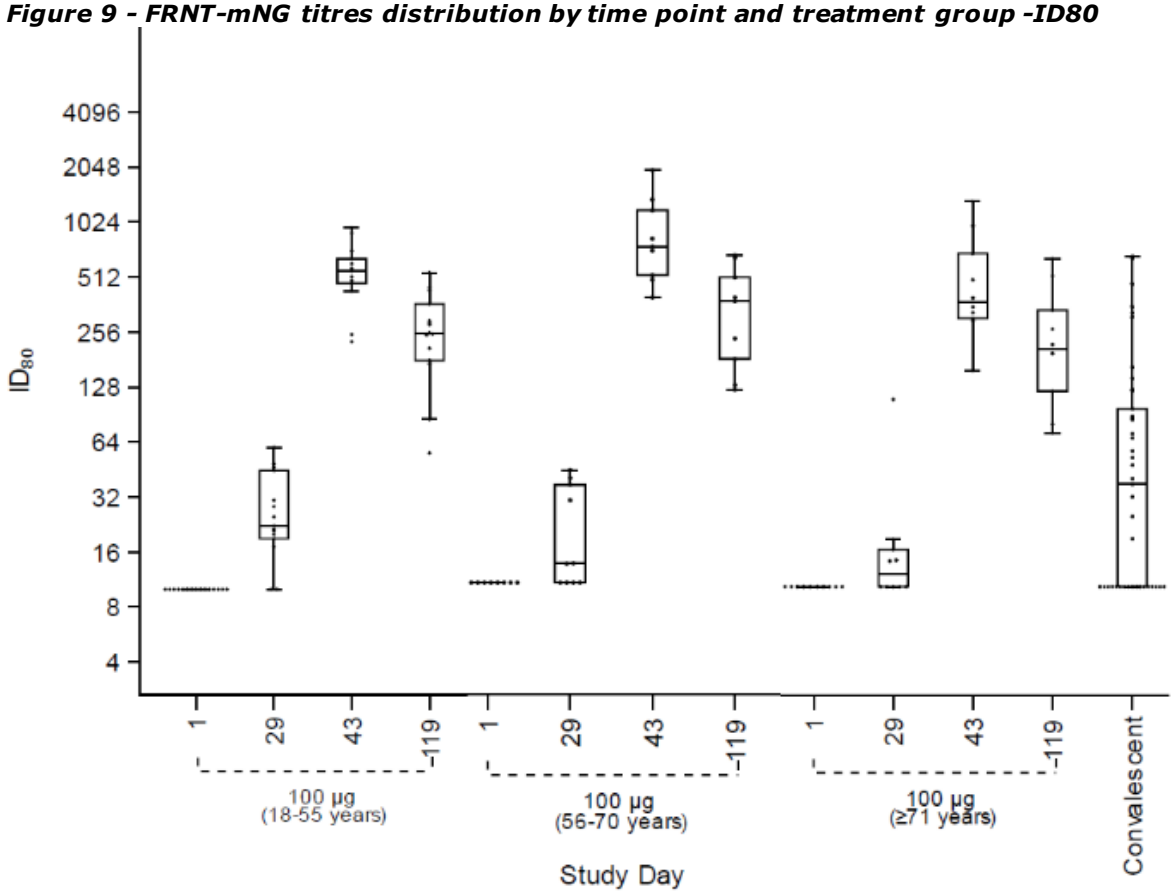


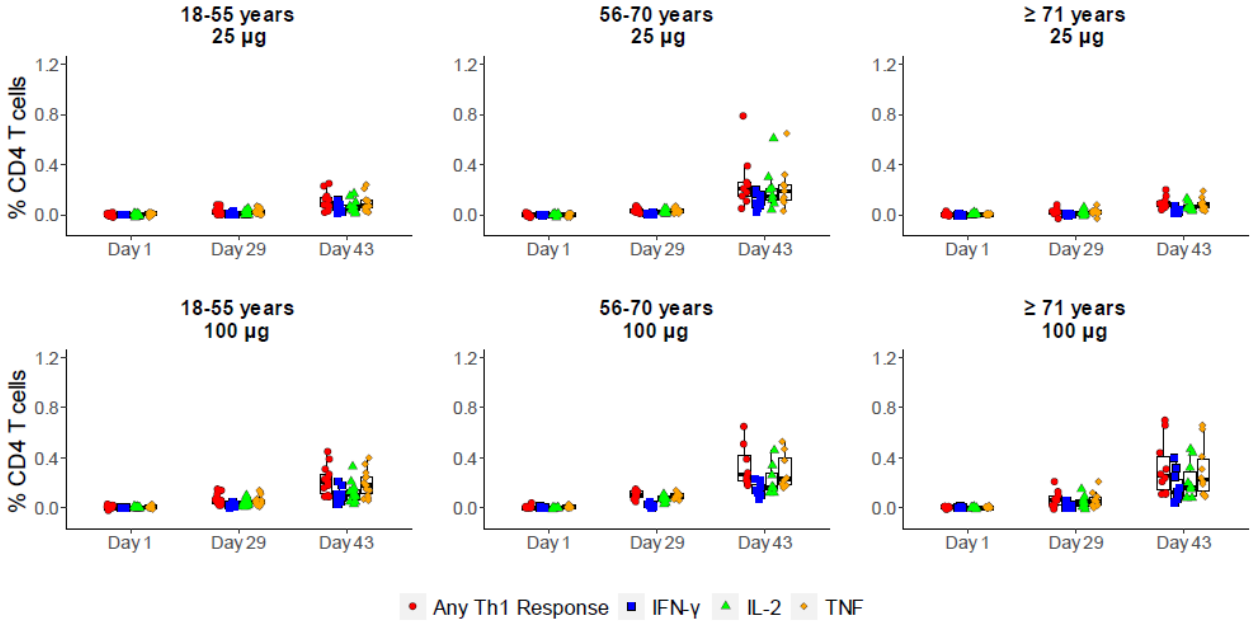
Figure 9 - FRNT-mNG titres distribution by time point and treatment group -ID80



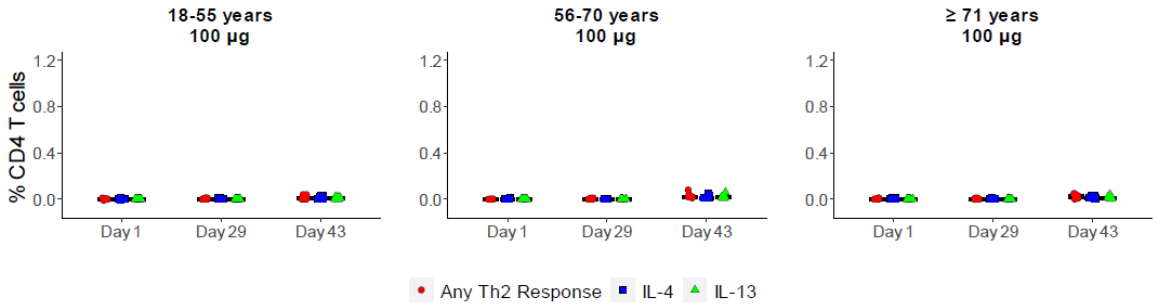
Cell mediated immunity (exploratory objective)

Cell mediated immunity was evaluated by intracellular cytokine staining in T cells isolated from vaccinated subjects (stimulated with SARS-CoV-2 S protein peptide pools). Data were presented from subjects vaccinated with the 25 µg or 100 µg mRNA-1273 dose. The figure below shows the percentages of CD4 T cells expressing Th1 cytokines upon stimulation with the S1 peptide pool (similar results for S2 peptide pool stimulation).

Figure 10 – Percentages pf CD4 T Cells expressing Th1 cytokines S1 peptide pool



The figure below shows the percentages of CD4 T cells expressing Th2 cytokines upon stimulation with the S1 peptide pool (100 µg dose only; similar results for 25 µg dose and S2 peptide pool stimulation).



The figures below show the percentages of CD8 T cells expressing cytokines upon stimulation with the S1 or S2 peptide pool.

Figure 11 – Percentage of CD8 T Cells expressing cytokines S1 peptide pool

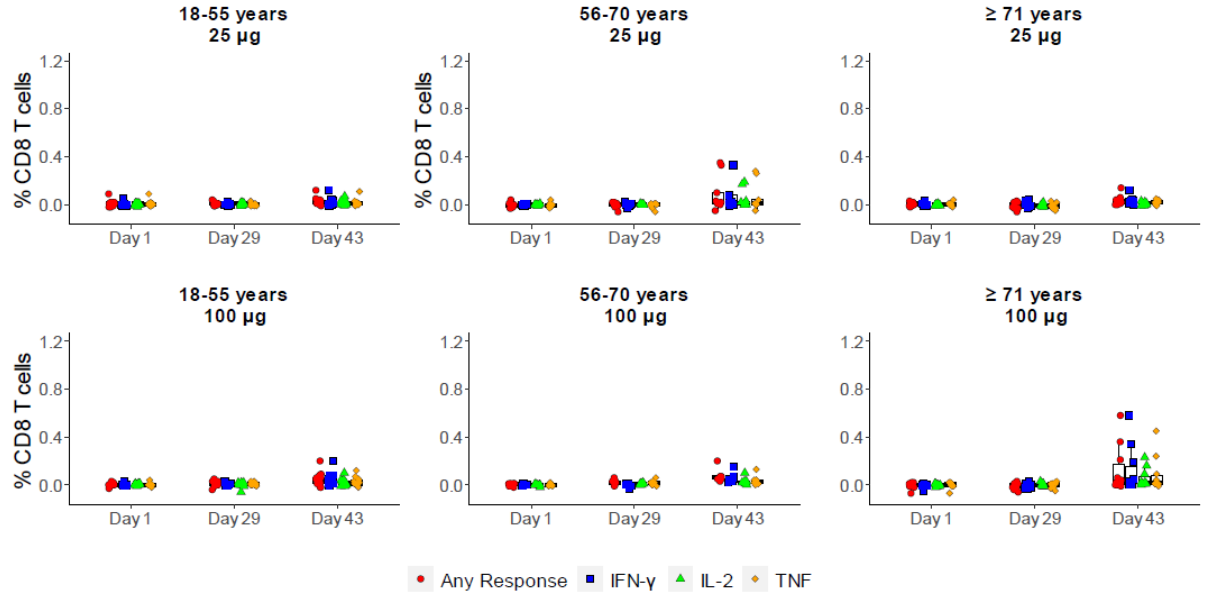
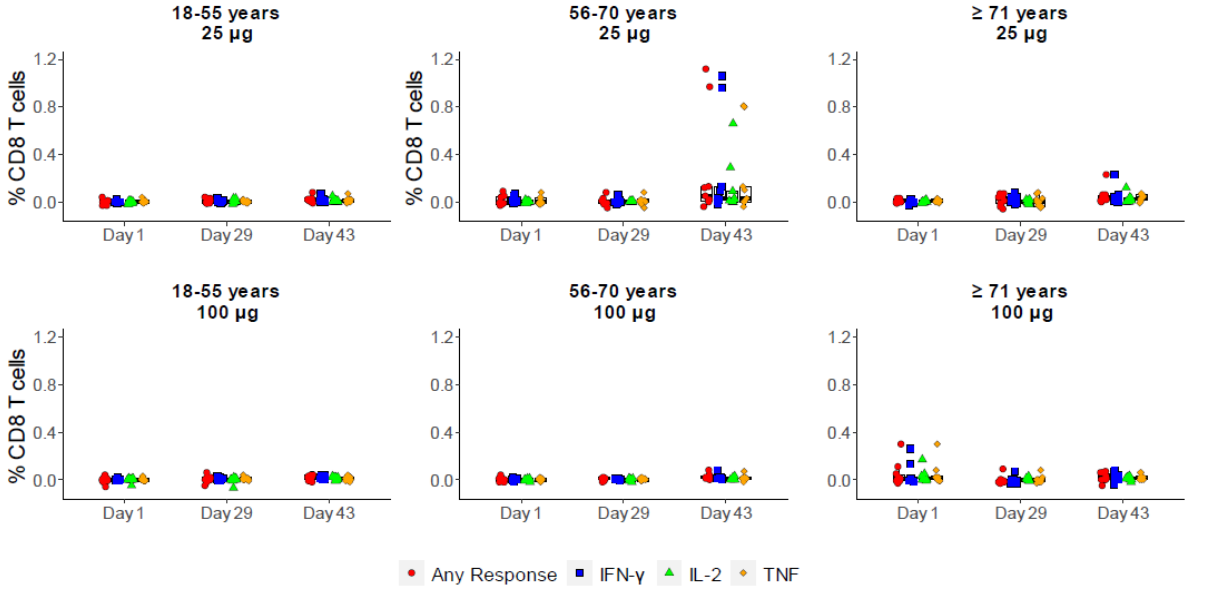


Figure 12 – Percentages of CD8 T cells expressing cytokines S2 peptide pool



In summary, the results of Phase 1 Study 20-0003 showed a consistent dose response across age groups by several measures of humoral immunogenicity for both binding and neutralising antibodies. Taking forward the 100 µg dose (administered as 2 injections, 28 days apart) to Phase 2a and 3 studies was based on several observations: (i) 2 injections of 100 µg stimulated serum bAb concentrations and titres greater than 2 injections of 25 µg in the 18 to 55 years of age stratum; (ii) 2 injections of 100µg induced nAb responses (measured by PsVNA) similar to those measured in recipients of the 250µg dose in the 18 to 55 years or age subjects evaluated; and (iii) 2 injections of 100µg led to a lower incidence of reactogenicity than 2 injections of 250µg (Jackson et al N Engl J Med. 2020; Anderson et al N Engl J Med. 2020). The 50µg dose induced comparable humoral immune responses to the 100ug dose (data for the 50µg dose available until day 57).

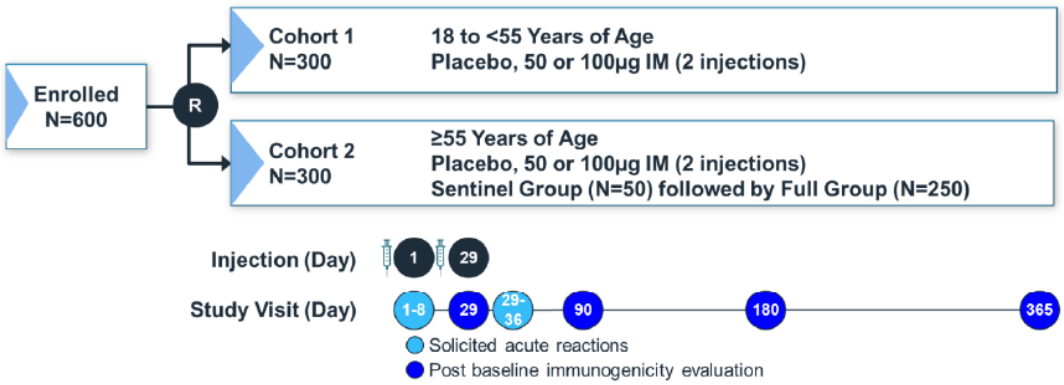
Phase 2a (Study mRNA-1273-P201)

This is a Phase 2a, randomised, 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 yrs, ≥55 yrs).

Table 5 - Overview of Study mRNA-1273-P201

Study Number (Country)/ Status	Key Efficacy and Immunogenicity Objectives	Key Safety Objectives	Age Groups (years) / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	Data Snapshot
mRNA-1273-P201 (US)/ Ongoing	• Immunogenicity of 2 dose levels of mRNA-1273 as assessed by the level of specific binding antibody (primary) • Immunogenicity of 2 dose levels of mRNA-1273 as assessed by the titer of neutralizing antibody (secondary)	Safety and reactogenicity of 2 dose levels of mRNA-1273 vaccine: • Solicited local and systemic ARs through 7 days after each injection (primary) • Unsolicited AEs through 28 days after each injection (primary) • MAAEs through the entire study period (primary) • SAEs throughout the entire study period (primary) • Safety laboratory abnormalities at Day 29 and Day 57 (Cohort 2 only; ≥55 years of age) (primary) • Vital sign measurements and physical examination findings (primary)	**Age Groups:** **Cohort 1**: ≥18 to <55 (n=300), **Cohort 2**: ≥55 (n=300) **Dose Groups:** Placebo (n=200) mRNA-1273 50 µg (n=200), mRNA-1273 100 µg (n=200)	Phase 2a, randomized, observer-blind, and placebo-controlled	50 or 100 µg mRNA-1273 or placebo 2 IM injections, 28 days apart	Immunogenicity: Day 57 Safety: Day 57

Figure 13 – Study 201 Design



Assays used

- IgG ELISA to the SARS-CoV-2 S (spike) protein (different assay compared to Phase 1)
- Microneutralisation assay using a live wild-type SARS-CoV-2 (USA/USA-WA1/2020)

Results

Binding and neutralising antibody responses (primary and secondary objectives, respectively)

The figures and table below summarise binding antibody titres (GMT) induced by mRNA-1273 vaccination (50 or 100 µg evaluated in strata 18-54 YOA and ≥55 YOA). The spike seen after day 29 coincides with the evaluation after the second vaccination.

Figure 14 – Cohort 1 (≥18 and ≤55 years) Antibody: VAC58 Spike IgG antibody (µg/ml) (LLOQ: 3.9, ULOQ: 487)

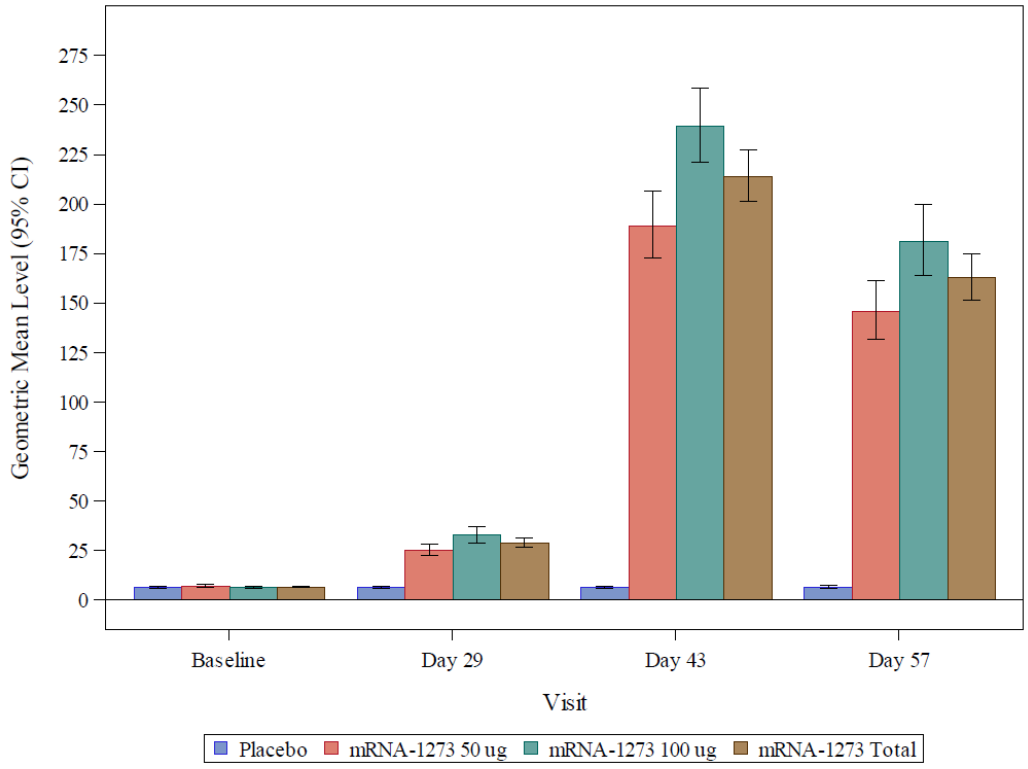


Figure 15– Cohort 2 (≥55 years) Antibody: VAC58 Spike IgG Antibody (µg/ml) (LLOQ: 3.9, ULOQ: 487)

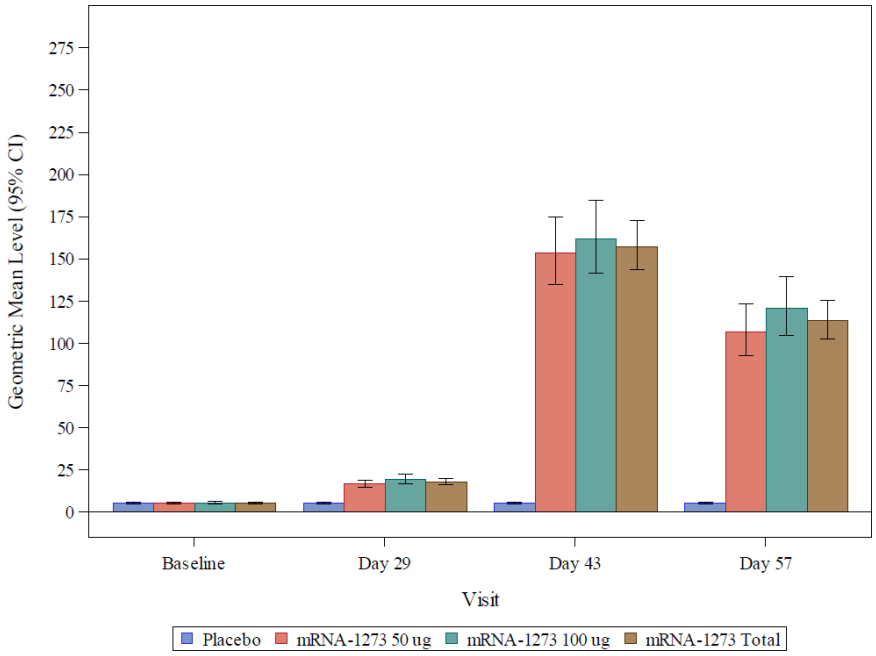


Table 6 – Summary of binding antibody levels Per-Protocol Set for SARS-CoV-2 specific bAb; Antibody: VAC58 Spike antibody (µg/ml) (LLOQ: 3.9, ULOQ: 487)

	Cohort 1 (Age >= 18 and age < 55)				Cohort 2 (Age >= 55)			
		mRNA-1273				mRNA-1273		
Timepoint Statistic	Placebo (N=92)	50 µg (N=90)	100 µg (N=95)	Total (N=185)	Placebo (N=94)	50 µg (N=95)	100 µg (N=94)	Total (N=189)
Baseline								
n[1]	92	90	95	185	94	95	94	189
GM Level	6.483	6.978	6.207	6.571	5.474	5.332	5.558	5.444
95% CI [2]	5.945, 7.070	6.266, 7.771	5.743, 6.709	6.153, 7.017	5.014, 5.976	4.845, 5.868	4.959, 6.230	5.056, 5.860
Median	6.450	6.650	6.500	6.500	5.600	5.500	5.850	5.800
Min, Max	1.95, 16.80	1.95, 37.70	1.95, 16.30	1.95, 37.70	1.95, 16.20	1.95, 12.30	1.95, 106.00	1.95, 106.00
Day 29								
n[3]	90	89	95	184	94	95	94	189
GM Level	6.319	25.291	32.678	28.868	5.349	16.561	19.424	17.928
95% CI [2]	5.737, 6.959	22.538, 28.379	28.761, 37.127	26.449, 31.509	4.862, 5.885	14.669, 18.696	16.826, 22.423	16.324, 19.689
Median	6.050	25.500	30.900	28.350	5.600	16.000	18.150	17.100
Min, Max	1.95, 40.40	7.30, 106.50	9.50, 285.00	7.30, 285.00	1.95, 22.10	4.10, 104.70	4.30, 431.60	4.10, 431.60
GM Fold-Rise	0.98	3.65	5.26	4.41	0.98	3.11	3.49	3.29
95% CI [2]	0.94, 1.02	3.20, 4.16	4.57, 6.06	3.99, 4.87	0.94, 1.02	2.71, 3.57	3.03, 4.03	2.98, 3.64
Day 43								
n[3]	87	84	94	178	93	91	87	178
GM Level	6.188	188.765	239.140	213.881	5.341	153.397	161.693	157.397
95% CI [2]	5.644, 6.784	172.505, 206.557	221.120, 258.629	201.166, 227.400	4.844, 5.890	134.640, 174.768	141.614, 184.620	143.540, 172.593
Median	6.300	196.550	238.750	217.800	5.600	154.300	183.200	168.550
Min, Max	1.95, 14.80	46.70, 487.00	71.10, 487.00	46.70, 487.00	1.95, 17.80	33.80, 487.00	20.10, 487.00	20.10, 487.00
GM Fold-Rise	0.97	26.82	38.47	32.45	0.98	28.05	28.86	28.44
95% CI [2]	0.94, 1.00	23.46, 30.67	34.54, 42.85	29.71, 35.45	0.94, 1.02	24.19, 32.53	24.49, 34.01	25.50, 31.73
Day 57								
n[3]	84	84	87	171	91	92	90	182
GM Level	6.536	145.710	181.147	162.776	5.300	106.837	120.792	113.524
95% CI [2]	5.914, 7.225	131.724, 161.182	164.168, 199.883	151.519, 174.869	4.811, 5.840	92.529, 123.357	104.603, 139.486	102.603, 125.607
Median	6.300	147.300	191.400	169.000	5.500	127.000	146.550	134.900
Min, Max	1.95, 62.50	36.70, 408.10	33.60, 487.00	33.60, 487.00	1.95, 14.00	21.40, 456.00	23.10, 487.00	21.40, 487.00
GM Fold-Rise	1.01	20.70	29.13	24.63	0.96	20.11	21.63	20.85
95% CI [2]	0.95, 1.08	17.92, 23.90	25.68, 33.03	22.33, 27.16	0.90, 1.01	17.12, 23.62	18.29, 25.59	18.58, 23.39

bAb = Binding antibody. GM = Geometric Mean. CI = Confidence intervals.
Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values that are greater than the upper limit of quantification (ULOQ) are converted to the ULOQ.
For visit Day 29, visit window (-3/+7 days) is used to define per-protocol. If the visit (Day 29) is disrupted and cannot be completed at Day 29 (-3/+7 days) as a result of the COVID-19 pandemic, the window is extended to Day 29 + 21 days.
[1] Number of subjects with non-missing baseline.
[2] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GM value and GM fold-rise, respectively, then back transformed to the original scale for presentation.
[3] Number of subjects in the Per-Protocol Set for SARS-CoV-2-specific bAb at the corresponding visit.

The figures and table below summarise neutralising antibody titres (MN50 and MN endpoint, respectively) induced by mRNA-1273 vaccination (50 or 100 µg evaluated in strata 18-54 YOA and ≥55 YOA). The spike seen after day 29 coincides with the evaluation after the second vaccination.

Figure 16 – Cohort 1 (≥18 and ≤55 years) Antibody: MN50

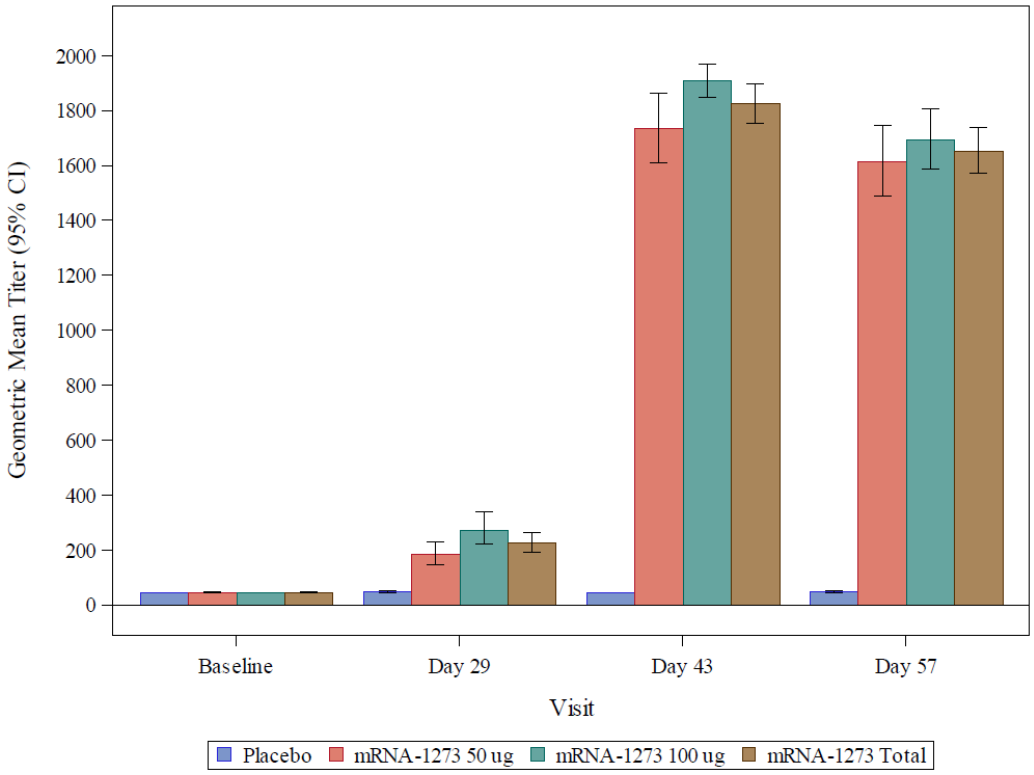


Figure 17 - Cohort 2 (≥55 years) Antibody: MN50

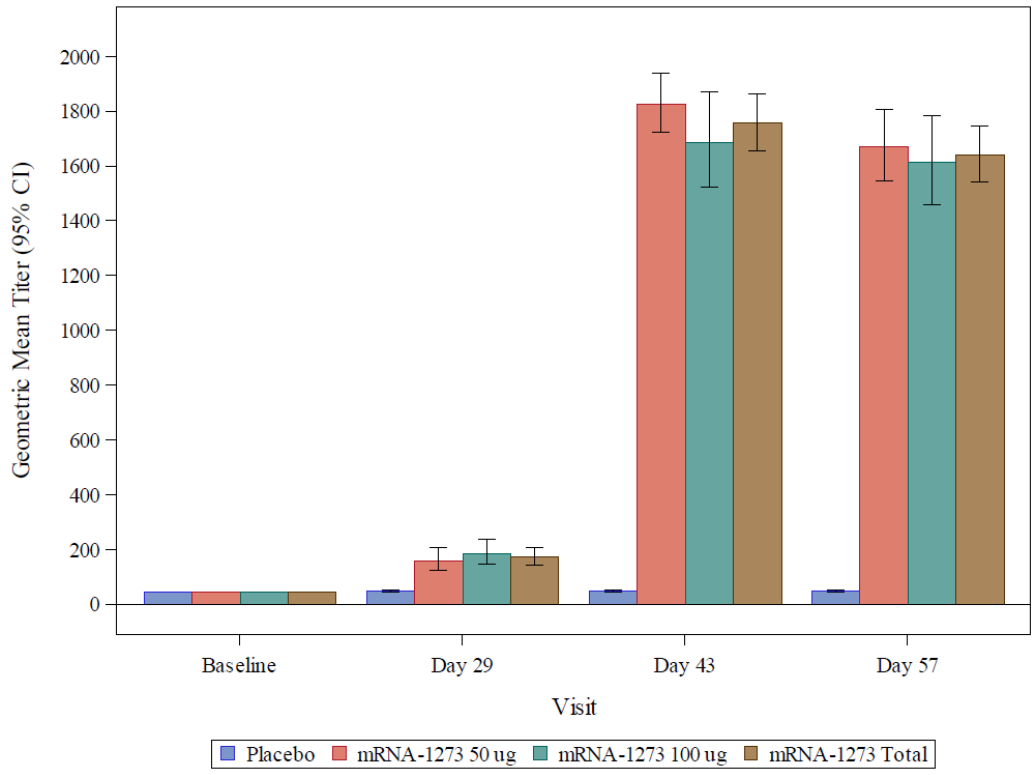


Table 7 – Summary of neutralising antibody titres Per-Protocol Set for SARS-CoV-2 specific nAb from the first lot; Antibody: MN endpoint titre

Timepoint Data Category Statistic	Cohort 1 (Age >= 18 and age < 55)				Cohort 2 (Age >= 55)			
		mRNA-1273				mRNA-1273		
	Placebo (N=92)	50 µg (N=90)	100 µg (N=95)	Total (N=185)	Placebo (N=89)	50 µg (N=89)	100 µg (N=91)	Total (N=180)
Baseline								
n[1]	92	90	95	185	89	89	91	180
GMT	20.0	20.4	20.0	20.2	20.0	20.2	20.0	20.1
95% CI [2]	NE, NE	19.6, 21.2	NE, NE	19.8, 20.6	NE, NE	19.8, 20.5	NE, NE	19.9, 20.2
Median	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Min, Max	20, 20	20, 120	20, 20	20, 120	20, 20	20, 40	20, 20	20, 40
Day 29								
n[3]	90	89	94	183	88	79	86	165
GMT	20.9	126.4	183.4	153.0	21.1	100.4	119.2	109.8
95% CI [2]	19.2, 22.7	100.8, 158.5	147.1, 228.7	130.6, 179.4	19.3, 23.0	74.9, 134.7	93.3, 152.4	91.0, 132.6
Median	20.0	160.0	240.0	200.0	20.0	120.0	120.0	120.0
Min, Max	20, 960	20, 960	20, 1280	20, 1280	20, 960	20, 1280	20, 1280	20, 1280
GMFR	1.04	6.19	9.17	7.58	1.05	4.98	5.96	5.47
95% CI [2]	0.96, 1.14	4.94, 7.77	7.36, 11.43	6.46, 8.89	0.96, 1.15	3.70, 6.70	4.66, 7.62	4.52, 6.61
Day 43								
n[3]	87	78	88	166	88	63	62	125
GMT	20.0	1132.8	1233.5	1185.1	20.9	1159.6	1106.7	1133.0
95% CI [2]	NE, NE	1060.0, 1210.5	1201.4, 1266.6	1145.0, 1226.6	19.1, 22.8	1092.3, 1231.0	1006.5, 1216.7	1072.1, 1197.4
Median	20.0	1280.0	1280.0	1280.0	20.0	1280.0	1280.0	1280.0
Min, Max	20, 20	240, 1280	640, 1280	240, 1280	20, 960	480, 1280	160, 1280	160, 1280
GMFR	1.00	55.35	61.68	58.62	1.04	57.34	55.33	56.34
95% CI [2]	NE, NE	51.16, 59.89	60.07, 63.33	56.32, 61.01	0.96, 1.14	53.31, 61.68	50.33, 60.84	53.11, 59.76
Day 57								
n[3]	84	80	82	162	87	70	70	140
GMT	21.5	1083.4	1126.9	1105.2	20.8	1099.7	1060.5	1079.9
95% CI [2]	19.4, 23.9	1006.1, 1166.7	1061.2, 1196.6	1054.3, 1158.5	19.2, 22.5	1020.0, 1185.5	965.9, 1164.4	1017.7, 1145.9
Median	20.0	1280.0	1280.0	1280.0	20.0	1280.0	1280.0	1280.0
Min, Max	20, 640	240, 1280	320, 1280	240, 1280	20, 640	320, 1280	200, 1280	200, 1280
GMFR	1.08	52.97	56.34	54.65	1.04	54.44	53.03	53.73
95% CI [2]	0.97, 1.20	48.69, 57.63	53.06, 59.83	51.93, 57.52	0.96, 1.13	49.94, 59.35	48.30, 58.22	50.46, 57.21

In summary, participants in Phase 2a who received 2 doses of either 50 or 100µg of mRNA-1273 separated by 28 days developed both binding and neutralising antibodies against SARS-CoV-2, with GMFRs > 20-fold (bAb) and > 50-fold (MN assay), regardless of dose level. These data support dose selection in principle because of the magnitude of the antibody response to 2 doses of mRNA-1273 even if the differentiation between 50µg and 100µg is close to negligible. Responses and dynamics observed across age cohorts was comparable.

Cell mediated immunity

Not investigated in Phase 2a.

2.4.3. Discussion on clinical pharmacology

The proposed mechanism of action of mRNA-1273 is 1) uptake of the lipid nanoparticles by antigen presenting cells through endocytic pathways both at the site of injection and in the draining lymph nodes, 2) release of mRNA (encoding modified SARS-CoV-2 S protein) into the cell, 3) S protein expression (mainly by dendritic cells and subcapsular sinus macrophages) and 4) stimulation of immune responses against SARS-CoV-2 S-2P protein to provide protection against COVID-19.

The clinical development includes immunogenicity assessments across the entire clinical study program i.e., Phase 1, 2a and 3 studies.

Phase 1 Study 20-003 is an open-label, dose-ranging study of the safety and immunogenicity of mRNA-1273 in healthy adults (3 age cohorts: 18-54 yrs, 55-70 yrs, ≥71 yrs). Phase 2a Study mRNA-1272-P201 is a randomised, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity and immunogenicity of mRNA-1273 in adults aged 18 years and older (2 age cohorts: 18-54 yrs, ≥55 yrs). Phase 3 study mRNA- 1273-P301 is a, randomised, stratified, observer-blind, placebo-controlled study to evaluate the safety, efficacy and immunogenicity of mRNA-1273 in adults aged 18 years and older.

The designs of all three clinical studies are adequate for characterising humoral immune response after mRNA-1273 vaccination across relevant age strata. Characterisation of cellular immune responses is only foreseen in the phase 1 study, which is considered a shortcoming particularly for the limited study size. The phase 2a study design includes two age strata, 18-54 yrs and ≥55 yrs, which might not allow an adequate characterisation of the humoral immune response in the older age groups (e.g. 65-74 year olds, ≥75 year olds), most vulnerable to COVID-19 and known to produce a reduced immune response upon vaccination.

Results for several pre-specified immunogenicity endpoints in both Phase 1 and Phase 2a studies have not been provided (such as immunoglobulin subclass analyses, binding to neutralising antibody ratios, or B cell epitope characterisation). No immunogenicity data from the phase 3 study were available for assessment at the time this report was written. The data cut-off was day 119 post-vaccination for Phase 1, and day 57 for post-vaccination for Phase 2. This means that immunokinetics over time and correlate of protection/ risk could not be characterised. This is acceptable for the time being, but these data should be provided with final CSRs.

Study endpoints (across studies) relevant to induction of humoral immunity induced by mRNA-1273 are mainly based on S protein binding and neutralising antibodies, measured by ELISA or (pseudo) virus neutralisation assays, respectively. All applied immunogenicity assays are adequate for determination of immunological endpoints relating to humoral immune response, albeit final validation reports have not been provided for all assays and are expected to be submitted once available. The use of different assays in Phase 1 and 2 limits comparability between studies, but the approach used is acceptable. Sampling schedules are appropriate to determine humoral kinetics (including peak responses as well as decay) and for investigating short-, mid- and long-term outcomes.

Immunogenicity assessments are based on a total of 116 subjects in Phase 1 (across 25-250 µg doses) and 587 subjects in Phase 2a (198, 195 and 194 subjects received 100µg, 50µg or placebo, respectively), who received both the first and second dose of mRNA-1273.

Evaluation of humoral immune response to mRNA-1273 in Phase 1 and 2a studies was based on a very limited number of SARS-CoV-2 strains and/ or pseudoviruses (mainly based on the initial Wuhan isolate), which is understood in the context of the pandemic with rapidly emerging strains. Importantly, neutralising activity induced by mRNA-1273 vaccination against the currently dominant D614G variant strain was confirmed. Plans for further evaluation of new strain variants were outlined during evaluation and are supported. The applicant confirmed that immune responses against strains such as A222V-D614G (EU1), a S447N-D614G (EU2) variant, a N439K-D614G variant, the mink adapted strain recently identified in Denmark as well as relevant new and emerging S protein variants (library of pseudoviruses) will be closely monitored in vaccinees sera (derived from both humans and animals). Deep sequencing of virus breakthrough cases is planned in the vaccine and placebo groups of the ongoing phase 3 trial to identify any potential gap in protection against mutant strains. New viral variant challenge stocks are being prepared, and once available will be used to challenge animals

vaccinated with mRNA-1273 to directly assess the ability of mRNA-1273 to protect animals from these variant strains.

The initial dose-ranging and clinical proof-of-concept in phase 1 study showed dose-dependent increases in binding and neutralising antibodies when comparing the lowest dose 25 µg to the 50µg dose. When comparing the 50 µg to the 100µg dose, differences were less pronounced. The 250µg dose was only tested in the 18-55 yrs. age group and not further pursued due to reactogenicity. The 50 µg and 100 µg dose were further evaluated in the phase 2a study, where comparable results were obtained, indicating a rather flat dose-response. Even though the 50µg compared to the 100µg dose does not show pronounced differences, 100 µg has been chosen because of comparable and acceptable reactogenicity and slightly higher immunogenicity. In addition, 100 µg may exert more sustainable kinetics of immune responses in the long term (putative at present). Overall, the selection of the 100µg dose for the phase 3 trial is reasonable and supported.

In both Phase 1 and 2a studies the humoral immune response in terms of induction of antibodies binding the S protein (full protein and RBD) and virus neutralising antibodies showed that two mRNA-1273 doses given 4 weeks apart resulted in substantially increased geometric mean titres (GMTs) if compared to responses after only the first dose across all age strata tested. While binding antibody levels generally started to rise after the first vaccination (day 15), this was not seen for neutralising responses which were only induced after the second vaccination. These results support the need of a second dose.

Human convalescent sera from up to 41 individuals recovered from mostly mild COVID-19 were routinely used as comparators in the Phase 1 study. mRNA-1273-induced humoral immune responses were generally within the upper range or above those measured in the convalescent comparator sera. It is noted, however, that mild disease has been associated with lower antibody levels. Moreover, convalescent sera were collected between 23-54 (median 34) days post-diagnosis which likely does not reflect peak antibody responses. While humoral response is generally reassuring as regards proof of concept, its magnitude and kinetics need to be interpreted with caution in the context of a currently unknown immune correlate of protection. Peak GMTs (binding and neutralising) across age groups and clinical trials were generally seen 7-14 days after the second vaccination (day 36-43). Decreases in GMTs became apparent soon thereafter and were reported until day 57 in the phase 2 and day 119 in the phase 1 study. Of note, despite decreases in GMTs over time, levels in the majority of participants were generally sustained within the upper range or above GMTs of human convalescent comparator sera. This is preliminarily reassuring as regards antibody persistence over time.

GMTs of S protein binding antibodies in the elderly (≥71 years of age) vaccinated in the phase 1 study with the 100µg mRNA-1273 dose were higher compared to the younger participants, while neutralising responses were generally comparable between age cohorts or superior in the younger participants. However, this finding on binding antibodies was not replicated in the larger phase 2a study. Upon request, the applicant provided more granular data by age for the Phase 2a study, even though the study was not powered for age subgroup. Peak median/mean binding antibody titres (day 43) induced by the 100 µg mRNA-1273 dose in the 18-54 YOA stratum were approximately 1.2-fold, 1.5-fold and 1.9-fold higher compared to the 55-64-year olds, 65-74-year olds and ≥75-year olds, respectively. Therefore, binding antibody levels declined in an age-dependent manner as expected, with more comparable neutralising activity across strata.

Cellular immune responses (T cell cytokine response) were only investigated in phase 1 until day 43 after the first vaccination (i.e. 14 days after the second vaccination). Analysis plans for phase 2a and phase 3 do not outline any further investigations on this important aspect likely contributing to protection against SARS-CoV-2. Data from phase 1 point towards a general Th1 over Th2 dominant

response indicative of a favourable cytokine profile as regards the theoretical risk of vaccine dependent enhancement of disease (VAED). However, it is noted that shortcomings in assay conduct, lack of reporting of Th2 controls and overall heterogeneous results do not permit to finally conclude on this. Likewise, it was not convincingly demonstrated whether CD8 T cell responses were induced by vaccination with mRNA-1273 in humans. Therefore, cellular immune response to mRNA-1273 vaccination is not considered comprehensively characterised. This limitation however does not prevent to conclude on a positive benefit/risk assessment as it is not expected to substantially change the outcome, considering that no VAED signals were observed in pre-clinical studies and in phase 3 study efficacy and safety data so far.

Immunogenicity data from Phase 3, once available, are expected to fill the current knowledge gaps on humoral immunity in subgroups with various comorbidities (e.g. diabetes, overweight, immunocompromised individuals etc.) and provide further information as to the impact of immunosenescence.

Immune responses in mRNA-1273 vaccinated patients who develop COVID-19 will be of relevance to furthering the understanding of immunity against SARS-CoV-2 as well as investigations towards an immune correlate of protection. Plans for establishing an immune correlate of protection seem to be based solely on humoral and not cellular responses, which is considered a shortcoming, but will likely expand the knowledge on antibody-mediated immunity against SARS-CoV-2. Of note, the Analysis Plan for immunogenicity data, including the sampling for the immunogenicity subset, is currently missing and will need to account for the study design changes in P301 introduced with Protocol Amendment 6. Focus should be on data analysis plans for the exploration of correlate of protection.

Longer-term data on humoral immunity are expected to emerge from all three clinical trials, which will inform on antibody kinetics beyond 3 months post-vaccination.

2.4.4. Conclusions on clinical pharmacology

While the overall dose-response towards mRNA-1273 in phase 1 and phase 2a clinical studies was rather flat, both the choice of the 100µg mRNA-1273 dose and the 2-dose schedule is deemed reasonable and acceptable by the CHMP. Proof-of-concept has been established.

Interpretation of immunogenicity results in terms of vaccine efficacy is limited as currently no immune correlate of protection against COVID-19 exists. In addition, no immunogenicity data from phase 3 are currently available. Notwithstanding, based on prior experience with vaccines, the data received so far from Phase 1 and 2a are considered reassuring.

The current gaps in understanding of the immune response against SARS-CoV-2 induced by mRNA-1273 vaccination mainly relate to the following aspects:

- No plans for establishing an immune correlate of protection/risk have been provided.
- No data on immunogenicity in certain subgroups (e.g. at-risk groups, immunocompromised, mRNA-1273-vaccinated individuals who develop COVID-19, etc.) have been generated.
- No data for several pre-specified immunogenicity objectives from Phase 1 and 2a have been provided (such as immunoglobulin subclass analyses, binding to neutralising antibody ratios, or B cell epitope characterisation).
- The data on immune responses in the elderly is currently based on observations from the Phase 1 and Phase 2a studies and thus derived from a limited number of subjects. Therefore,

final conclusions on immunogenicity for this most vulnerable populations cannot be drawn at this time.

- The current understanding of humoral immune response towards mRNA-1273 vaccination is based on a limited dataset of up to 3 months after the second vaccination. Mid-and long-term data are important to inform on the need for and timing of further boosters to achieve long-lasting protection.
- The level of protection conferred by mRNA-1273 against different SARS-CoV-2 variants is currently limited to a small number of strains. The applicant's proposal to monitor clinically relevant and emerging SARS-CoV-2 strains by testing both sera from vaccinated animals and human trial participants in functional *in vitro* assays as well as conducting challenge/protection studies in animals is endorsed and data should be submitted as soon as available.

Final clinical study reports are expected to generate the data needed to address the remaining points mentioned above. The final clinical study report of the pivotal phase 3 study should be submitted as a specific obligation in the context of the conditional marketing authorisation by December 2022.

The final clinical study reports for the phase 1 and phase 2 studies are required to be submitted as reflected in the RMP (respectively by November 2021 and November 2022).

Some of the above-mentioned data are however required as soon as available (see list of recommendations in Annex I).

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

See section 2.4.

2.5.2. Main study

Title of study P301

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).

Methods

Study Participants

Key Inclusion Criteria

- Adults, ≥18 years of age at time of consent, who are at high risk of SARS-CoV-2 infection, defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19.
- Female participants of non-childbearing potential and female participants of childbearing potential who fulfil the following criteria:
  - Has a negative pregnancy test at Screening and on the day of the first dose (Day 1).

- Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first dose (Day 1).
- Has agreed to continue adequate contraception through 3 months following the second dose (Day 29).
- Is not currently breastfeeding.

- Healthy adults or adults with pre-existing medical conditions who are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 3 months before enrolment.

Key Exclusion Criteria

- The subject is acutely ill or febrile (≥ 38.0°C/100.4°F) 72 hours prior to or at Screening.
- The subject is pregnant or breastfeeding.
- Known history of SARS-CoV-2 infection
- Prior administration of an investigational coronavirus (SARS-CoV, MERS-CoV) vaccine or current/planned simultaneous participation in another interventional study to prevent or treat COVID-19.
- Known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients.
- Immunosuppressive or immunodeficient state, asplenia, recurrent severe infections. HIV positive participants on stable antiretroviral therapy were permitted.
- The subject has received systemic immunoglobulins or blood products within 3 months prior to the day of screening.
- The subject has donated ≥ 450 mL of blood products within 28 days prior to Screening.
- The subject has received or plans to receive a non-study vaccine within 28 days prior to or after any dose of IP (except for seasonal influenza vaccine which is not permitted within 14 days before or after any dose of IP).

The protocol further required that at least 25% of enrolled participants be either ≥ 65 years of age or < 65 years of age and at risk for severe COVID-19. Participants were considered at risk for severe COVID-19 illness if they had at least one of the following:

- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma;
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension);
- Severe obesity (body mass index ≥ 40 kg/m^2);
- Diabetes (Type 1, Type 2 or gestational);
- Liver disease;
- Human Immunodeficiency Virus (HIV) infection.

Treatments

The mRNA-1273 vaccine is a lipid nanoparticle (LNP) dispersion of 100 µg mRNA encoding the pre-fusion stabilised S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids: lipid SM-102, cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). mRNA-1273 Injection is provided as a sterile liquid for injection, white to off white dispersion in appearance, at a concentration of 0.5 mg/mL in Tris buffer containing sucrose and sodium acetate at pH 7.5.

The placebo is 0.9% sodium chloride (normal saline) injection, United States Pharmacopeia (USP).

Study participants received two doses of either the vaccine mRNA-1273 or placebo intramuscularly 28 days apart. The window for receiving the second dose was defined between 24-35 days following the first dose. At the time of definition of major protocol deviations, which was to happen before unblinding, the acceptable visit window was widened to 21 – 42 days (-7/+14 days around day 28).

Objectives

Study objectives (see below) are appropriate. It is noted that for several of them no outcome data were provided as part of this submission.

Primary Objectives

- To demonstrate the efficacy of mRNA-1273 to prevent COVID-19.
- To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart.

Secondary objectives

- To evaluate the efficacy of mRNA-1273 to prevent severe COVID-19.
- To evaluate the efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity. (no data available)
- To evaluate vaccine efficacy (VE) against a secondary definition of COVID-19.
- To evaluate VE to prevent death caused by COVID-19.
- To evaluate the efficacy of mRNA-1273 to prevent COVID-19 after the first dose of investigational product (IP).
- To evaluate the efficacy of mRNA-1273 to prevent COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection.
- To evaluate the efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection. (no data available)

Exploratory

- To evaluate the effect of mRNA-1273 on the viral infection kinetics as measured by viral load at SARS-CoV-2 infection diagnosis by RT-PCR and number of days from the estimated date of SARS-CoV-2 infection until undetectable SARS-CoV-2 infection by RT-PCR. (no data available)
- To assess VE to reduce the duration of symptoms of COVID-19. (no data available)
- To evaluate VE against all-cause mortality.

- To assess VE against burden of disease (BOD) due to COVID-19. (no data available)
- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence. (no data available)
- To evaluate immune response markers after dosing with IP as correlates of risk of COVID-19 and as correlates of risk of SARS-CoV-2 infection. (no data available)
- To conduct additional analyses related to furthering the understanding of SARS-CoV-2 infection and COVID-19, including analyses related to the immunology of this or other vaccines, detection of viral infection, and clinical conduct. (no data available)

Outcomes/endpoints

Efficacy endpoints

Endpoint	**Statistical Analysis Methods**
Primary endpoint: Vaccine efficacy (VE) of mRNA-1273 to prevent the first occurrence of COVID-19 in baseline seronegative participants	• The primary endpoint analysis included cases starting 14 days after the second injection in the PP Set, as adjudicated by an independent adjudication committee that was blinded to vaccine group assignment. VE was to be estimated with 1 - HR (mRNA-1273 vs. placebo) using a Cox proportional hazard regression model with treatment group as a fixed effect and adjust for stratification factor based on the PP Set. • Analysis using the same model based on the mITT Set. • Sensitivity analysis using the same model based on the PP Set, with cases counted starting either immediately after the second dose of IP or immediately after the first dose of IP. • Subgroup analysis of the primary efficacy endpoint will be performed to assess consistency of VE, such as in the age groups ≥ 18 and < 65 years and ≥ 65 years. • Supportive analysis of VE to be estimated with 1 - ratio of incidence rates with 95% confidence interval (CI) using the exact method conditional upon the total number of cases. • Supportive analysis of cumulative incidence VE
Secondary endpoints: • Vaccine efficacy of mRNA-1273 to prevent severe COVID-19 • Vaccine efficacy of mRNA-1273 to prevent serologically confirmed SARS-CoV-2 infection or COVID-19 regardless of symptomatology or severity • Vaccine efficacy of mRNA-1273 to prevent COVID-19 using a secondary definition of symptoms • Vaccine efficacy of mRNA-1273 to prevent death caused by COVID-19 • Vaccine efficacy of mRNA-1273 to prevent COVID-19 after the first dose of IP • Vaccine efficacy of mRNA-1273 to prevent asymptomatic SARS-CoV-2 infection	• Similar analysis method as for the primary endpoint analysis. • For each of the secondary endpoints: – Primary analysis: VE will be estimated with 1 - HR (mRNA-1273 vs placebo) using a Cox proportional hazard regression model with treatment group as a fixed effect and adjusting for stratification factor based on the PP Set, with cases counted starting 14 days after the second dose of IP. – Analysis using the same model based on the mITT Set. • Supplementary analyses with cases counted starting immediately after the second dose of IP, 14 days after the first dose of IP, immediately after the first dose of IP, and immediately after randomisation. • Vaccine efficacy and 95% CI based on the case incidence will be estimated with 1 - ratio of incidence rates using the exact method conditional upon the total number of cases.

• Vaccine efficacy of mRNA-1273 to prevent COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection	• The FAS population will be used for this secondary objective, using similar analysis methods as for the primary endpoint analysis. • Primary analysis: VE will be estimated with 1 - HR (mRNA-1273 vs placebo) using a Cox proportional hazard regression model with treatment group as a fixed effect and adjusting for stratification factor based on the FAS, with cases counted starting 14 days after the second dose of IP. • Sensitivity analyses with cases counted starting immediately after the second dose of IP, 14 days after the first dose of IP, immediately after the first dose of IP, and immediately after randomisation.

Safety endpoints

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AEs leading to discontinuation, abnormal vital signs, and physical examination findings.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment group unless otherwise specified. The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will be also provided for the percentage of participants with any solicited AR for each treatment group.

The number and percentage of participants with solicited ARs, unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarised. Unsolicited AE will be presented by MedDRA preferred term and system organ class.

For all other safety parameters, descriptive summary statistics will be provided.

Methods used for efficacy evaluations

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 (≥38ºC), 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 hospitalised) positive for SARS-CoV-2 by RT-PCR.

Secondary Efficacy Endpoint Assessments:

To be considered a **severe COVID-19 case**, the following criteria must be met: a confirmed COVID-19 as per the Primary Efficacy Endpoint case definition, plus any of the following:

- Clinical signs indicative of severe systemic illness, Respiratory Rate ≥30 per minute, Heart Rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level or PaO2/FIO2 <300 mm Hg, **OR**
- Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), **OR**
- Significant acute renal, hepatic or neurologic dysfunction, **OR**
- Admission to an intensive care unit or death.

An alternative less stringent case definition of COVID-19 was used for secondary analyses requiring any of the systemic symptoms: fever (temperature ≥38ºC) or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches or body aches, headache, new loss of taste or smell, sore throat, nasal congestion or rhinorrhoea, nausea or vomiting or diarrhoea,

AND

a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalised) for SARS-CoV-2 by RT-PCR.

Death attributed to COVID-19 is defined as any participant who dies during the study with a cause directly attributed to a complication of COVID-19.

Asymptomatic SARS-CoV-2 infection is determined by seroconversion due to infection assessed by bAb levels against SARS-CoV-2 as measured by a ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein and a negative NP swab sample for SARS-CoV-2 at Day 1.

SARS-CoV-2 Infection is defined as:

SARS-CoV-2 infection by seroconversion due to infection measured by bAb against SARS-CoV-2 nucleocapsid. Seroconversion is defined differently for participants seronegative at Baseline and seropositive at Baseline:

- Participants seronegative at Baseline: bAb levels against SARS-CoV-2 nucleocapsid either from below the limit of detection (LOD) or lower limit of quantification (LLOQ) at Study Day 1 that increase to above or equal to LOD or LLOQ starting at Study Day 57 or later.
- Participants seropositive at Baseline: bAb levels against SARS-CoV-2 nucleocapsid above the LOD or LLOQ at study Day 1 that increase by 4-fold or more in participants starting at Study Day 57 or later.

Surveillance for COVID-19 Symptoms

Surveillance for COVID-19 symptoms was conducted via weekly telephone calls or eDiary starting after enrolment and throughout the study. If there is no response to an eDiary prompt for 2 days, the site staff should contact the study participant by phone.

To screen for COVID-19 occurring, pre-specified symptoms were elicited weekly from the participant and the presence of any one of these symptoms lasting at least 48 hours (except for fever and/or respiratory symptoms) shall result in the site arranging an Illness Visit to collect an NP swab within 72 hours. All study participants who experience COVID-19 symptoms and subsequently present for an Illness Visit (in-clinic or at home) will be given instructions and material to record disease course during the convalescent period, i.e. severity grading system, thermometer, oxygen saturation monitor, and saliva collection tubes.

Case adjudication

Ambiguous in terms of study protocol/SAP specifications, efficacy results based on adjudicated cases have been presented as primary in this submission. Whereas including a blinded adjudication committee (AC) for COVID-19 cases was devised in the protocol, this was not reflected in the analysis plan. Adjudication criteria and re-adjudications performed have only been roughly described upon request. This can be accepted but some residual uncertainty remains as regards involvement and procedures of AC and case-related information flow involving study site personnel, sponsor, CRO and AC up to a final decision. Adjudicated and unadjudicated analyses have therefore been considered during assessment of main efficacy endpoints for robustness.

Assays used for efficacy assessment

- **RT- PCR**

The RT-PCR assay used is a real-time reverse transcription polymerase chain reaction (RT-PCR) to confirm SARS-CoV-2 in probable COVID-19 individuals and is performed by the Viracor Eurofins Clinical Diagnostics, which is a Clinical Laboratory Improvement Amendments of 1988 (CLIA), a certified high-complexity laboratory.

The RT-PCR is intended for the qualitative detection of SARS-CoV-2 viral RNA in nasopharyngeal swab, nasal swab, nasopharyngeal wash, nasal wash, oropharyngeal swab and bronchoalveolar lavage from individuals suspected of COVID-19. It is approved for use under the Food and Drug Administration's Emergency Use Authorisation for *in vitro* diagnostics. Detailed information on the conduct of the RT PCR assay and the interpretation of results was provided. The SARS-CoV-2 primer and probe sets are designed to detect RNA from SARS-CoV-2 in respiratory specimens from patients as recommended for testing by public health authority guidelines. The chosen primer design is acceptable.

Validation data include various protocols and validation results for extraction PCR performance and stability of test samples using different matrices (swabs and saliva). Overall, the results indicate that the test method is acceptably validated.

- **SARS-CoV-2 nucleocapsid protein specific IgG ELISA– PPD Laboratories**

Serum will be tested using the ligand-binding assay specific to the SARS-CoV-2 nucleocapsid to determine the immunologic status of study participants at baseline and assess for seroconversion due to infection during the course of the study.

The ELISA for the Detection of IgG Specific to SARS-CoV-2 Nucleocapsid Protein in Human Serum was developed, qualified and validated by PPD Laboratories, in Richmond, Virginia, USA. This assay is employed to confirm asymptomatic infections of SARS-CoV-2 in study participants during the course of the study in participants RT-PCR negative at baseline.

Assay validation covered the quantifiable range (LLOQ to ULOQ), the limit of detection (LOD), precision and ruggedness, dilutional linearity, selectivity, specificity, and relative accuracy of the SARS CoV-2 N proteins. Validity of an assay run and individual test samples within an assay run were determined.

Selectivity was tested by spiking experiments employing reference material. During assay validation LOD of 4.8 AU/ml was confirmed, and the LLOQ was 9 AU/ml and all pre-defined acceptance criteria were met. Due to the expected depletion of the coating antigen used in the ELISA a new lot (Lot #053020) was qualified.

Of note, the assay was not tested for selectivity as regards the capability to differentiate between SARS-CoV-2 and other circulating human coronaviruses.

- **Elecsys Anti-SARS-CoV-2 (N) immunoassay, Roche**

Elecsys anti-SARS-CoV-2 (N) immunoassay is an automated commercially available antibody-based electrochemiluminescence assay employing recombinant derived nucleocapsid-(N-)-protein to measure antibodies directed against SARS-CoV-2. The assay is intended to confirm asymptomatic SARS-CoV-2 infections in study participants as it is capable to determine whether a vaccinated subject was exposed to natural infection.

According to the applicant the Roche Elecsys anti-N assay will be used in study P301 for the detection of seroconversion. For those that are seropositive at baseline, the Anti-N ELISA is used for generating the data to calculate the fold-rise. The serological (Dx) data will be available for all participants, and the anti-N fold rise data will be available for those seropositives at baseline. Baseline SARS-CoV-2 negative status requires both a negative RT-PCR test at baseline (pre-dose 1) and a negative bAb levels against SARS-CoV-2 nucleocapsid as measured by Roche Elecsys assay.

In addition, seroconversion due to infection assessed by bAb against SARS-CoV-2 nucleocapsid protein will be taken into considerations for two secondary efficacy endpoints:

- COVID-19 or SARS CoV-2 infection. This endpoint is a combination of COVID-19 (symptomatic, defined as for the primary endpoint), and SARS-CoV-2 infection, determined by seroconversion due to infection assessed by bAb levels against SARS-CoV-2 nucleocapsid protein in those who were baseline SARS-CoV-2 negative participants. In participants who were baseline SARS-CoV-2 negative, seroconversion will be measured by Roche Elecsys assay.
- Asymptomatic infection, defined as in the absence of symptoms, with SARS-CoV-2 infection determined by seroconversion due to infection assessed by bAb levels against SARS-CoV-2 nucleocapsid protein in those who were baseline SARS-CoV-2 negative participants.

Validation reports were made available and confirmed high specificity without cross reactivity to other human and endemically circulating coronaviruses (OC43, HKU1, NL63 or 229E). In addition, samples from symptomatic patients with a RT-PCR confirmed SARS-CoV-2 infection were tested after various time intervals during the convalescent phase. Antibodies against nucleocapsid could be detected up to 40 days after RT-PCR test negative results.

Of note, data of the above mentioned two secondary efficacy endpoints are not available yet.

Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following each injection (i.e., the day of dosing and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each dose of IP (i.e., the day of dosing and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol defined solicited ARs.
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- MAAEs from Day 1 through Day 759 or withdrawal from the study.
- SAEs from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Pregnancy and accompanying outcomes.

Sample size

The sample size was driven by the total number of cases required to demonstrate VE (mRNA-1273 vs. placebo) to prevent COVID-19. Under the assumption of proportional hazards over time and with 1:1 randomisation of mRNA-1273 and placebo, a total of 151 COVID-19 cases were to provide 90% power to detect a 60% reduction in hazard rate (60% VE), rejecting the null hypothesis H0: VE ≤30%, with 2 interim analyses at 35% and 70% of the target total number of cases using a 1-sided O'Brien-Fleming boundary for efficacy and a log-rank test statistic with a 1-sided false positive error rate of 0.025. Approximately 30,000 participants were to be randomised. It was assumed that approximately 15% of participants were to be excluded from the PP population, and that participants were considered to be at risk for COVID-19 starting 14 days after the second dose.

Randomisation

Participants were planned to be randomly assigned in 1:1 ratio to receive either mRNA-1273 or placebo in a blinded manner using a centralised Interactive Response Technology (IRT). Randomisation was stratified based on age and, if participants were < 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 March 2020. Consequently, there were three strata for randomisation. With protocol amendment 5, at least 25% and up to 50% of enrolled participants were planned to be either ≥65 years of age or < 65 years of age and at risk at screening.

Blinding (masking)

Up to Protocol Amendment 5, the study was an observer-blind study. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) were to be blinded to the IP administered until study end with protocol-specified exceptions such as site personnel for vaccine administration, site monitors, specific unblinded statisticians and programmers, and the independent DSMB. Further personnel were to be unblinded in case criteria for efficacy were met at any of the pre-specified analyses.

An opaque sleeve over the syringe used for injection was to maintain the blind at the time of injection, as the doses containing mRNA-1273 look different than placebo. The vaccine was administered by unblinded site staff while all further assessments and interactions were performed by blinded staff. COVID-19 and severe COVID-19 cases were adjudicated by a blinded Adjudication Committee (AC).

Correctly assuming treatment allocation seems likely for those patients with pronounced and typical reactogenicity pattern. The same concern applies for blinded study personnel accessing eCRFs. The impact this may have had on study results, if any, cannot be estimated.

Per study protocol (up to Amendment 5) participants were to remain blinded until the end of study visits after 25 months of enrolment. This plan was later revised to allow individual participants to be unblinded upon request in December 2020 when all participants have reached the day 57 visit. As per protocol amendment 6 (dated 23 Dec 2020), the applicant plans to offer unblinding to all participants at once under the EUA authorisation. No suitable analysis plan for the unblinded study part is currently in place (see efficacy discussion, section 2.5.3).

Statistical methods

The primary efficacy analysis set was defined as the **Per Protocol set** (PPS) consisting of all randomised participants without major protocol deviations or virologic/immunologic evidence of prior COVID-19 who received all planned doses of study medication. Supportive efficacy analyses were

defined in the **Full Analysis Set** (FAS; all randomised participants with at least one study dose regardless of previous COVID-19 infection) and the **modified ITT (mITT) set** (all participants in FAS without virologic/immunologic evidence of prior COVID-19).

The primary endpoint was defined as the vaccine efficacy (VE) to prevent COVID-19 starting from 14 days after second dose. In the statistical analysis plan (SAP) it was further defined that adjudicated cases were to be preferably used for the primary endpoint when available. In the presented primary analysis adjudicated cases only were used. The primary endpoint was to be evaluated using Cox proportional hazards regression with Efron's method of tie handling, stratification factors as used for randomisation and treatment group as covariate. VE was calculated as 1 – HR (hazard rate), with a 2-sided score-based 95% CI and 2-sided p-value for testing H0: VE≤30%. Adjusted 95% confidence intervals taking interim analyses into account were to be provided. In the study protocol, the applicant defined a primary estimand, which was not fully comprehensible, not well defined, and not aligned with the primary estimate. The primary estimate was acceptable however. In the primary analysis, participants were censored for COVID-19 cases prior to day 14 after the second dose and deaths unrelated to COVID-19 at any time. Censoring patients from the risk set before the first countable event apparently corresponds to an analysis excluding those participants. Furthermore, participants who missed a dose of study treatment or who were SARS-CoV-2 positive at baseline were excluded from the PP analysis.

To account for two interim and one final analysis after 53, 106, and 151 COVID-19 events in the primary endpoint, a Lan-DeMets O'Brien-Fleming approximation spending function was foreseen. The actual timing of analyses markedly deviated from the original plan. The first interim analysis was conducted after 95 adjudicated cases, the second interim analysis was seemingly dropped, and the final analysis was conducted after 196 adjudicated cases. Regarding the operational system in place to monitor case-accrual during trial conduct, with focus on safeguarding trial integrity and keeping the blind, all personnel involved in decision making regarding the trigger for the first IA were kept fully blinded to treatment assignment. Furthermore, the severe overrunning occurred due to the speed up of the pandemic and due to safety data requirements as set out by the FDA. While these arguments are in principle understood, they do not explain why the interim analyses were not conducted as scheduled. Decisions based on accruing information cannot be fully excluded. However, also given the compelling efficacy results, the impact of the deviation from pre-planned primary efficacy evaluation on the assessment of vaccination benefit is considered low.

In the SAP three key secondary endpoints were defined, which were to be tested at the full 2.5% significance level if the primary endpoint was met in any of the interim or final analyses. These endpoints were to be tested in a hierarchical pre-defined order:

1. COVID-19 regardless of evidence of prior SARS-CoV-2 infection (same follow-up period)
2. infection regardless of symptomatology or severity (same follow-up period)
3. severe COVID-19 (with ≥20 cases, otherwise to test at the end of the study)

As discussed in Hung et al. (J. Biopharm. Stat. 2007; 17:1201–1210) and Glimm et al. (Statist. Med. 2010; 29: 219-228) this procedure does not control the type 1 error in the strong sense and substantial error inflation is possible. While formally the type 1 error of the overall study was not controlled, no relevant impact on the primary endpoint analysis is seen.

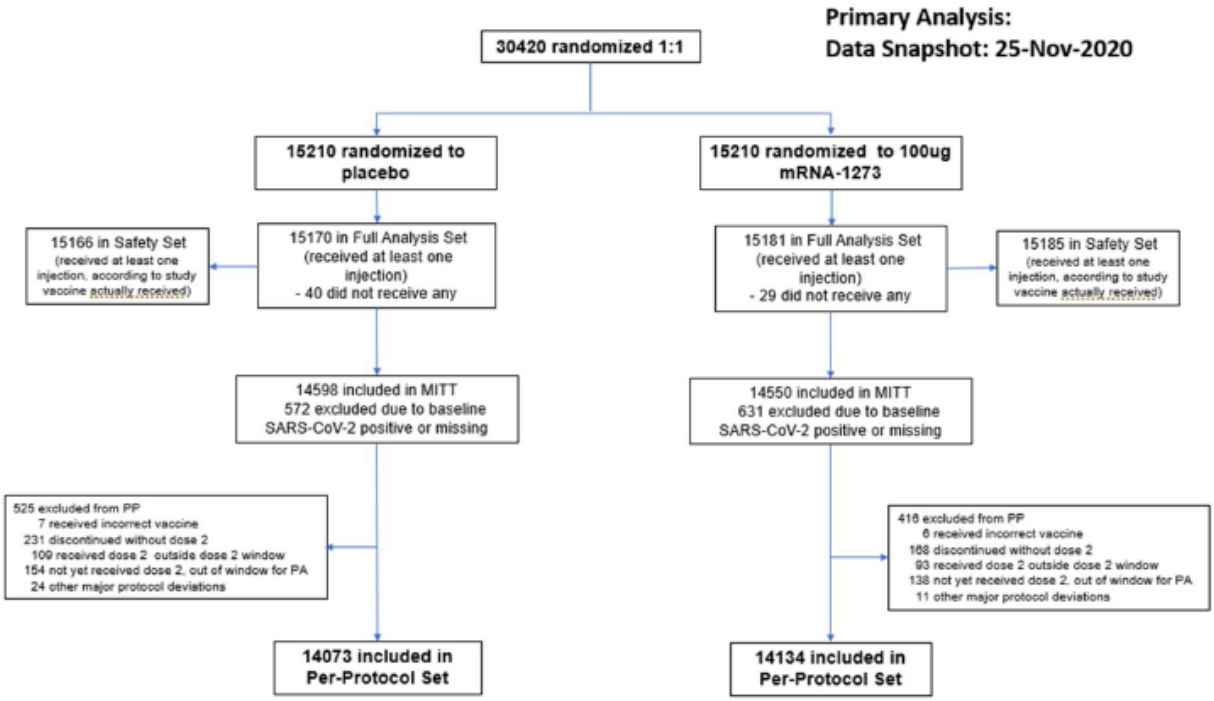
Subgroup analyses were predefined for a range of important subgroups based on risk factors, age, sex and race.

Results

The first participant-first visit/dose in the study occurred on 27 July 2020, and the last participant-first visit/dose on 23 October 2020 (enrolment completed on 23 October 2020).

There were 30,420 participants randomised, of which 30,351 (99.8%) received at least one injection. Of the 30,351 participants who received a first injection, 29,328 (96.6%) received a second injection by 25 November 2020. Median study duration was 92 days (range: 1-122 days) from randomisation; median follow-up after the second dose was 63 days, i.e. 9 weeks (range: 0-97 days).

Participant flow



Recruitment

Enrolment of P301 was completed in less than 3 months on 23 October 2020 with a total of 30,420 randomised participants. The study is since ongoing. Follow-up milestones and corresponding subject numbers are shown in the tables below:

	Vaccine Group (N = 15210) n (%)	Placebo Group (N = 15210) n (%)	Total (N= 30420) n (%)
Enrolled	15210	15210	30420
Randomized[1]	15210	15210	30420
Exposed	15185	15166	30351 (99.8)
Safety Set[2]	15185	15166	30351
Completed at least 1 month follow up after dose 1[3]	14095 (92.8)	14095 (92.9)	28190 (92.9)
Completed at least 2 months follow up after dose 1[3]	13498 (88.9)	13454 (88.7)	26952 (88.8)
Completed at least 1 month follow up after dose 2[3]	13386 (88.2)	13297 (87.7)	26683 (87.9)
Completed at least 2 months follow up after dose 2[3]	8163 (53.8)	8111 (53.5)	16274 (53.6)

Table 8 – Summary of study duration Per-Protocol Set (data extraction date: 25 November 2020)

	Placebo (N=14073)	mRNA-1273 (N=14134)	Total (N=28207)
Number of Subjects, n (%)			
Received First Injection	14073 (100)	14134 (100)	28207 (100)
Received Second Injection	14025 (99.7)	14104 (99.8)	28129 (99.7)
>= 49 Days Since First Injection	13173 (93.6)	13217 (93.5)	26390 (93.6)
>= 56 Days Since First Injection	12862 (91.4)	12930 (91.5)	25792 (91.4)
>= 2 Months Since First Injection	12605 (89.6)	12702 (89.9)	25307 (89.7)
>= 28 Days Since Second Injection	12786 (90.9)	12881 (91.1)	25667 (91.0)
>= 56 Days Since Second Injection	8987 (63.9)	9102 (64.4)	18089 (64.1)
>= 2 Months Since Second Injection	7849 (55.8)	7903 (55.9)	15752 (55.8)
< 28 Days Since Second Injection	1239 (8.8)	1223 (8.7)	2462 (8.7)
>= 28 and < 56 Days Since Second Injection	3799 (27.0)	3779 (26.7)	7578 (26.9)
>= 56 Days Since Second Injection	8987 (63.9)	9102 (64.4)	18089 (64.1)
Study Duration from Randomization (Days)			
Mean (SD)	89.2 (20.49)	89.4 (20.40)	89.3 (20.45)
Median	93.0	93.0	93.0
Q1, Q3	78.0, 105.0	78.0, 105.0	78.0, 105.0
Min, Max	29, 122	29, 122	29, 122
Study Duration from First Injection (Days)			
Mean (SD)	89.2 (20.50)	89.4 (20.40)	89.3 (20.45)
Median	93.0	93.0	93.0
Q1, Q3	78.0, 105.0	78.0, 105.0	78.0, 105.0
Min, Max	29, 122	29, 122	29, 122
Study Duration from Second Injection (Days) [1]			
Mean (SD)	60.0 (20.56)	60.2 (20.46)	60.1 (20.51)
Median	63.0	64.0	64.0
Q1, Q3	49.0, 76.0	49.0, 76.0	49.0, 76.0
Min, Max	0, 97	0, 97	0, 97
Study Duration from Second Injection in Subjects Who Received Second Injection (Days)			
n	14025	14104	28129
Mean (SD)	60.2 (20.29)	60.3 (20.30)	60.2 (20.30)
Median	64.0	64.0	64.0
Q1, Q3	49.0, 76.0	49.0, 76.0	49.0, 76.0
Min, Max	1, 97	1, 97	1, 97

Conduct of the study

The study has gone through extensive changes. The currently available study protocol version is Version 6, dated 23 December 2020, which details the modification of the unblinding process after EUA authorisation in the USA. The study now consists of two parts, the blinded Part A and the unblinded follow-up in Part B. Protocol version 4 and 5 were provided and the main amendments in the study protocol include clarifications for safety surveillance and the aim to increase to 50% the upper limit for stratification of enrolled participants considered "at risk" at screening. No other versions of the study protocol were provided. Important amendments with potential implications for case detection/adjudication were made at a time point where no biased impact on the primary efficacy readout is assumed.

Baseline data

Study mRNA-1273-P301 was designed to evaluate the safety and efficacy of the 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 enrol at least 25% and up to 50% of participants most at risk for severe complications of COVID-19, including those ≥ 65 years of age or < 65 years of age with co-morbid

medical conditions such as diabetes mellitus (Type 1, Type 2, or gestational), significant cardiac disease, chronic pulmonary disease, severe obesity, liver disease, and human immunodeficiency virus infection (actual enrolment in these 2 strata was 25.3% and 16.7%, respectively). Overall, the study included 42% of participants at high risk for severe COVID-19 (i.e., the sum of participants < 65 and at risk and ≥65 years).

Overall, the demographic characteristics were well balanced between the study populations. Individuals at risk of severe COVID-19, i.e. 18 to 64 years with identified risk factors such as underlying chronic diseases, and elderly ≥65 years of age, are adequately represented and are equally distributed between the two treatment groups according to their risk factors.

In addition, a high proportion of individuals with high risk of exposure to SARS-CoV-2 due to their occupation such as health care and frontline workers were enrolled. The majority (25.1%) of participants with a specified occupational risk for acquisition of SARS-CoV-2 were health care workers.

Distribution of elderly subjects over 65 years of age was well balanced between the two treatment groups. A substantial proportion (n= 7520; ~25%) of the population in the pivotal trial P301 was aged 65 or older. Approximately 12% (n= 3722) of the total population was 65-69, about 8% (n=2398) was aged 70-74, about 3% (n=975) was in the age range between 75 and 79, and 1.4% or 425 subjects were 80 or older.

The percentage of participants enrolled who self-reported as Black or African American (10.2%) or Hispanic or Latino (20.5%) approached that of the US population (US Census Bureau 2019: Black [13.4%], Hispanic or Latino [18.5%]). Communities of colour represented 37.2% of the study population.

Table 9 – Baseline demographic and characteristics in Study mRNA-1273-P301 (PPS, data cut-off 21 November 20202)

	Vaccine Group (N=14134) n (%)	**Placebo Group (N= 14073) n (%)**	**Total (N=28207) n (%)**
Sex			
Female	6768 (47.9)	6611 (47.0)	13379 (47.4)
Male	7366 (52.1)	7462 (53.0)	14828 (52.6)
Age (years)			
Mean (SD)	51.6 (15.44)	51.6 (15.54)	51.6 (15.49)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
18 to <65	10551 (74.6)	10521 (74.8)	21072 (74.7)
65 and older	3583 (25.4)	3552 (25.2)	7135 (25.3)
Race			
American Indian or Alaska Native	108 (0.8)	111 (0.8)	219 (0.8)
Asian	620 (4.4)	689 (4.9)	1309 (4.6)
Black or African American	1385 (9.8)	1349 (9.6)	2734 (9.7)
Native Hawaiian or Other Pacific Islander	35 (0.2)	31 (0.2)	66 (0.2)
White	11253 (79.6)	11174 (79.4)	22427 (79.5)
Other	299 (2.1)	295 (2.1)	594 (2.1)
Ethnicity			
Hispanic or Latino	2789 (19.7)	2780 (19.8)	5569 (19.7)
Not Hispanic or Latino	11212 (79.3)	11165 (79.3)	22377 (79.3)
Race and Ethnicity			
Non-Hispanic White	9023 (63.8)	8916 (63.4)	17939 (63.6)
Communities of colour	5088 (36.0)	5132 (36.5)	10220 (36.2)
Occupational Risk*	11586 (82.0)	11590 (82.4)	23176 (82.2)
Healthcare worker	3593 (25.4)	3581 (25.4)	7174 (25.4)

[2] Data snap shot 2 was dated 25.11.2020, however efficacy cut-off happened on 21.11.2020 and only safety cut-off was on 25.11.2020.

	Vaccine Group (N=14134) n (%)	Placebo Group (N= 14073) n (%)	Total (N=28207) n (%)
High Risk Condition**			
One high risk condition present	2616 (18.5)	2591 (18.4)	5207 (18.5)
Two or more high risk conditions present	590 (4.2)	576 (4.1)	1166 (4.1)
No high risk condition	10928 (77.3)	10906 (77.5)	21834 (77.4)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8189 (57.9)	8200 (58.3)	16389 (58.1)
18 to <65 years and at risk	2367 (16.7)	2324 (16.5)	4691 (16.6)
≥ 65 years	3578 (25.3)	3549 (25.2)	7127 (25.3)

* Occupational risk includes: Healthcare Workers; Emergency Response; Retail/Restaurant Operations; Manufacturing and Production; Operations, Warehouse Shipping and Fulfilment centres, Transportation and Delivery Services, Border Protection and Military Personnel Personal care and in-home services; Hospitality and Tourism Workers, Pastoral; Social or Public Health Workers; and Educators and Students.

** High risk for severe COVID-19 is defined as patients who meet at least one of the following criteria (protocol-defined):

- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and
- pulmonary hypertension)
- Severe obesity (body mass index ≥ 40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- Human immunodeficiency virus (HIV) infection

*** Age and health risk for severe COVID-19 is used as stratification factor for randomisation.

Overall, 2.2% of participants (~700) had detectable viral RNA or antibodies against SARS-CoV-2 at baseline across both arms.

High level data on co-medication were presented upon request (not displayed here), showing largely balanced co-medication use for the first two months of study with paracetamol and ibuprofen being the main exceptions with a large overuse observed in the mRNA-1273 vaccine arm (i.e. double the patient level incidence or more compared to placebo). This is likely explained by the acute AE profile of vaccination and not related to baseline imbalances.

Numbers analysed

As of 21 November 2020, a total of 30,420 individuals were randomly assigned with 15,210 subjects each enrolled either in the mRNA-1273 group or the placebo group. In the randomised set 15,181 (99.8%) and 15,170 (99.8%) received their first dose of either mRNA-1273 or placebo, respectively, and 14,711 (96.7%) and 14,617 (96.1%) received their second dose of mRNA-1273 and placebo, respectively. As the study is currently ongoing, the number of patients who received the second dose is still expected to rise.

Table 10 - Subject Disposition - mRNA-1273-P301 as of 21 November 2020 (data cut-off)

	Vaccine Group (N = 15210) n (%)	Placebo Group (N = 15210) n (%)	Total (N= 30420) n (%)
Enrolled	15210	15210	30420
Randomised[1]	15210	15210	30420
Exposed	15185	15166	30351 (99.8)
Safety Set[2]	15185	15166	30351
Completed at least 1 month follow up after dose 1[3]	14095 (92.8)	14095 (92.9)	28190 (92.9)
Completed at least 2 months follow up after dose 1[3]	13498 (88.9)	13454 (88.7)	26952 (88.8)
Completed at least 1 month follow up after dose 2[3]	13386 (88.2)	13297 (87.7)	26683 (87.9)
Completed at least 2 months follow up after dose 2[3]	8163 (53.8)	8111 (53.5)	16274 (53.6)
Full Analysis Set[1]	15181 (99.8)	15170 (99.7)	330351 (99.8)

	Vaccine Group (N = 15210) n (%)	Placebo Group (N = 15210) n (%)	Total (N= 30420) n (%)
Per Protocol Set[1]	14134 (92.9)	14073 (92.5)	28207 (92.7)
Completed at least 7 weeks follow up[4]	13217 (93.5)	13173 (93.6)	26390 (93.6)
Completed at least 8 weeks follow up[4]	12930 (91.5)	12862 (91.4)	25792 (91.4)
Completed at least 2 months follow up[4]	12702 (89.9)	12605 (89.6)	25307 (89.7)
Completed at least 4 weeks follow up after dose 2[4]	12881 (91.1)	12786 (90.9)	25667 (91.0)
Completed at least 8 weeks follow up after dose 2[4]	9102 (64.4)	8987 (63.9)	18089 (64.1)
Completed at least 2 months follow up after dose 2[4]	7903 (55.9)	7849 (55.8)	15752 (55.8)
Randomised Set			
Completed 1 dose	15181 (99.8)	15170 (99.7)	30351 (99.8)
Completed 2 doses	14711 (96.7)	14617 (96.1)	29328 (96.4)
Discontinued from Study	159 (1.0)	206 (1.4)	365 (1.2)
Reason for Discontinuation			
Adverse Event	4 (<0.1)	1 (<0.1)	5 (<0.1)
Serious Adverse Event	9 (<0.1)	15 (<0.1)	24 (<0.1)
Death	4 (<0.1)	6 (<0.1)	10 (<0.1)
Withdrawal by Subject	85 (0.6)	146 (1.0)	231 (0.8)
Lost to Follow-up	33 (0.2)	35 (0.2)	68 (0.2)
Protocol Deviation	1 (<0.1)	0	1 (<0.1)
Physician Decision	15 (<0.1)	3 (<0.1)	18 (<0.1)
Other	14 (<0.1)	13 (<0.1)	27 (<0.1)
Per-Protocol Set[1]	14134 (92.9)	14073 (92.5)	28207 (92.7)
Completed 1 dose[4]	14134 (100)	14073 (100)	28207 (100)
Completed 2 doses[4]	14104 (99.8)	14025 (99.7)	28129 (99.7)
Discontinued from Study[4]	36 (0.3)	51 (0.4)	87 (0.3)
Reason for Discontinuation[4]			
Adverse Event	0	0	0
Serious Adverse Event	0	0	0
Death	1 (<0.1)	3 (<0.1)	4 (<0.1)
Withdrawal by Subject	25 (0.2)	35 (0.2)	60 (0.2)
Lost to Follow-up	5 (<0.1)	10 (<0.1)	15 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	3 (<0.1)	1 (<0.1)	4 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

[1] Numbers are based on planned treatment group and percentages are based on the number of randomized subjects.
[2] Numbers are based on actual treatment group and percentages are based on the number of safety subjects.
[3] Percentage based on number of subjects in the Safety Set.
[4] Percentage based on number of subjects in the Per-Protocol Set.

Discontinuation from study for the time being is very low (1.2%) and mostly due to withdrawal by the subject (0.8%). Only 39 subjects in total discontinued due to experience of an AE (5) or SAE (24) or death (10). Out of 29,148 subjects randomised, 680 subjects were excluded due to laboratory confirmed SARS-CoV-2 infection prior to dose 1, i.e. the mITT set represents 95.8% of the randomised population. In FAS, baseline RT-PCR test results were missing in 1.2% of participant; baseline serology as measured by SARS-CoV-2 nucleocapsid binding antibody test results were missing in 1.1% of participants. Approximately 2.2% of participants were baseline SARS-CoV-2 positive.

Table 11 - Reason and number of subjects excluded from the Per-Protocol Set

Reasons for exclusion from Per Protocol Set	**Placebo**	**mRNA-1273**
	N= 15210	**N= 15210**
Subjects excluded from PP Set	**1137** (7.5%)	**1076** (7.1%)
Randomised but not received any IP	40 (0.3%)	29 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	572 (3.8%)	631 (4.2%)

Received IP other than what the subject was randomised to	7 (<0.1%)	6 (<0.1%)
Discontinued study or study vaccine without receiving the second dose	231 (1.5%)	168 (1.1%)
Did not receive second dose of IP	154 (1.0%)	138 (0.9%)
Received vaccine out of window	109 (0.7%)	93 (0.6%)
Major protocol deviation*	24 (0.2%)	11 (0.1%)

*Major protocol deviations other than the categories listed earlier in the table:

- Inclusion criteria not met, but subject randomised
- Exclusion criteria met, but subject randomised
- Study treatment impacted by a temperature excursion which was not reported or approved or which was disapproved for further use
- Prohibited concomitant medication or vaccine received by subject

Outcomes and estimation

Two analyses of efficacy were performed: an interim analysis based on data snapshot 1 (11 November 2020; cut-off date for efficacy 7 November 2020) and the final analysis based on data snapshot 2 (25 November 2020; cut-off date for efficacy 21 November 2020). There were 95 and 196 adjudicated cases of COVID-19 14 days or more after the second dose included in each analysis, respectively.

Primary efficacy endpoint as determined in the interim analysis (data cut-off 7 November 2020)

The inferential statistical analysis of vaccine efficacy based on the interim analysis was performed on 95 adjudicated cases of COVID-19 accrued in the Per-Protocol set, with 5 cases occurring in the mRNA-1273 group and 90 cases occurring in the placebo group.

The analysis indicates a vaccine efficacy (VE) point estimate of 94.5% (unadjusted 95% CI: 86.5, 97.8; p <0.0001) for prevention of laboratory confirmed COVID-19 in subjects without evidence of SARS-CoV-2 infection prior dose 1. The adjusted 95% CI, reflecting the additional uncertainty due to interim analyses, was reported as (81.8%, 98.3%). The primary objective was met.

Primary efficacy endpoint as determined in the final analysis (data cut-off 21 November 2020)

The final efficacy analysis was conducted on the efficacy data set as of 21 November 2020, which included 28,207 participants in the PP set with a median follow-up time of 9 weeks after the second dose. A total of 196 adjudicated COVID-19 cases were accrued and the estimated VE was 94.1% (95% CI 89.3%, 96.8%). These results support the conclusion on vaccine efficacy based on the first interim analysis.

Table 12 - Primary Efficacy Analysis: COVID-19 cases Starting 14 Says After the Second Dose –PP Set

	Vaccine Group N= 13934 Cases n (%) (Incidence Rate per 1,000 Person-Years)*	**Placebo Group** N= 13883 Cases n (%) (Incidence Rate per 1,000 Person-Years)*	**Vaccine Efficacy (VE) % (95% Confidence Interval)****
All subjects	11 (<0.1); 3.328	185 (1.3); 56.510	94.1% (89.3%, 96.8%)
18 to <65 years[1]	7 / 10551 (<0.1);	156 / 10521 (1.5);	95.6%;

	2.875	64.625	(90.6%, 97.9%)
65 years and older[2]	4 / 3583 (0.1); 4.595	29 / 3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)

COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose. All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cut-off date for efficacy).

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

**VE and 95% CI from the stratified Cox proportional hazard model

[1] Percentage based on number of subjects in the 18 to <65 years of age group.

[2] Percentage based on number of subjects in the ≥65 years of age group.

Supplementary analyses of the primary endpoint (based on data cut-off 21 November 2020)

Based on the mITT set, which includes all participants in the FAS who had no immunologic or virologic evidence of prior SARS-CoV-2 infection or COVID-19 at Day 1 before the first dose, the VE 14 days after dose 2 was estimated to be 93.6% (95% CI 88.5; 96.4). This suggests that the reasons rendering subjects ineligible for PPS had no major impact on VE, thus refuting potential selection bias.

Table 13 - Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee - Assessments Starting 14 Days After Second Injection (mITT)

	Placebo (N=14598)	mRNA-1273 (N=14550)
Number of Subjects with Secondary Definition of COVID-19 n (%) Number of Subjects Censored, n (%)	185 (1.3) 14413 (98.7)	12 (<0.1) 14538 (>99.9)
Vaccine Efficacy Based on Hazard Ratio (95% CI) [1]		0.936 (0.885, 0.964)
Person-Years [2]	3282.9	3390.1
Incidence Rate per 1,000 Person-Years (95% CI) [3]	54.688 (47.091, 63.161)	3.540 (1.829, 6.183)
Vaccine Efficacy Based on Incidence Rate (95% CI) [4]		0.935 (0.884, 0.967)

[1] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are 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.

[2] Person-years is defined as the total years from randomisation date to the date of COVID-19, last date of study participation, or efficacy data cut-off date, whichever is earlier.

[3] Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.

[4] VE is defined as 1 — ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

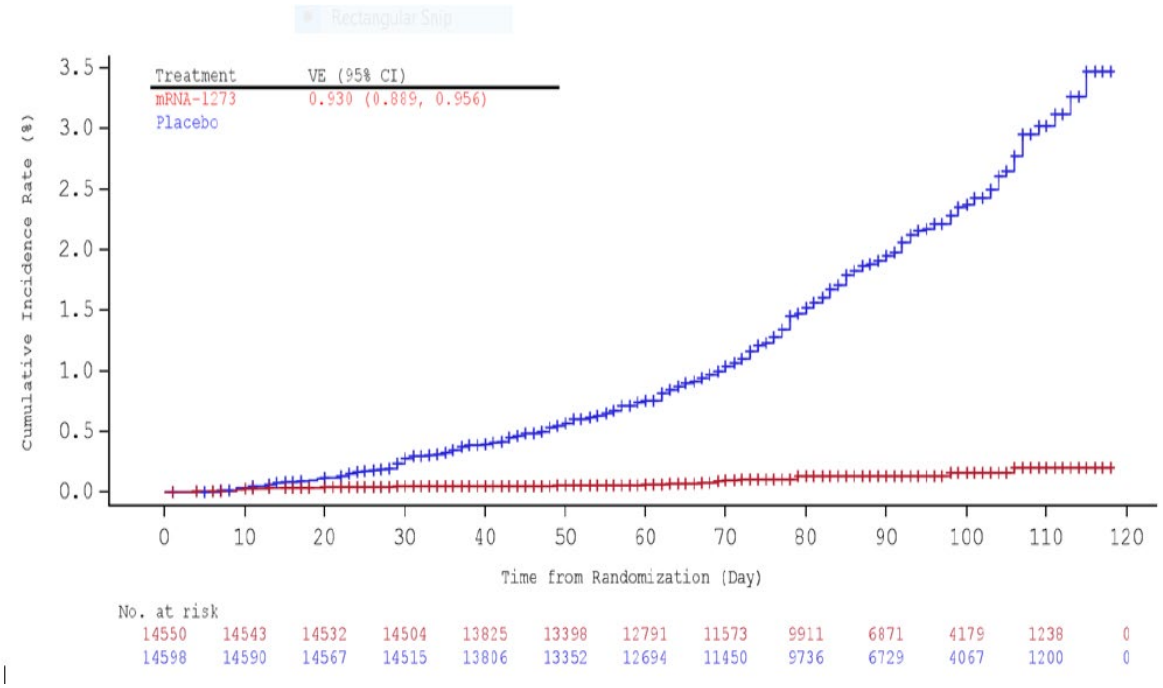
The cumulative incidence rates of COVID-19 starting after randomisation, which corresponds to day 1, start to continuously increase in the placebo group thereafter while they remain low in the vaccine group. However, it is noted that a high percentage of individuals in the mITT set has received a second dose (i.e. mRNA-1273: 97.7% and placebo: 97.0%). This analysis, closer to the ITT principle than the primary analysis, by accounting for all cases accruing after IP administration and less stringent in set eligibility, further serves to support VE. This also applies for a similar analysis done in the full analysis set (FAS).

Table 14 - Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Starting after Randomisation regardless of prior SARS-COV-2 infection (mITT & FAS)

	mRNA n/N (%)	Placebo n/N (%)	VE (95% CI)
FAS	26/15181 (0.2)	276/15170 (1.8)	90.7% (86.1%, 93.8%)

mITT	19/14550 (0.1)	269/14598 (1.8)	93.0% (88.9%, 95.6%)

Figure 18 - Cumulative incidence curve of COVID starting after randomisation regardless of prior SARS-COV-2 infection (mITT)



Secondary efficacy endpoint analyses (data cut-off 21 November 2020)

Vaccine efficacy to prevent severe COVID-19

The vaccine efficacy analysis presented for prevention of severe cases of COVID-19 shows that no cases occurred in the mRNA-1273 group but 30 severe COVID-19 cases were reported in the placebo group indicating protection from development of severe COVID-19 starting 14 days after dose 2 up to the data cut-off.

Table 15 - Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Severe COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection (PP)

	Placebo (N=14073)	mRNA-1273 (N=14134)
Number of Subjects with Severe COVID-19 n (%) Number of Subjects Censored, n (%)	 30 (0.2) 14043 (99.8)	 0 14134 (100)
Vaccine Efficacy Based on Hazard Ratio (95% CI) [1]		1.000 (NE, 1.000)
Person-Years [2]	3282.9	3305.4
Incidence Rate per 1,000 Person-Years (95% CI) [3]	9.138 (6.166, -13.046)	0.000 (NE, -1.116)
Vaccine Efficacy Based on Incidence Rate (95% CI) [4]		1.000 (0.870, NE)

[1] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are 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.
[2] Person-years is defined as the total years from randomisation date to the date of severe COVID-19, last date of study participation, or efficacy data cut-off date, whichever is earlier.
[3] Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
[4] VE is defined as 1 — ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Vaccine efficacy to prevent COVID-19 using a secondary definition of symptoms

Based on a less stringent definition of a case of COVID-19 with only one symptom present at time of reporting (as defined by CDC) and a confirmation of SARS-CoV-2 infection by RT-PCR in subjects without evidence of SARS-CoV-2 infection prior to dose 1, the VE at 14 days after dose 2 was estimated to be 95.1% (95% CI 91.1; 97.3).

Table 16 - Analysis of Vaccine Efficacy of mRNA-1273 to Prevent Secondary Definition of COVID-19 Starting 14 Days After Second Injection (Per-Protocol Set)

	Placebo (N=14073)	mRNA-1273 (N=14134)
Number of Subjects with Secondary Definition of COVID-19 n (%) Number of Subjects Censored, n (%)	221 (1.6) 13852 (98.4)	11 (<0.1) 14123 (>99.9)
Vaccine Efficacy Based on Hazard Ratio (95% CI) [1]		0.951 (0.911, 0.973)
Person-Years [2]	3269.8	3304.8
Incidence Rate per 1,000 Person-Years (95% CI) [3]	67.589 (58.971, 77.112)	3.329 (1.662, 5.956)
Vaccine Efficacy Based on Incidence Rate (95% CI) [4]		0.951 (0.910, 0.976)

[1] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are 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.
[2] Person-years is defined as the total years from randomisation date to the date of secondary definition of COVID-19, last date of study participation, or efficacy data cut-off date, whichever is earlier.
[3] Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
[4] VE is defined as 1 — ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Vaccine efficacy to prevent death caused by COVID-19

In the PP set, one participant died due to COVID-19 in the placebo group and none in the vaccine group during the course of the study.

VE to prevent COVID-19 starting 14 days after dose 2 regardless of prior SARS-CoV-2 Infection

Vaccine efficacy regardless of prior SARS-CoV-2 infection is consistent with VE in subjects without prior evidence of SARS-CoV-2. Based on the FAS population VE at 14 days after dose 2 was estimated to be 93.6% (95% CI 88.6; 98.6) in subjects with or without evidence of SARS-CoV-2 infection prior to dose 1. Evidence of prior SARS-CoV-2 at baseline, however, was reported only in approx. 2.2% of study participants suggesting a low infection rate in the general population at time of enrolment.

Table 17 **- Analysis of Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 Based on Adjudication Committee Assessments Starting 14 Days After Second Injection Regardless of Prior SARS-CoV-2 Infection (FAS)**

	Placebo (N=15170)	mRNA-1273 (N=15181)
Number of Subjects with COVID-19 n (%) Number of Subjects Censored, n (%)	187 (1.2) 14983 (98.8)	12 (<0.1) 15169 (>99.9)
Vaccine Efficacy Based on Hazard Ratio (95% CI) [1]		0.936 (0.886, 0.965)
Person-Years [2]	3507.9	3325.1
Incidence Rate per 1,000 Person-Years (95% CI) [3]	53.309 (45.942, 61.521)	3.404 (1.759, 5.946)
Vaccine Efficacy Based on Incidence Rate (95% CI) [4]		0.936 (0.886, 0.968)

[1] Vaccine efficacy (VE), defined as 1 - hazard ratio (mRNA-1273 vs. placebo), and 95% CI are 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.
[2] Person-years is defined as the total years from randomisation date to the date of COVID-19, last date of study participation, or efficacy data cut-off date, whichever is earlier.
[3] Incidence rate is defined as the number of subjects with an event divided by the number of subjects at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
[4] VE is defined as 1 — ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Ancillary analyses

Subgroup analyses of vaccine efficacy confirmed that efficacy was consistent across major demographic and baseline characteristics. Although the clinical development was solely performed in the USA, the demographic characteristics are relevant for the European population too in general.

Based on the primary efficacy endpoint to prevent COVID-19 starting 14 days after the 2nd dose in subjects without prior evidence of SARS-CoV-2 infection, results of subgroup analysis of VE according to specific age subgroups are presented below. The vaccine efficacy of mRNA-1273 indicates good protection from COVID-19 although with lower efficacy estimates in the ≥65 to <75 years old (82.4%; 95% CI: 46.9; 93.9) and an estimated VE of 100% in subjects aged 75 years and older.

As regards subjects 75 years of age and older, the number included in the study and the number of cases observed are limited as few participants were enrolled in this age group and the median follow-up was of approx. 9 weeks post-dose 2. Long-term protection from disease remains unknown for the time being including for subjects of high-risk groups.

Table 18 - Subgroup Analyses of Vaccine Efficacy - COVID-19 cases 14 Days After Dose 2 per Adjudication Committee Assessments – PP Set, primary efficacy analysis, Data cut-off: 21 November 2020

Subgroup	**Vaccine Group** Cases N (%) Incidence Rate in 1,000 Person-Years	**Placebo Group** Cases N (%) Incidence Rate in 1,000 Person-Years	**VE %** (95% Confidence Interval)
Age (years)[1]			
18 to <65	7 / 10551 (<0.1); 2.875	156 / 10521 (1.5); 64.625	95.6% (90.6%, 97.9%)
65 and older	4 / 3583 (0.1); 4.595	29 / 3552 (0.8); 33.728	86.4% (61.4%, 95.2%)
≥65 to ≤75	4/2,953; (0.1) 5.586	22/2864; (0.8) 31.744	82.4% (46.9%, 93.9%)
75 and older	0 / 630	7 / 688 (1.0); 41.968	100% (NE, 100%)
At risk for severe COVID-19 due to comorbidity, regardless of age[1]*			
Yes	4 / 3206 (0.1);	43 / 3167 (1.4);	90.9%

Subgroup	**Vaccine Group** Cases N (%) Incidence Rate in 1,000 Person-Years	**Placebo Group** Cases N (%) Incidence Rate in 1,000 Person-Years	**VE %** (95% Confidence Interval)
	5.227	57.202	(74.7%, 96.7%)
No	7 / 10928 (<0.1); 2.756	142 / 10906 (1.3); 56.304	95.1% (89.6%, 98.1%)
Age and risk for severe COVID-19[1]**			
18 and <65 and at risk	2 / 2155 (<0.1) 3.947	35 / 2118 (1.7) 70.716	94.4% (76.9%, 98.7%)
≥65 and at risk	0 / 1041 (<0.1)	2 / 8403 (1.4) 1.049	75.2% (NE, 94.7%)
Baseline SARS-CoV-2[1]***			
Positive	0 / 343	1 / 336 (0.3); 13.915	100%
Negative	12 / 14550 (<0.1); 3.540	185 / 14598 (1.3); 54.688	93.6% (88.5%, 96.4%)
Sex[1]			
Female	7 / 6768 (0.1); 4.364	98 / 6611 (1.5); 62.870	93.1% (85.2%, 96.8%)
Male	4 / 7366 (<0.1); 2.3.52	87 / 7462 (1.2); 50.730	95.4% (87.4%, 98.3%)
Race and Ethnicity[1]			
Non-Hispanic White	10 / 9023 (0.1); 4.413	144 /8916 (1.6); 64.608	93.2% (87.1%, 96.4%)
Communities of colour	1 / 5088 (<0.1); 0.967	41 / 5132 (0.8); 39.443	97.5% (82.2%, 99.7%)
Ethnicity[1]			
Hispanic or Latino	1 / 2789 (<0.1); 1.758	28 / 2780 (1.0); 49.662	96.5% (74.4%, 99.5%)
Not Hispanic or Latino	10 / 11212 (<0.1); 3.699	156 / 11165 (1.4); 58.211	93.7% (88.1%, 96.7%)
Race[1]			
American Indian or Alaska Native	0 / 108	1 / 111 (0.9); 44.788	100%
Asian	0 / 620	5 / 689 (0.7); 35.599	100%
Black or African American	0 / 1385	6 / 1349 (0.4); 22.283	100%
Native Hawaiian or Other Pacific Islander	0 / 35	0 / 31	
White	11 /11253 (<0.1); 4.032	166 / 11174 (1.5); 61.606	93.5% (88.0%, 96.5%)
Multiple	0 / 295	3 / 307 (1.0); 48.476	100%
Other	0 / 299	2 / 295 (0.7); 36.221	100%

1 Percentage based on number of subjects in each subgroup
* At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined):

- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥ 40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease

Human immunodeficiency virus (HIV) infection
** Age and health risk for severe COVID-19 is used as stratification factor for randomisation
***Endpoint based on the FAS Set.

Table 19 – Summary of subgroup analysis results by number of risk factors[1] for severe COVID-19 based on adjudicated COVID-19 cases starting 14 days after 2nd dose, PP set, data cut-off 25 November 2020

	mRNA-1273 #cases / N (%)	Placebo #cases / N (%)	VE* (%) (95%CI)
No risk	7/ 10928 (<0.1)	142 /10906 (1.3)	95.1 (89.6, 97.7)
Only 1 risk factor	3/2616 (0.1)	35/2591 (1.4)	91.7 (73.0, 97.4)
≥ 2 risk factors	1/590 (0.2)	8/576 (1.4)	87.2 (-2.7, 98.4)

N: number of participants in specified subgroups
*VE: 1-hazard risk, using cox proportional hazard model
1: At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined):

- Chronic lung disease (e.g., emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥ 40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial mRNA-1273-P301

Title: 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		
Study identifier	P301 NCT04470427	
Design	Phase 3, randomised, observer-blind, placebo-controlled study	
	Duration of main phase:	24 months post-dose 2, ongoing
Hypothesis	Superiority	
Treatments groups	mRNA-1273+LNP	2 doses of 100 µg/0.5ml given 28 days apart. N=14134
	Placebo, 0.9% NaCl, sterile	2 doses of 0.5ml given 28 days apart. N=14073

Endpoints and definitions	Primary endpoint	To prevent confirmed COVID-19 starting 14 days after Dose 2	VE will be estimated with 1 - HR (mRNA-1273 vs placebo) using a Cox proportional hazard regression model with treatment group as a fixed effect and adjust for stratification factor based on the PP Set, with cases counted starting 14 days after the second dose of IP.
	Secondary Endpoint	To prevent severe COVID-19 starting 14 days after Dose 2	VE will be estimated with 1 - HR (mRNA-1273 vs placebo) using a Cox proportional hazard regression model with treatment group as a fixed effect and adjusting for stratification factor based on the PP Set, with cases counted starting 14 days after the second dose of IP.
	Secondary endpoint	To prevent COVID-19 starting 14 days after dose 2 regardless of prior SARS-CoV-2 infection	VE will be estimated with 1 - HR (mRNA-1273 vs placebo) using a Cox proportional hazard regression model with treatment group as a fixed effect and adjusting for stratification factor based on the FAS Set, with cases counted starting 14 days after the second dose of IP.
Data snapshots	Interim efficacy analysis: 11 Nov 2020 (clinical data cut-off: 7 Nov 2020) Final efficacy analyses: 25 Nov 2020 (clinical data cut-off: 21 November 2020)		
<u>Results and Analysis</u>			
Analysis description	**Inferential Analysis –** This analysis was used for formal proof of efficacy		
Analysis population and time point description	Per protocol: All participants in the who were baseline seronegative, received all planned doses and without major protocol deviations (data cut-off 07 Nov 2020)		
Descriptive statistics and estimate variability	Treatment group	mRNA-1273+LNP	placebo
	Number of subject	13934	13883
	To prevent confirmed COVID-19 starting 14 days after Dose 2 Cases n (%) (Incidence Rate per 1,000 Person-Years)	5 (<0.1); 1.840	90 (0.6); 33.365
Effect estimate per comparison	Primary endpoint	Comparison groups	mRNA-1273 to placebo (N=14134/14073)
		VE: 1 - hazard ratio (mRNA-1273 vs. placebo)	94.5

		Unadjusted 95% CI Adjusted 95% CI*	86.5%, 97.8% 81.8%, 98.3%
		p-value (H_0: VE ≤ 30%)	< 0.0001
Notes	*Adjusted for interim analyses based on O'Brien-Fleming alpha-spending function. The nominal significance level to be used at the first interim was 0.0045 (one-sided) leading to a nominal 99.1% CI.		
Analysis description	**Final Analysis –** These analyses were used to refine estimates based on more mature data		
Analysis population and time point description	Per protocol: All participants who were without prior evidence of SARS-CoV-2 before dose 1 and received all planned doses and were without major protocol deviations (data cut-off 21 Nov 2020)		
Descriptive statistics and estimate variability	Treatment group	mRNA-1273+LNP	placebo
	Number of subjects	14134	14073
	To prevent confirmed COVID-19 starting 14 days after Dose 2 Cases n (%) (Incidence Rate per 1,000 Person-Years)	11 (<0.1); 3.328	185 (1.3); 56.510
Effect estimate per comparison	Primary endpoint	Comparison groups	mRNA-1273 to placebo (N=14134/14073)
		VE: 1 - hazard ratio (mRNA-1273 vs. placebo)	94.1
		95% CI	89.3%, 96.8%
Effect estimate per comparison	Secondary endpoint: To prevent severe COVID-19 starting 14 days after Dose 2	Comparison groups	mRNA-1273 to placebo (N=14134/14073)
		VE: 1 - incidence rate (mRNA-1273 vs. placebo)	100% *(based on 30 cases)*
		95% CI	87.0%, NE
	Secondary endpoint (FAS set): To prevent COVID-19 starting 14 days after dose 2 regardless of prior SARS-CoV-2 infection	Comparison groups	mRNA-1273 to placebo (N=15181/15170)
		VE: 1 - hazard ratio (mRNA-1273 vs. placebo)	93.6%
		95% CI	88.6%, 96.5%

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal phase 3 clinical trial mRNA-1273-P301 is a multicentre, randomised, placebo-controlled, observer blind, efficacy and safety study. Since the study is case-driven, high number of centres and rate of enrolment together with planned interim analyses for early evaluation of vaccine efficacy resulted in a short time to last patient enrolled/vaccinated and primary efficacy readouts. This resulted in short follow-up duration and, related to that, the inability to inform long-term efficacy and safety objectives at present. Two data snapshots with data cut-off date 7 November 2020 and 21 November 2020 were provided for assessment. Of note, these snapshots are not fully cleaned, monitored and validated as opposed to usual data base locks. The dose for phase 3 was selected based on emergent safety and immunogenicity data from the phase 1 study 20-0003 and supported by the reactogenicity data after dose 2 from the phase 2a P201 study. Immunogenicity results from the phase 2a study were not available at the time of the dose selection.

All studies are ongoing. The study duration of the pivotal study is 24 months after the second dose to collect long-term efficacy, immunogenicity and safety data. Currently, efficacy data are available from a median duration of 9 weeks after the second dose.

The study population comprises subjects 18 years of age and older including individuals with underlying but stable chronic disease (e.g. diabetes, chronic lung disease, obesity) and elderly subjects over 65 years of age with a substantial proportion over 75 years known to have an increased risk of development of severe disease, hospitalisation and death following SARS-CoV-2 infection. Randomisation was stratified based on age and, if participants were < 65 years of age, based on the presence or absence of risk factors for severe illness from COVID-19 according to CDC recommendation as of March 2020. With protocol amendment 4 the applicant aimed to increase the enrolment of these two high-risk groups to achieve higher inclusion rates: at least 25% and up to 50% of enrolled participants, were planned to be either ≥ 65 years of age, or < 65 years of age but at risk for severe COVID-19 at screening. A high proportion of the finally randomised study population represents these two high-risk groups (25.3% and 16.7%, respectively). In addition, individuals with a high risk of exposure to SARS-CoV-2 due to their occupation such as health care and frontline workers were included (82%, of which 25% heath care workers).

Recruitment was limited to the US (99 study sites overall). There are no major intrinsic/extrinsic differences seen between regions to question applicability of main efficacy results to the EU given study objectives and main endpoints. It is also considered that the time of study conduct had no negative impact on generalisability of results to the present situation due to relative stability of dominant US/EU clades during phase 3 and since then.

Pregnant and breastfeeding women were excluded from the studies as this vaccine class is new and no vaccine was yet approved based on Moderna's mRNA technology platform at the time the trials were initiated. Based on lack of experience in humans and the fact that animal data from the DART study was only available very recently after study start, this approach is supported. In addition, no immune suppressed subjects or subjects with immunodeficiencies were enrolled except for a limited number of HIV infected individuals. This approach is considered acceptable for a pivotal study, moreover conducted during an emergency situation, to avoid exposing vulnerable population before having a

clear understanding of the benefits of the vaccine. Further data on immunocompromised individuals are needed (see requirements for post-authorisation in Section 2.7 on RMP).

The primary efficacy endpoint specified in the study is prevention of COVID-19 starting 14 days post-dose 2 in individuals with no prior evidence of SARS-CoV-2 infections before receiving any study treatment. Secondary efficacy endpoints include prevention of severe COVID-19 in baseline seronegative subjects, prevention of COVID-19 regardless of prior SARS-CoV-2 infection, and prevention of asymptomatic infection.

The primary analysis population was the per protocol (PP) set defined as all subjects without major protocol deviations who received all planned doses of the study treatment and who had not developed COVID-19 prior to the second dose. In the protocol the acceptable window for receiving the second dose was defined as -3/+7 days around day 28. At the time of definition of major protocol deviations, which was to happen before unblinding, the acceptable visit window was widened to days 21 – 42 (-7/+14 days around the interval of 28 days). The impact of this change cannot be fully assessed at this point in time. Only around 600 study participants in the PP set were outside the initially defined window but fell in the widened window. Consequently it is considered that the widening will not negatively impact the study outcome but does not add relevant information. Additional analyses were to be conducted in the modified intent-to-treat (mITT) set including all baseline SARS-CoV-2 negative participants who received at least one dose of the study treatment and the full analysis set (FAS) including all randomised patients (i.e. regardless of serostatus) who received at least one dose of study treatment.

Conducting the primary analysis in subjects who receive the two doses as scheduled without (other) major protocol deviation (i.e. PPS) only, and furthermore counting cases for the primary analysis only *14 days after the second dose* onwards is acceptable (and was pre-specified as such), but this has evident implications for the target of estimation. Aligned with the ITT principle and the subjects being exposed to potential IP-related risks already after the first dose, analyses investigating vaccine efficacy in preventing cases occurring already after the first dose and in a broader analysis set thus have been considered in addition.

Assessment of probable COVID-19 cases was carried out following reporting by study participants of at least two systemic or one respiratory clinical sign/symptom recognised to be predictive of COVID-19 (predefined) and subsequent laboratory confirmation of infection of SARS-CoV-2 in nasal swabs or saliva samples by RT-PCR.

Nasal swabs and saliva samples were either collected at the study site or through self-collection by individuals. The RT-PCR assay is acceptably validated and additional validation studies to evaluate stability of clinical samples at various temperatures and freeze/thawing cycles to cover shipping and storage conditions were provided. Data are available to assure that reliable results are obtained by self-collection and shipping of samples.

Besides RT-PCR testing at time of randomisation, evaluation of seropositivity by employing a SARS-CoV-2 specific nucleocapsid IgG ELISA was performed to confirm any asymptomatic infection prior to vaccination. The assay was validated and all specified acceptance criteria are met. This assay is used also to assess two secondary efficacy endpoints (combined evaluation of prevention of COVID-19 as determined by RT-PCR and of asymptomatic infection as determined by seroconversion in those who were seronegative at baseline; prevention of asymptomatic infection). Data on these secondary efficacy endpoints are not available for the time being and should be submitted as soon as they become available (see list of recommendations in Annex I).

During rolling review assessment, it was found difficult (also due to the operational and time constraints) to completely comprehend the process from incident COVID-19 symptom occurrence in a study participant to final decision as to whether or not a 'case' was declared (and considered for primary efficacy analyses). This relates to roles of site investigators, sponsor, CRO and Adjudication Committee, DSMB all involved in this process, procedural rules and pre-specification, and documentation/comprehensibility of decisions made at different steps throughout. In principle, all suspected COVID-19 cases were to be adjudicated by a central, blinded Adjudication Committee (AC). This is endorsed. At the time of the provided data snapshots none of the cases that occurred prior to dose 2 and not all suspected cases 14 days after the second dose were adjudicated. This leads to some uncertainties for the primary analysis regarding the exclusion/censoring or early COVID-19 cases, and for sensitivity and (key) secondary analyses. The lack of full adjudication of suspect cases after 14 days of the second dose mainly reduces the number of observed cases. As it was stated that both the Sponsor and the AC were to be blinded in the adjudication process, it is assumed that adjudicated cases are a random subset of all suspect cases. Hence, no substantial bias is to be expected for the primary analysis based on adjudicated cases. Analyses based on all adjudicated cases are said to be provided with the final CSR. Overall, no major uncertainties remain that would alter benefit/risk conclusions. However, it cannot be entirely ruled out that some source of bias occurred during case monitoring/processing and that the efficacy estimation may be optimistic to a certain degree.

Immunogenicity endpoints were defined in the study protocol to evaluate binding and neutralising antibody responses following vaccination in a subset of study participants. These endpoints are appropriately chosen and relevant to assess any decline of antibody responses over time and to eventually bridge to other populations not included in the current clinical development. Any attempts to define a correlate of protection or surrogate marker for protection are supported. Assay validation is pending and no immunogenicity results from study P301 are yet available. These data should be provided with the final study report.

The study was planned to be observer blind and all relevant sponsor personnel and participants were to remain blinded until the end of study visit after 25 months of enrolment. With protocol amendment 6 the applicant planned to offer unblinding to all participants at once at the time of the US Emergency Use Authorisation. This is not endorsed from a scientific point of view. As outlined in EMA's considerations on COVID-19 vaccine approval (EMA/592928/2020) it is "recommended that clinical trial participants should be followed for safety and efficacy within their randomised groups for at least one year after completing vaccination" whenever feasible. More mature study data with a longer follow-up are required despite positive early (interim) analyses. Hence, the applicant should thoroughly consider pre-planning analyses in a dedicated supplementary SAP (sSAP; to be submitted to EMA as soon as available), which allows to extract the best available information from the ongoing Phase 3 study with respect to duration of protection, correlate of protection, vaccine-enhanced disease, and other long-term safety data. This sSAP should be further discussed and agreed with the EMA. The applicant is recommended to seek EMA scientific advice (see list of recommendations, Annex I).

Two interim and one final analyses were planned after 53, 106 and 151 accrued cases. In the conduct of the study, the timing and number of analyses was changed. The first interim analysis was conducted after 95 adjudicated cases. The second interim analysis was dropped. The final analysis was conducted after 196 adjudicated cases for the primary endpoint instead of 151 cases. At both analyses severe overrunning was obvious. The applicant explained that the modified timing of analyses was mainly based on safety data requirements as set out by FDA and that overrunning occurred due to the speed up of the pandemic. While these arguments are in principle understood, these reasons are not sufficient to well justify the observed changes. Potential opportunistic choices based on accruing

information cannot be fully excluded. The impact of the deviation from pre-planned primary efficacy evaluation on the assessment of vaccination benefit is considered low.

The primary endpoint was analysed using a Cox proportional hazards model accounting for stratification factors. Vaccine efficacy was estimated as 1 – HR (hazard ratio). The same methods were to be used for comparable secondary endpoints. A sensitivity analysis using a Fine and Gray model accounting for competing risks due to early COVID-19 cases before the second dose or deaths unrelated to COVID-19 was provided.

Multiplicity control for primary and key secondary endpoints was defined in the SAP. The proposed procedure does not control the type 1 error for secondary endpoints in the strong sense and substantial error inflation is possible. The conclusion on the primary endpoint is not considered to be impacted.

In conclusion, the design and conduct of the study were appropriate overall and were in line with the requirements as laid down in the Guideline on clinical evaluation of new Vaccines (EMA/CHMP/VWP/164653/2005) and as recommended via Scientific Advice. The primary and secondary efficacy objectives as defined in the phase 3 study are of clinical relevance and follow ICMRA recommendations for the evaluation of COVID-19 vaccines (ICMRA SARS-CoV-2 Vaccines Workshop; July 2020). The pivotal study is still ongoing. Participant retention is very high based on information up to the latest reported cut-off point. Close to 90% of participants had at least 4 weeks of follow-up after the second dose and around 55% had been followed for at least 2 months. Follow-up is short, but this is acceptable given the circumstances of the ongoing SARS-COV-2 pandemic.

Efficacy data and additional analyses

Vaccine efficacy according to the primary efficacy endpoint was demonstrated on an interim analysis with data cut-off date of 7 November 2020 including 27,817 individuals in the PP set, when 95 cases were accrued. The inferential analysis at this first interim analysis indicated a VE point estimate of 94.5% with an adjusted 95% CI of 81.8%, 98.3% (unadjusted 95% CI: 86.5%, 97.8%; p <0.0001). VE was confirmed in the final efficacy analyses with data cut-off date 21 November 2020 after accrual of 196 adjudicated COVID-19 cases based on the efficacy population of 28,207 subjects (overall efficacy 94.1% CI not adjusted for multiplicity 89.3, 96.8). The final efficacy evaluation is based on a median follow-up of 9 weeks. The study is ongoing and further data on long-term protection are expected with the final study report.

The disposition of study participants in the various analyses sets were well balanced across treatment groups. Few individuals withdrew from the study and only a very small number due to occurrence of an AE. Based on the provided data in the PP set, the three risk strata were well balanced between placebo and mRNA-1273 with n = 16,631 (59.8%) participants <65 years of age and not at risk, n = 4,159 (15.0%) participants < 65 years of age and at risk, and n = 7,026 (25.3%) participants ≥ 65 years of age.

VE to prevent COVID-19 of any severity was high in the per protocol population starting 14 days post-dose 2, which included subjects without prior evidence of SARS-CoV-2 infection before dose 1.

Regarding severe COVID-19, 30 cases were reported for placebo and no cases for the vaccine arm. Vaccine efficacy against severe COVID-19 was thus estimated to be 100% (95% CI 87.0%, NE). One severe COVID-19 case in the vaccine group was reported as SAE but was not adjudicated at the time of the data snapshot. Given the low numbers of severe cases, further follow up data are needed to consolidate the observed protective effect against severe COVID-19. Based on limited case narratives there were 9 hospitalisations among those cases (of which 2 ICU admitted of which one fatal). The

majority of the severe cases were adjudicated as such based on SpO2 below the defining threshold of 93% for varying duration. Whereas reassuring for efficacy across varying disease severity, the cases overall seem mostly mild, which is a limitation of the dataset. Reflecting these findings in SmPC 5.1 should account for the available information about severity of cases observed thus far.

At the second data snapshot (final analysis), VE was 94.1% (95% CI 89.3%, 96.8%). Of note, one subject in the placebo group died of COVID-19 while none died in the vaccine group. The Fine and Gray model based on the mITT set accounting for competing events confirmed the primary analysis with a VE of 94.2% (95% CI: 89.6%, 96,7%).

These results are confirmed when a less stringent definition of COVID-19 based on only one clinical symptom according to CDC was employed.

For sensitivity analysis in mITT population and counting cases from dose 1 onwards, which include all individuals without prior evidence of SARS-CoV-2 infection before the first dose was given, but regardless whether they received a full 2-dose regimen or not, again high vaccine efficacy was estimated. Cumulative incidence rates were increasing constantly after randomisation in the placebo group but remained low in the vaccine group. Although these analyses suggest that one dose might provide some protection, a very high percentage of individuals in the mITT set received the second dose and the vast majority of subjects received their second dose within the specified window of 23-36 days after the first dose. No definitive conclusion on clinical efficacy after one dose can be drawn based on the very short time window between the two doses and consequently very few cases.

Based on the FAS population, which included individuals with and without prior evidence of SARS-CoV-2 infection at randomisation, no difference in vaccine efficacy was reported compared to vaccine efficacy estimated in subjects without prior evidence of SARS-CoV-2 prior to dose 1.

In addition, subgroup analyses showed that vaccine efficacy is consistent across different risk groups, subjects with various underlying diseases and different demographic characteristics. VE decreases with the number of risk factors for severe COVID-19 from 95.1% (95% CI: 89.6, 97.7; no risk factors), 91.7% (95% CI: 73.0, 97.4; one risk factor) to 87.2% (95% CI: -2.7, 98.4; 2 or more risk factors). Given the very low number of participants with more than one risk factor, this trend cannot be confirmed. Since the risk of severe disease with hospitalisation and death is specifically high with increasing age further analyses of VE following stratification in finer age categories was presented. Given the few participants (n = 1318) above 75 and only 7 accrued cases in the placebo arm (none in the active arm) no reliable estimates in this group can be derived. VE is consistent in the over 65-year olds, although a slightly lower VE was estimated (86.4%, 95% CI: 61.4, 95.2).

No information is currently available on prevention from asymptomatic infection and these data should be provided with the clinical study report for part A of the study as soon as these data become available (see list of recommendations in Annex I).

Only a small number of HIV positive subjects were enrolled. Individuals under immunosuppressive or immune-modifying therapy or immunodeficient patients were excluded from the pivotal study. As some of these individuals depending on the level of immunosuppression might not develop an appropriate immune response following a two-dose regimen, further doses might be needed to achieve appropriate protection. This is reflected in the SmPC section 4.4 and the RMP (see section 2.7) includes studies to be conducted post-authorisation in these populations.

Co-administration with other vaccines was not investigated, hence this should be followed up post-authorisation (see section 2.7 on RMP).

No data on pregnant women and breastfeeding women is available as these were excluded from the study. Dedicated studies are planned in the post-authorisation phase as indicated in the RMP (see section 2.7).

As already mentioned in section 2.4.2, no information is available on cross-neutralisation to evaluate whether the vaccine protects against all circulating strains. No gene sequence data on SARS-CoV-2 strains detected by RT-PCR in the mRNA-1273 vaccine or the placebo group are available. These data are important to assess the capability of the vaccine to protect against currently circulating rare or non-dominant strains and newly emerging variants of SARS-CoV-2 (see list of recommendations in Annex I).

Additional efficacy data needed in the context of a conditional MA

The final clinical study report for study mRNA-1273-P301 will be submitted no later than December 2022 and is subject to a specific obligation laid down in the MA, to provide long term follow up data, including data to confirm efficacy in subgroups or data on specific endpoints that were not yet available at the time this assessment was carried out.

2.5.4. Conclusions on the clinical efficacy

Based on the data available for the COVID-19 vaccine developed by Moderna, a robust and high protective vaccine efficacy against COVID-19 (94.1% CI 89.3, 96.8) was shown in individuals aged 18 years and older without evidence of prior SARS-Cov2 infection. Vaccine efficacy was consistent across relevant subgroups including elderly subjects and subjects considered at increased risk of severe disease due to underlying chronic disease.

It is likely that the vaccine also protects against severe COVID-19, though these events were limited in the study and the definition of severe COVID-19 could have been more stringent from a clinical perspective. It is presently not known if the vaccine protects against asymptomatic infection, or its impact on viral transmission. The duration of protection is not known.

As regards a robust estimation of lower bound of the CI for VE, there remain open questions, partly due to lack of documentation/nature of RR, partly due to some residual doubts as to case ascertainment in the pivotal study. None of these issues are however expected to have impacted either the reported efficacy estimates or the overall benefit profile to a degree that would raise important concerns.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- The final clinical study report will be submitted no later than December 2022 and is subject to a specific obligation laid down in the MA. This will provide long-term data.

Regarding missing data to confirm efficacy in subpopulations that were not studied or whose data are limited please refer to sections 2.7 and 3.3.

In addition, certain data should be provided as soon as they become available and are defined in several recommendations to the applicant (see Annex I).

2.6. Clinical safety

2.6.1. Patient exposure

The safety of mRNA-1273 has been examined in a clinical development program comprising 15,420 subjects exposed to a dose of 100 µg. 35 subjects were enrolled in the phase 1 study P101, 200 were enrolled in the phase 2 study P201 and 15,185 (Safety Dataset, cut-off 25 November 2020) were enrolled in the pivotal phase 3 trial P301.

In the phase 3 trial, slightly more male (52.7%) than female (47.3%) subjects were recruited, of whom the majority was White (79.2%), followed by Black or African American (10.2%) and Asian (4.6%). 24.8% of the recruited subjects were ≥ 65 years of age. Among subjects <65 years of age, 16.7% of the total population had risk factors for severe COVID-19. In the total study population, subjects had the following risk factors: diabetes (9.5%), severe obesity (6.7%), significant cardiac disease (4.9%), chronic lung disease (4.8%), liver disease (0.6%), and HIV infection (0.6%). The majority of subjects were seronegative at baseline for SARS-CoV-19, except for 680 subjects (2.2%) with a positive baseline serostatus (FAS). The mean BMI was 29.32 in both arms.

Among the 30,351 subjects in the safety set, 82.2% had an occupational risk for infection with SARS-CoV-19 (e.g. health care workers [25.1%], educators or students [10.2%], retail or restaurant operations [6.4%]).

Overall, there were no clinically meaningful differences in the treatment groups of the safety set regarding demographics, risk factors, or SARS-CoV-2 status at baseline.

At the latest data cut-off (25 November 2020), of the 30,351 enrolled subjects (vaccine n=15,185, placebo n=15,166), 14,715 vaccine recipients and 14,613 placebo recipients have received the second vaccination. The median study follow-up after the second injection was 63.0 days.

Table 20 : Summary of Study Duration in Study 301 (Safety Set)

	Nov 25 Dataset		
	mRNA-1273 (N = 15185)	Placebo (N=15166)	Total (N=30351)
Number of participants, n (%) Received first injection Received second injection ≥ 28 days since second injection ≥ 56 days since second injection	 15185 (100) 14715 (96.9) 13386 (88.2) 9406 (61.9)	 15166 (100) 14613 (96.4) 13297 (87.7) 9299 (61.3)	 30351 (100) 29328 (96.6) 26683 (87.9) 18705 (61.6)
Study duration from randomisation (days) Median (min, max)	92.0+ (1+, 122+)	92.0+ (1+, 122+)	92.0+ (1+, 122+)
Study duration from first injection (days) Median (min, max)	92.0+ (1+, 122+)	92.0+ (1+, 122+)	92.0+ (1+, 122+)
Study duration from second injection (days)[a] Median (min, max)	63.0+ (0+, 97+)	63.0+ (0+, 97+)	63.0+ (0+, 97+)
Study duration from second injection in participants who received second injection (days) Median (min, max)	63.0+ (0+, 97+)	63.0+ (0+, 97+)	63.0+ (0+, 97+)

Abbreviations: max = maximum; min = minimum.
Notes: + indicates ongoing participants. Percentages were based on the number of participants in the Safety Set.
[a] Study duration from the second injection is zero days for participants who did not receive the second injection.
Source: Table 14.1.6.2, Table 14.1.6.2.1

2.6.2. Adverse events

Adverse events are reported up to the data cut-off of 25 November 2020.

Solicited Adverse Reactions

Solicited local and systemic ARs with an onset within 7 days after each injection (i.e., the day of dosing and 6 subsequent days) were assessed. Solicited ARs were recorded daily by the study participants using eDiaries. The local solicited ARs included pain, erythema, swelling, and lymphadenopathy and the general solicited ARs included fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting. Of note, lymphadenopathy was defined as localised axillary swelling or tenderness ipsilateral to the vaccination arm. The eDiary solicited daily participant to report ARs using a structured checklist. If an AR persisted beyond Day 7, the participant was prompted to continue to record until resolution.

Solicited Local reactions

Solicited local ARs were reported by a majority of participants in the mRNA-1273 group and were reported at a higher incidence in the mRNA-1273 group (92.4%) than in the placebo group (29.3%) after any injection. The most common solicited local AR was pain, and the incidence was similar after the first and second injection (vaccine: 83.7% post-dose 1, 88.2% post-dose 2; placebo: 17.5% post-dose 1, 17.0% post-dose 2). The other solicited local ARs were reported at a higher incidence after the second injection: erythema (vaccine: 2.8% post-dose 1, 8.6% post-dose 2; placebo: 0.4% after each dose), swelling (vaccine: 6.1% post-dose 1, 12.2% post-dose 2; placebo: 0.3% after each dose), and lymphadenopathy (vaccine: 10.2% post-dose 1, 14.2% post-dose 2; placebo: 4.8% post-dose 1, 3.9% post-dose 2).

The majority of solicited local ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, grade 3 solicited local ARs were more common after the second injection than after the first injection (7.0% versus 3.5%; placebo: 0.5% after each injection); the most common grade 3 solicited local AR after the second injection was pain (604 [4.1%] participants). No grade 4 solicited local ARs were reported, and only grade 3 pain was reported at a frequency > 2% after either injection.

The majority of the solicited local ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after injection and generally persisted for a median of 1 to 3 days. There was a higher incidence of participants who reported solicited local ARs that persisted beyond 7 days in the mRNA-1273 group than in the placebo group after the first injection (2.2% versus 0.7%, respectively) and after the second injection (2.1% versus 0.7%).

Solicited systemic reactions

Solicited systemic ARs were reported by the majority of participants in the mRNA-1273 group and were more prevalent in the mRNA-1273 group (84.1%) than in the placebo group (53.5%) after any IP injection. In the mRNA-1273 group, the incidence and severity of solicited systemic ARs appeared to increase after the second injection. The solicited systemic ARs were reported with the following incidences (*PD = post-dose*):

Fever (vaccine: 0.8% PD1, 15.5% PD2; placebo: 0.3% after each dose),

Headache (vaccine: 32.7% PD1, 58.6% PD2; placebo: 26.6% PD1, 23.4% PD2),

Fatigue (vaccine: 37.2% PD1, 65.3% PD2; placebo: 27.3% PD1, 23.4% PD2),

Myalgia (vaccine: 22.7% PD1, 58.0% PD2; placebo: 13.7% PD1, 12.4% PD2),

Arthralgia (vaccine: 16.6% PD1, 42.8% PD2, placebo: 11.8% PD1, 10.8% PD2),

Nausea/vomiting (vaccine: 8.3% PD1, 19% PD2; placebo: 7.1% PD1, 6.4% PD2), and

Chills (vaccine: 8.3% PD1, 44.2% PD2; placebo: 5.8% PD1, 5.6% PD2).

The majority of solicited systemic ARs were grade 1 to grade 2 in severity. In the mRNA-1273 group, grade 3 solicited systemic ARs were more common after the second injection than after the first injection (15.8% versus 2.9%%; placebo: ~2% after each injection). In the mRNA-1273 group, grade 3 solicited systemic ARs after the second injection occurred at the following incidences: fever 1.4%, headache 4.5%, fatigue 9.7%, myalgia 9%, arthralgia 5.2%, nausea/vomiting 0.1%, and chills 1.3%. After the first injection, grade 4 solicited systemic ARs were reported by 5 participants in the vaccine group vs. 6 participants in the placebo group. After the second injection, grade 4 events occurred in 14 vs. 3 subjects. Nearly all grade 4 events were fever >40°C, except for single reports of fatigue, arthralgia and nausea/vomiting in the mRNA-1273 group.

The majority of the solicited systemic ARs in participants who received mRNA-1273 occurred within the first 1 to 2 days after IP injection and generally persisted for a median of 1 to 2 days. The incidence of participants who reported solicited systemic ARs that persisted beyond 7 days after the first injection (vaccine: 5.8%, placebo: 5.7%) and second injection (vaccine: 5.7%, placebo: 4.9%) was comparable between the groups.

Unsolicited AEs

Unsolicited AEs observed or reported during the 28 days after each IP injection (i.e., the day of dosing and 27 subsequent days) were collected. Adverse events leading to discontinuation from dosing and/or study participation, SAEs, and MAAEs (= medically attended AEs, events leading to an unscheduled visit to a health care practitioner) are being collected through completion of the study or until withdrawal from the study.

The incidences of unsolicited TEAEs (vaccine: 23.9%; placebo: 21.6%), severe TEAEs (1.5%; 1.3%), and MAAEs (9.0%; 9.7%) during the 28 days after any injection were generally similar in participants who received mRNA-1273 and those who received placebo. The most commonly reported unsolicited AEs up to 28 Days After Any Injection (reported by at least 1% of participants in any group) were headache (vaccine: 3.1% vs. placebo: 3.0%), cough (1.1% vs. 1.0%), oropharyngeal pain (1.0% vs. 1.3%), diarrhoea (1.2% vs. 1.1%), arthralgia (1.4% vs. 1.1%), myalgia (1.3% vs 1.2%), fatigue (2.4% vs. 2.2%), and injection site pain (1.0% vs 0.4%).

The majority of unsolicited TEAEs were considered not related to the IP; treatment-related TEAEs were reported in 8.2% and 4.5% of participants in the mRNA-1273 and placebo groups, respectively. Until 28 days after any vaccination, 0.5% of subjects in the mRNA-1273 group reported severe TEAEs that were considered as treatment related (vs. 0.2% in placebo). Treatment-related MAAEs were reported in 0.9% and 0.5% of participants in the mRNA-1273 and placebo groups, respectively.

The incidence of SAEs during the 28 days after injection was low (0.6% overall), with no notable differences between treatment groups (0.6% for mRNA-1273 and 0.6% for placebo). Few participants (< 0.1% for mRNA-1273 and placebo groups) reported treatment-related SAEs (**Table 21**).

The incidence of participants who discontinued IP due to TEAEs during the 28 days after injection was low (0.4% overall), and discontinuations of IP due to TEAEs were less frequent in the mRNA-1273 group than in the placebo group (0.3% for mRNA-1273 and 0.5% for placebo).

Table 21 - Summary of Unsolicited AEs up to 28 Days After Any Vaccination in Study 301 (Safety Set)

	mRNA-1273 (N=15185) n (%)	Placebo (N=15166) n (%)
Unsolicited AEs regardless of relationship to study vaccination		
All	3632 (23.9)	3277 (21.6)
Severe	234 (1.5)	202 (1.3)
Fatal	2 (< 0.1)	3 (< 0.1)
Leading to discontinuation from study vaccine	50 (0.3)	80 (0.5)
Leading to discontinuation from participation in the study	2 (< 0.1)	2 (< 0.1)
Serious	93 (0.6)	89 (0.6)
Medically-attended AEs	1372 (9.0)	1465 (9.7)
Unsolicited AEs related to study vaccination		
All	1242 (8.2)	686 (4.5)
Severe	71 (0.5)	28 (0.2)
Fatal	0	0
Leading to discontinuation from study vaccine	18 (0.1)	15 (<0.1)
Leading to discontinuation from participation in the study	0	0
Serious	6 (<0.1)	4 (<0.1)
Medically-attended AEs	140 (0.9)	83 (0.5)

Source: mRNA-1273-P301 Table 14.3.1.7.1. (data cut-off 25 Nov 2020)

Overall, also including AEs that were reported after the 28 days after any injection (until 25 November 2020), the incidences of unsolicited AEs (vaccine: 26.7%; placebo: 25.6%), severe AEs (2.0%; 1.8%), and MAAEs (11.5%; 12.9%) increased, but the relative incidence between vaccine and placebo remained similar to the previously described incidences. Treatment-related unsolicited AEs were experienced by 8.3% in the mRNA-1273 group, and by 4.6 % in the placebo group overall.

In summary, the incidences of unsolicited AEs, severe AEs, serious AEs and medically-attended AEs (regardless of severity) were comparable between vaccine and placebo.

However, there were some imbalances for certain preferred terms (PT) or system organ classes (SOC):

Until the data cut-off of 25 November 2020, 3 events of acute peripheral facial paralysis (Bell's palsy) were reported in the mRNA-group, compared to 1 event in the placebo group.

There were more reports of muscle spasms in the vaccine group (33 events, 0.2%) than in the control group (19 events, 0.1%). The number of medically attended events (vaccine: 13 events, placebo: 9 events) and events considered as treatment-related by the Investigator (vaccine: 5 events, placebo: 4 events) were comparable.

There were also more events of paraesthesia (29 vaccine, 26 placebo, treatment-related: 11 vs. 7), hypoaesthesia (12 vaccine, 8 placebo, treatment-related: 4 vs. 0) and hyperaesthesia (6 vaccine, 0 placebo, treatment-related: 5 vs. 0) in the mRNA-1273 group. However, fewer events were reported for the PTs of pharyngeal paraesthesia (0 vaccine, 1 placebo), paraesthesia oral (2 vaccine, 4 placebo, treatment-related: 0 vs 4) and injection site paraesthesia (2 vaccine, 3 placebo, treatment-related: 1 vs. 3). The number of medically attended events was in total smaller in the vaccine group (paraesthesia 6 vs. 9, hypoaesthesia 2 vs. 3, hyperaesthesia 1 vs. 0) and only one subject in the placebo group reported serious paraesthesia.

The PT of gastroesophageal reflux disease was reported by 41 subjects (medically attended: 21 events, treatment-related: 2 events) in the vaccine group, compared to 18 subjects in the placebo group (medically attended: 9 events, treatment-related: 0 events). Overall, the incidences of events in the SOC of gastrointestinal disorders were similar (478 vs. 440 events).

There was an imbalance for the events of insomnia (vaccine: 17 events vs. placebo: 14 events), abnormal dreams (5 vs. 0 events), sleep disorder (5 vs. 0 events), and nightmare (3 vs. 1 event). However, most of the reported events had an onset on day 1 or 2 and resolved within a few days.

As described in a later section (2.6.6 Immunological events), a SMQ of hypersensitivity events revealed a slightly higher incidence of hypersensitivity events in the vaccine group versus the placebo group (1.5% vs. 1.1%, respectively), which was mainly driven by injection site rash (n=37 (0.2%) vs. n=1 (<0.1%)), injection site urticaria (n=15 (<0.1%) vs. n=0) and rash (n=45 (0.3%) vs. n= 34 (0.2%)).

Based on the latest listing of autoimmune events, there is an imbalance regarding the SOC Skin and subcutaneous tissue disorders (12 events in the vaccine group vs. 4 events in placebo, PT psoriasis 4 vs. 1). This imbalance was mainly caused by the events of alopecia (7 vs. 3) and psoriasis (4 vs. 1). See the section "autoimmune diseases" below.

Another imbalance was noted for the SOC of hepatobiliary disorders, with 15 events in the vaccine group, compared to 3 events in the placebo group. The disparity was mainly caused by the events of cholelithiasis (vaccine: 6 events, placebo 1 event) and cholecystitis (vaccine: 4 events, placebo: none). At the present time it appears likely that this imbalance is caused by chance.

An imbalance was also observed for anaemia regardless of relationship to vaccine (1 case in the placebo group versus 10 cases in the vaccine group). This imbalance was not observed for cases of anaemia considered vaccine related (no case in the placebo and 1 case in the vaccine group). It should be noted that the listings of safety laboratory results submitted for the phase 1 and phase 2 trial did not reveal cases of anaemia. Haemoglobin levels were within the normal range during all visits.

2.6.3. Serious adverse event/deaths/other significant events

Serious adverse events

Among the 30,351 subjects with a median follow-up of 63 days, the incidence of SAEs was similar in the mRNA-1273 (1.0%, 147 events) and placebo (1.0%, 153 events) groups during the overall study period until 25 November 2020.

However, there were some imbalances between the groups, with noticeably more subjects reporting SAEs in the vaccine arm for the following SOCs, as described hereafter.

More serious AEs were reported in the vaccine group for the SOC of nervous system disorders (16 subjects), compared to placebo (10 subjects). In study participants who received the vaccine, 3 SAEs of cerebrovascular accident (1 placebo), 2 SAEs of embolic stroke (none in placebo), and 1 SAE of transient ischaemic attack (none in placebo) were reported. However, none of these events were considered as related to vaccination by the Investigator as all subjects had a significant medical history or increased risk for these events.

In the SOC of vascular disorders there were 2 SAEs of deep vein thrombosis in the mRNA-1273 group (none in the placebo group). The Investigator did not consider these events as treatment related.

SOC Gastrointestinal disorders: vaccine 23 subjects vs. placebo 10 subjects; (e.g., abdominal pain upper [3 vs. 0], nausea [3 vs. 1], colitis [2 vs. 1], diarrhoea [2 vs. 1], hiatus hernia [2 vs. 1] and

pancreatitis [1 vs. 0]). One subject experienced serious (Grade 4) events of nausea and intractable vomiting following the second dose of the vaccine that required hospitalisation Day 3 following dose 2. The event resolved after 7 days. The study participant had a medical history of headaches with nausea that led to hospitalisation in the past.

The PT of facial swelling was reported in 2 subjects in the mRNA-1273 group, compared to 1 event in the placebo group. Of note, both subjects in the vaccine group received dermal filler injection prior to vaccination (one subject received a Botox/modified hyaluronic acid filler combination 11 days prior dose 2, the other subject bilateral cheek injections of hyaluronic acid 5 months prior to enrolment). Both events resolved within a week.

The event of rheumatoid arthritis was reported once during the clinical trials. The event occurred in a subject with a medical history of joint pain. The participant reported muscle and joint aches/pain in the e-diary on the same day as dose 1. Approximately 10 days post-Dose 1, the participant experienced recurrent muscle joint aches/pain. The quality of the pain was different than the joint aches/pain previously reported, with the left knee and right shoulder bothering him the most. Approximately 29 days post-Dose 1, the participant saw a rheumatologist who noted a high level of CCP antibody and rheumatoid factor and diagnoses included rheumatoid arthritis and lateral epicondylitis. An SMQ for autoimmune related adverse events revealed 32 events in the vaccine group vs. 28 events in the placebo group. At the time being, the single event of RA does not raise a concern. Autoimmune disorders are listed as AESI in the RMP.

Treatment-related SAE

Until the data cut-off, there were 7 subjects with treatment-related SAEs in the vaccine group, compared to 5 subjects in the placebo group. The treatment-related SAEs in the mRNA group were B-cell small lymphocytic lymphoma, autonomic system imbalance, dyspnoea, nausea and vomiting, rheumatoid arthritis, oedema peripheral, and two events of facial swelling. In the placebo group, the treatment related SAEs were polymyalgia rheumatica, hypomagnesaemia, paraesthesia, acute myocardial infarction, atrial fibrillation, organising pneumonia, pulmonary embolism, respiratory failure, acute kidney injury, feeling hot, immunisation anxiety related reaction, procedural haemorrhage and facial swelling. The events considered being treatment related are individual cases in the placebo and the vaccine group. The clinical information does not allow for a robust conclusion on relatedness or possible causality.

Deaths

Based on the pharmacovigilance database which includes data from study start through 3 December 2020, there have been 13 deaths during the study. Six participants who died received mRNA 1273 and 7 received placebo. The most common preferred term was myocardial infarction, reported by 3 participants, 2 who received placebo and 1 who received mRNA-1273. The participant who received mRNA-1273 had a history of hypercholesterolemia and died 45 days from administration of the study product. Another death, due to cardiopulmonary arrest, occurred 21 days after mRNA-1273 dose 1 in a patient with a history of cerebrovascular accident. The other deaths which were reported in participants who received mRNA-1273 included suicide, head trauma due to fall, multisystem organ failure, and death due to unknown causes. None of the deaths were assessed by Investigator or Sponsor as related to study product. According to the provided narratives, all subjects of the mRNA-1273 group who died during the trial had a relevant medical history to explain the event.

2.6.4. Laboratory findings

In the **non-clinical** repeat-dose toxicity studies, haematology changes included increases in white blood cells, neutrophils, and eosinophils and decreased lymphocytes; coagulation changes included increases in fibrinogen and activated partial thromboplastin time; and clinical chemistry changes included decreases in albumin, increases in globulin, and a corresponding decrease in albumin/globulin ratio. Clinical pathology changes generally reversed or were reversing by the end of the 2-week recovery period.

Clinical safety laboratory evaluations (WBCs, Hgb, PLTs, ALT, AST, ALP, T. Bili, Cr, and Lipase) collected immediately prior to the first vaccination served as the baseline (Day 1), and were repeated on Days 8, 29 and 36 in the phase 1 clinical trial. Total blood volume drawn for laboratory and immunogenicity assessments until D29 was 300mL and until D57 was a cumulative 476mL. It should be noted that haemoglobin values in the listings of safety laboratory results in the phase 1 and the phase 2 trial were within the normal range through all study visits and no significant decrease was observed.

With regard to clinical chemistry, in people 18-55 YOA (n=4) and 56-70 YOA (n=1) an increase in liver enzymes was observed in a few subjects, while in the latter (n=1) and >71 YOA group (n=3) few increase of lipase were recorded.

No specific pattern emerges with regards to the clinical haematology and chemistry evaluation.

In the phase 2 clinical trial, blood draws were scheduled for D0, D29 and D57. Repeat draws were done 4 weeks post-dose for each vaccination in Cohort 2 (≥ 55 years of age) only, at which point in time potentially test-related changes were most likely already resolved.

No safety laboratory tests are foreseen for the pivotal phase 3 study as no specific concerns arose from earlier clinical trials, which can be considered acceptable.

2.6.5. Safety in special populations

Pregnant and lactating women

In all three clinical studies, pregnant or breastfeeding women were excluded from participation and consequently no data are available with regards to the safety profile in this subpopulation. Six pregnancies were reported in subjects who received the study vaccine, and all six pregnancies are progressing without complications (Data cut-off: 3 December 2020).

Elderly subjects (≥65)

A substantial proportion (n= 7520; ~25%) of the population in pivotal trial P301 was aged 65 or older. Approximately 12% (n= 3722) of the total population was 65-69 YOA, about 8% (n=2398) was aged 70-74, about 3% (n=975) was in the age range between 75 and 79 years, and 1.4% or 425 subjects was 80 YOA or older.

Local solicited ARs were more commonly reported by younger adults (≥ 18 to < 65 years; 87.4% and 90.5% after the first and second injection of mRNA-1273, respectively) than older adults (≥ 65 years; 74.6% and 83.9% after the first and second injection of mRNA-1273, respectively). Local solicited AES were reported at grade 3 or 4 after the first injection by 452 (4.0%) younger vs. 77 (2.0%) older subjects, and by 802 (7.3) younger vs. 218 (5.9) older subjects after the second injection. The median duration of local adverse events was 2 days after the first injection and 3 days after the second injection in both age groups.

Systemic solicited ARs were also more commonly reported by younger adults (≥ 18 to < 65 years; 57.0% and 81.9% after the first and second injection of mRNA-1273, respectively) than older adults (≥ 65 years; 48.3% and 71.9% after first and second injection of mRNA-1273, respectively). Systemic solicited AEs were reported at grade 3 or 4 after the first injection by 368 (3.2%) younger subjects vs. 84 (2.2%) older subjects after the first vaccination, and by 1940 (17.7%) younger vs. 399 (10.8%) older subjects. For systemic adverse events, the median duration after both the first and second injection was 2 days in both age cohorts.

With regards to unsolicited AES, the rates for all TEAE are comparable for older and younger adults, and between placebo and vaccine subjects. For treatment related TEAE, in both older and younger adults an incidence of ~4% was observed in placebo recipients vs. an incidence of ~8% in vaccine recipients.

In both younger and older adults, the incidence of hypersensitivity events is driven by injection site rash, injection site urticaria and rash.

In conclusion, the observed safety profile in older adults shows fewer instances of solicited AEs and a comparable incidence of unsolicited AEs and does not give rise to concerns.

Baseline SARS-CoV-2 Status

342 baseline seropositive subjects received the first and 230 of these subjects received the second vaccination with mRNA-1273 in the solicited safety set. The incidence and severity of local and systemic reactions were comparable to those observed in the baseline negative subjects and no concerns arise with regards to reactogenicity in baseline seropositive subjects.

The incidence of unsolicited TEAE is similar for seropositive subjects in the vaccine and placebo arm and comparable to that of seronegative subjects. No specific concerns arise in the observed safety profile so far.

Immunocompromised Subjects

179 or 0.6% of the total population in trial P301 had a stable infection with HIV at baseline and were randomised into the two arms of the pivotal trial P301.

The incidence of local and systemic solicited adverse reactions is comparable to that of the complete dataset.

The incidence of unsolicited TEAE is similar for HIV+ subjects in the vaccine and placebo arm and comparable to that in the total safety population.

No specific concerns arise in the observed safety profile so far. However, the number of such subjects is very small, therefore no definitive conclusions can be drawn.

Subjects suffering from an Autoimmune Disease at Baseline

2455 subjects or 8% of the total population in trial P301 suffered from an autoimmune disease at baseline and were randomised into the two arms of the pivotal trial P301.

The incidence of local and systemic solicited adverse reactions is comparable to that of the complete dataset.

The incidence of unsolicited TEAE is similar for subjects in the vaccine and placebo arm and comparable to that in the total safety population.

No specific concerns arise in the observed safety profile so far.

2.6.6. Immunological events

The formation of antibodies against the SARS-CoV-2 S protein is one of the objectives of vaccination with mRNA-1273, and available data on immunogenicity are discussed in section 2.4.2 of this report.

Hypersensitivity Events

An SMQ of hypersensitivity revealed a slightly higher incidence of all hypersensitivity events in the vaccine group versus the placebo group (1.5% vs. 1.1%, respectively), which was driven mainly by injection site rash (n=37 (0.2%) vs. n=1 (<0.1%)), injection site urticaria (n=15 (<0.1%) vs. n=0) and rash (n=45 (0.3%) vs. n= 34 (0.2%)).

An SMQ of angioedema revealed a balanced incidence of 0.3% in each study arm.

Autoimmune diseases

The frequency of autoimmune related adverse events is comparable, for both arms of trial P301, with 28 (0.2%) of subjects in the placebo arm and 32 (0.2%) of subjects in the vaccine arm reporting such events.

A further numerical imbalance is observed for the SOC skin and subcutaneous tissue disorders, which is mainly driven by hair loss. Based on current knowledge, this is most likely due to chance.

2.6.7. Safety related to drug-drug interactions and other interactions

Study P301 was not intended to measure drug interactions or the impact of other vaccines being administered in a close temporal relationship to mRNA-1273, based on exclusion criterion 'Has received or plans to receive a non-study vaccine within 28 days prior to or after any dose of IP (except for seasonal influenza vaccine which is not permitted within 14 days before or after any dose of IP)'.

2.6.8. Discontinuation due to adverse events

In the P101 and P201 studies, no subjects terminated study participation due to an AE, while 3 subject in phase 2 as well as 3 subjects in phase 1 did not receive the second vaccination due to an AE.

Study discontinuation due to an AE or SAE were rare in both arms in the pivotal trial P301, with rates below 0.1% and comparable for both arms. Numerically, slightly more subjects (n=7) discontinued due to an AE or SAE in the vaccine arm compared to the placebo arm (n=3).

With regards to AEs leading to discontinuation of the vaccine, similar small proportions of subjects in the vaccine and placebo arms experienced such an adverse event (0.2% in both arm). With regards to SAEs leading to discontinuation of the vaccine, again similar proportions of subjects in the vaccine and placebo arms (<0.1%) were reported, with a numerically more subjects in the placebo arm (n=15) compared to the vaccine arm (n=9).

Overall, no signals or specific concerns emerge from either study or IP discontinuation rates.

2.6.9. Post-marketing experience

COVID-19 Vaccine Moderna is not yet authorised in any country. An Emergency Use Authorisation was granted in the US by the FDA on 18 December 2020.

2.6.10. Discussion on clinical safety

Size of the Safety Database

The safety of mRNA-1273 has been examined in a clinical development program comprising 15,420 subjects exposed to a dose of 100 µg. 35 subjects were enrolled in the phase 1 study P101, 200 were enrolled in the phase 2 study P201 and 15,179 (Safety Dataset, Cut-off 25 November 2020) were enrolled in the pivotal phase 3 trial P301.

In the phase 3 trial, slightly more male (52.7%) than female (47.3%) subjects were recruited, of whom the majority was White (79.2%), followed by Black or African American (10.2%) and Asian (4.6%). 24.8% of the recruited subjects were ≥ 65 years of age. Among subjects <65 years of age, 16.7% of the total population had risk factors for severe COVID-19. In the total study population, subjects had the following risk factors: diabetes (9.5%), severe obesity (6.7%), significant cardiac disease (4.9%), chronic lung disease (4.8%), liver disease (0.6%), and HIV infection (0.6%). The majority of subjects were seronegative at baseline for SARS-CoV-19, except for 680 subjects (2.2%) with a positive baseline serostatus (FAS).

Duration of follow-up

At the 25 November 2020 data cut, 9406 (61.9%) subjects in the mRNA-1273 group of the pivotal trial were followed for ≥56 days since the second injection. The median study duration from the second injection was 63.0 days.

Participants in the clinical trials will be followed until 24 months after the second dose (P301) or 12 months after the second dose (P201, P101). Long-term safety is considered as missing information in the RMP so the final clinical study reports are required, and a PASS will be conducted post-authorisation.

Solicited Adverse Events

Solicited Local Adverse Reactions

The adverse reactions of injection site pain, erythema, injection site swelling (hardness) and lymphadenopathy are typical local reactions that may occur after vaccinations. These adverse reactions were more often reported in the mRNA-1273 group (92.4%) compared to injection of a saline solution (29.3%).

The reactogenicity in the vaccine group was generally higher after the second injection for all reported local reactions. The most common solicited local AR was pain (vaccine: 83.7% post-dose 1, 88.2% post-dose 2; placebo: 17.5% post-dose 1, 17.0% post-dose 2). The other solicited local ARs were: erythema (vaccine: 2.8% post-dose 1, 8.6% post-dose 2; placebo: 0.4% after each dose), swelling (vaccine: 6.1% post-dose 1, 12.2% post-dose 2; placebo: 0.3% after each dose), and lymphadenopathy (vaccine: 10.2% post-dose 1, 14.2% post-dose 2; placebo: 4.8% post-dose 1, 3.9% post-dose 2).

The majority of solicited local ARs were grade 1 to grade 2 in severity. Grade 3 events were reported in 3.5% of the subjects after the first injection, and 7.0% after the second injection. The mean duration of solicited local adverse reactions after any injection was 3.4 days (SD 3.08) in the mRNA-1273 group compared to 2.1 days (SD 3.67) in the placebo group. After any injection, the number of subjects reporting solicited local adverse events that persisted beyond 7 days was 579 (3.8%) in the mRNA-1273 group vs. 204 events (1.3%) in the placebo group. These numbers were mainly driven by subjects reporting Lymphadenopathy (301 subjects (2.0%) in the mRNA-1273 group, 95 subjects

(0.6%) in the Placebo group) and pain (227 subjects (1.5%) mRNA-1273 group, 103 subjects (0.7%) in the placebo group).

Of note, the event of Lymphadenopathy was defined as local axillary swelling or tenderness ipsilateral to the vaccination arm. The mean duration of these axillary swellings after any injection was similar between the mRNA-1273 (mean 2.4 (SD 3.21), median 1.0) and the placebo group (mean 2.3 days (SD 4.23), median 1.0). The incidence of Grade 3 Lymphadenopathy after the second injection was 0.5% (67 subjects) in the vaccine group compared to 0.1% (19 subjects) in the control group. The median duration of severe (grade 3) axillary swelling after the second dose was 1.0 days (range 1, 15) and 1.0 days (range 1, 6), as reported by participants who received mRNA-1273 or placebo, respectively.

Solicited Systemic Adverse Reactions

The incidence of solicited systemic adverse reactions was generally higher in the mRNA-1273 group and the difference between vaccine and control group was especially increased after the second injection (incidence mRNA-1273: 79.4% vs. Placebo: 36.5%).

While fever was reported in only 115 (0.8%) subjects after receiving the first dose of mRNA-1273 (Placebo: 44 subjects, 0.3%), this number increased to 2278 (15.5%) subjects (Placebo: 43 subjects, 0.3%) after the second dose. The incidence of grade 3 (39°C – 40°C) or grade 4 (> 40°C) events combined after dose 2 of the vaccine was 1.4% (215 subjects), compared to <0.1% (5 subjects) in the placebo group.

The incidence of nausea/vomiting after dose 1 was relatively similar between mRNA-1273 (8.3%) and placebo (7.1%). However, after dose 2 the incidence was nearly 3-fold higher in the vaccine group (19.0%) vs. the placebo group (6.4%).

After the first injection, 8.3% of the subjects in the mRNA-1273 group reported chills, compared to 5.8% in the placebo group. The prevalence of chills after the second injection did strongly increase in the mRNA-1273 group (44.2%), while less events were reported in the placebo group (5.6%).

The incidence of the other solicited systemic adverse reactions after the second mRNA-1273 injection was also high, with arthralgia reported in 42.8%, myalgia in 58.0%, headache in 58.6%, and fatigue in 65.3% of the subjects.

Severe solicited systemic events (Grade 3) occurred in 2325 subjects (15.8%) after the second vaccination with mRNA-1273. This number was mainly driven by the events of fatigue, myalgia, arthralgia and headache.

The majority of solicited systemic events after the second dose occurred within the first two days. The mean duration of solicited systemic events after any injection was 3.5 days (SD 4.98) in the mRNA-group, compared to 3.6 days (SD 5.55) in the placebo group. The median duration was either 1.0 or 2.0 days for all events, regardless of treatment group. The incidence of solicited systemic events persisting beyond 7 days was 9.9% (1498 subjects) for mRNA-1273 vs. 8.9% (1348 subjects) for placebo.

In summary, there was a pronounced reactogenicity for both local and systemic adverse reactions, particularly after the second vaccination with mRNA-1273. However, most of the events were grade 1 or 2 in severity and resolved within a few days.

Unsolicited Adverse Events

The prevalence of all unsolicited AEs up to 28 Days after any vaccination was comparable between the treatment groups (mRNA-1273: 3632 events = 23.9%; Placebo: 3277 events = 21.6%). Regarding

treatment-related unsolicited AEs, there is a difference between the groups (mRNA-1273: 1242 events = 8.2%; Placebo: 686 events = 4.5%). The applicant states that the difference appears to result from solicited ARs that were assessed as severe or required medical attention. However, these events can only explain part of the relative and absolute difference between unsolicited treatment-related events.

The incidences of severe, serious and medically-attended unsolicited AEs up to 28 days after any vaccination (regardless of severity) were similar between vaccine and placebo.

However, there were some imbalances for certain preferred terms (PT) or system organ classes (SOC):

Three events of acute peripheral facial paralysis (Bell's palsy) were reported in the mRNA-group, compared to 1 event in the placebo group. While the incidence is relatively low (0.02%), a possible causal relationship to vaccination cannot be excluded, due to a close temporal connection of two events after dose 2 and the fact that this event was reported at a similar rate during the clinical trials of another mRNA vaccine against COVID-19. Therefore, the event of acute peripheral facial paralysis/Bell's palsy is included in section 4.8 of the SmPC with a frequency of "rare" and will be followed up as an AESI in the ongoing phase 3 trial.

There were more reports of muscle spasms in the vaccine group (33 events, 0.2%) than in the control group (19 events, 0.1%). The number of medically-attended events (vaccine: 13 events, placebo: 9 events) and events considered as treatment-related by the Investigator (vaccine: 5 events, placebo: 4 events) were comparable. Therefore, no concern is raised.

There were also more events of paraesthesia (29 vaccine, 26 placebo, treatment-related: 11 vs. 7), hypoaesthesia (12 vaccine, 8 placebo, treatment-related: 4 vs. 0) and hyperaesthesia (6 vaccine, 0 placebo, treatment-related: 5 vs. 0) in the mRNA-1273 group. However, fewer events were reported for the PTs of pharyngeal paraesthesia (0 vaccine, 1 placebo), paraesthesia oral (2 vaccine, 4 placebo, treatment-related: 0 vs 4) and injection site paraesthesia (2 vaccine, 3 placebo, treatment-related: 1 vs. 3). The number of medically attended events was in total smaller in the vaccine group (paraesthesia 6 vs 9, hypoaesthesia 2 vs. 3, hyperaesthesia 1 vs. 0) and only one subject in the placebo group reported serious paraesthesia. While the overall imbalance for these adverse events is noted, the totality of data does not suggest a safety signal.

The PT of gastroesophageal reflux disease was reported by 41 subjects (medically attended: 21 events, treatment-related: 2 events) in the vaccine group, compared to 18 subjects in the placebo group (medically attended: 9 events, treatment-related: 0 events). Overall, the incidences of events in the SOC of gastrointestinal disorders were similar (478 vs. 440 events) and currently it seems biologically not plausible that the vaccine would cause reflux. Routine post-marketing pharmacovigilance surveillance is considered sufficient.

There was an imbalance for the events of insomnia (vaccine: 17 events vs placebo: 14 events), abnormal dreams (5 vs. 0 events), sleep disorder (5 vs. 0 events), and nightmare (3 vs. 1 event). However, most of the reported events had an onset on day 1 or 2 and resolved within a few days. It is considered likely that these events are secondary effects of solicited reactions like fever, myalgia or chills.

There was an imbalance for some events of the SOC of Nervous system disorders: cerebrovascular accident (4x vaccine vs. 1x placebo), embolic stroke (2x vaccine, 0x placebo) and transient ischaemic attack (2x vaccine vs. 1x placebo). Several of these events were considered as serious (3x cerebrovascular accident, 1x transient ischaemic attack, and 2x embolic stroke). For further details please see the paragraph on SAEs below.

Another imbalance was noted for the SOC of hepatobiliary disorders, with 15 events in the vaccine group, compared to 3 events in the placebo group. The disparity was mainly caused by the events of cholelithiasis (vaccine: 6 events, placebo 1 event) and cholecystitis (vaccine: 4 events, placebo: none). At the present time it appears likely that this imbalance is caused by chance.

Serious Adverse Events and Deaths

Serious Adverse Events

The incidence as well as the number of reported serious TEAE were low and similar between both groups. However, there were some imbalances for certain preferred terms (PT) or system organ classes (SOC) among the number of subjects reporting serious unsolicited adverse events.

More serious AEs were reported in the vaccine group for the SOC of nervous system disorders (16 events), compared to placebo (10 events). Of the study participants that received the vaccine, there were 3 SAEs of cerebrovascular accident (1x placebo), 2 SAEs of embolic stroke (none in placebo), and 1 SAE of transient ischaemic attack (none in placebo). Of note, there were 2 reports of deep vein thrombosis in the mRNA-1273 group (none in the placebo group). However, none of these events were considered as related by the Investigator. The applicant provided detailed background information for the events of stroke and transient ischaemic attack from which is evident that all subjects had a significant medical history or increased risk for these events. Though no concerns were raised from the submitted clinical information, the current list of adverse events of special interest (AESI) in the RMP includes the events of stroke and coagulation disorders (including deep vein thrombosis and cerebrovascular accident) because of the numerical imbalance, and will provide post-marketing surveillance of these diseases. This approach is endorsed by the CHMP.

The PT of facial swelling was reported in 2 subjects in the mRNA-1273 group, compared to 1 event in the placebo group. Of note, both events in the vaccine group were considered as serious and both subjects received dermal filler injection prior to vaccination. Both events resolved within a week. These events are reflected in section 4.8 of the SmPC due a reasonable possibility of causal relationship.

At the time of the latest data cut-off (25 November 2020), there were single events of anaphylaxis in each treatment group, but without a temporal connection to injection. There have been no other cases of severe hypersensitivity or anaphylactic reactions reported immediately after vaccination in the trial to date. However, there was one post-marketing report of anaphylaxis during vaccination campaigns in an individual with a severe shellfish allergy. The applicant provided information about two further cases of possible hypersensitivity. These cases, based on rather limited clinical information, currently do not appear to meet Brighton Collaboration Anaphylaxis Case Definition criteria. The two cases have entered case processing and efforts will be made to contact the reporter to obtain additional information. Anaphylaxis must be included as important identified risk in the RMP, because of the confirmed case mentioned above. The event was included in sections 4.4 and 4.8 of the SmPC (frequency not known).

Treatment-related SAE

Until the data cut-off, there were 7 subjects with treatment-related SAEs in the vaccine group, compared to 5 subjects in the placebo group. The treatment-related SAEs in the mRNA group were B-cell small lymphocytic lymphoma, autonomic system imbalance, dyspnoea, nausea, vomiting, rheumatoid arthritis, oedema peripheral, and two events of facial swelling. In the placebo group, the treatment related SAEs were polymyalgia rheumatica, hypomagnesaemia, paraesthesia, acute myocardial infarction, atrial fibrillation, organising pneumonia, pulmonary embolism, respiratory failure, acute kidney injury, feeling hot, immunisation anxiety related reaction, procedural haemorrhage and facial swelling. It should be noted that the events considered as being treatment

related are individual cases in the placebo and the vaccine group. The clinical information does not allow for a conclusion on relatedness or possible causality.

Deaths

There were 13 patients who died during the Phase 3 trial, with 6 fatalities in the mRNA-1273 group, compared to 7 in the placebo group. None of the above reported deaths were considered related to vaccination. According to the provided narratives, all subjects of the mRNA-1273 group who died during the trial had a relevant medical history to explain the event.

Safety in special populations

Pregnant and lactating women

No conclusive data are available for use of the mRNA-1273 vaccine during pregnancy. This is a missing information in the RMP and was reflected in the SmPC section 4.6. Twelve pregnancies have been reported in study P301, of which 6 in subjects who received the study vaccine and 6 in the placebo. As of 11 November 2020, all 6 pregnancies in the vaccine group were ongoing with no reported complications. In the placebo group, one participant was lost to follow up and the pregnancy outcome is not known. For the 2 pregnancies with known outcome in the placebo group, the following was reported:

- One participant experienced a spontaneous abortion at approximately 7 gestation weeks;
- One participant had an elective abortion at approximately 6 gestation weeks.

Elderly subjects (≥65)

A substantial proportion (n= 7520; ~25%) of the population in pivotal trial P301 was aged 65 or older: Approximately 12% (n= 3722) of the total population were 65-69 years old, about 8% (n=2398) were aged 70-74, about 3% (n=975) were in the age range between 75 and 79 and 1.4% or 425 subjects were 80 or older.

Trial participants aged 65 or older experienced local and systemic solicited adverse events at a lower frequency than their younger counterparts. Similarly, a lower proportion of older subjects experienced solicited AEs of grade 3 or 4 than the adults below 65. The median duration of local adverse events was 2 days after the first injection and 3 days after the second injection in both age groups. For systemic adverse events, the median duration after both the first and second injection was 2 days in both age cohorts.

With regards to unsolicited AES, the rates for all TEAE are comparable for older and younger adults, and between placebo and vaccine subjects. For treatment related TEAE, in both older and younger adults an incidence of ~4% was observed in placebo recipients vs. an incidence of ~8% in vaccine recipients.

In both younger and older adults, the incidence of hypersensitivity events is driven by injection site rash, injection site urticaria and rash.

In conclusion, the observed safety profile in older adults shows fewer instances of solicited AEs and a comparable incidence of unsolicited AEs and does not give rise to concerns.

Baseline SARS-CoV-2 Status

680 participants were seropositive at baseline and were randomised into the two trial arms. 342 baseline seropositive subjects received the first and 230 of these subjects received the second vaccination in the solicited safety set. The incidence and severity of local and systemic reactions were

comparable to those observed in the baseline negative subjects and no concerns arise with regards to reactogenicity in baseline seropositive subjects.

The incidence of unsolicited TEAE is similar for seropositive subjects in the vaccine and placebo arm and comparable to that of seronegative subjects. No specific concerns arise in the observed safety profile so far.

Immunocompromised Subjects

179 or 0.6% of the total population in trial P301 had a stable infection with HIV at baseline and were randomised into the two arms of the pivotal trial P301. The incidence of local and systemic solicited adverse reactions is comparable to the total safety population, and the frequency of unsolicited TEAE is similar for HIV+ subjects in the vaccine and placebo arm and comparable to that in the total safety population. No specific concerns arise in the observed safety profile so far. However, the number of such subjects is very small, therefore no definitive conclusions can be drawn.

Subjects Suffering from an Autoimmune Disease at Baseline

2455 subjects or 8% of the total population in trial P301 suffered from an autoimmune disease at baseline and were randomised into the two arms of the pivotal trial P301. The incidence of local and systemic solicited adverse reactions in these subjects is comparable to that of the total safety population. The incidence of unsolicited TEAE is similar for subjects in the vaccine and placebo arm and comparable to that in the total safety population. No specific concerns arise in the observed safety profile at this point in time.

Immunological Events

Subjects with a known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients were excluded from the pivotal trial, while subjects with a history of allergy or anaphylaxis against other substances were not excluded from participation.

A slightly higher incidence of all hypersensitivity events was reported in the vaccine group versus the placebo group (1.5% vs. 1.1%, respectively), which was driven mainly by injection site rash (n=37 (0.2%) vs. n=1 (<0.1%)), injection site urticaria (n=15 (<0.1%) vs. n=0) and rash (n=45 (0.3%) vs. n= 34 (0.2%)). These events were added to section 4.8 of the SmPC, because a causal relationship with vaccination can be considered as very likely.

The frequency of autoimmune related adverse events is comparable, for both arms of trial P301, with 28 (0.2%) of subjects in the placebo arm and 32 (0.2%) of subjects in the vaccine arm reporting such events.

A further numerical imbalance is observed for the SOC skin and subcutaneous tissue disorders, which is mainly driven by hair loss. It is concluded that, at the present level of information, this is most likely due to chance.

Concomitant Administration of Other Vaccines

No specific interaction studies with other vaccines have been performed and due to the exclusion criteria in the mRNA-1273 clinical program no experience exists with vaccines within 28 days prior to the first dose or any dose of mRNA-1273 except for seasonal influenza vaccine <14 days. A non-interventional study is planned in the RMP which will inform on the concomitant administration with non COVID vaccines e.g. seasonal flu.

Vaccine-Enhanced Disease (VAED)

The potential risk of VAED was assessed in non-clinical animal models in mice and non-human primates and raised no concerns based on a Th1 skewed type of immune response (see section 2.3).

In the pivotal trial, up to the data cut-off, 30 cases of severe COVID-19 were reported in the placebo group, while 0 case was reported in the vaccine group, providing no signal for a possible disease enhancement after vaccination with mRNA-1273.

Generally, it cannot be foreseen whether potential future mutations of the SARS-CoV-2 virus may lead to a reduced susceptibility to the neutralising antibodies induced by vaccination with mRNA-1273. Therefore, even though the currently available data (non-clinical, clinical, neutralising capacity of antibodies) do not raise a concern at the time being, the possibility of enhanced disease cannot be excluded with certainty. The current version of the RMP lists vaccine-associated enhanced respiratory disease as a safety concern and an important potential risk. The applicant will report any COVID 19 cases requiring hospitalisation and provide monthly safety updates including numbers of and information about relevant cases.

Additional safety data needed in the context of a conditional MA

The final clinical study report for study mRNA-1273-P301 will be submitted no later than December 2022 and is subject to a specific obligation laid down in the MA, in order to allow a comprehensive safety assessment on long-term data and more data in specific subpopulations, e.g. elderly.

2.6.11. Conclusions on the clinical safety

The safety evaluation of mRNA-1273 is based mainly on 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.

There was pronounced reactogenicity observed for both local and systemic adverse reactions, particularly after the second vaccination with mRNA-1273. However, most of the events were grade 1 or 2 in severity and resolved within a few days (median 1-3 days).

The incidences of severe, serious and medically-attended unsolicited AEs were similar between vaccine and placebo recipients. However, there were some imbalances for events such as facial swelling, acute peripheral facial paralysis, or certain hypersensitivity events (injection site urticaria, rash).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics appropriately.

In conclusion, the observed safety profile is considered favourable. Longer term safety data is awaited from the ongoing clinical trials.

There are very limited data on the use of the vaccine in immunocompromised individuals and on use in pregnancy and breastfeeding. No data was generated with mRNA-1273 when administered concomitantly with other vaccines.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- The final clinical study report will be submitted no later than December 2022 and is subject to a specific obligation laid down in the MA. This will provide long-term data.

Regarding missing data to confirm safety in subpopulations that were not studied or whose data are limited please refer to section 2.7.

2.7. Risk Management Plan

Safety specification

Summary of safety concerns

The applicant has submitted an RMP including the following summary of safety concerns:

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

Risks considered important for inclusion of the summary of safety concerns

The review of available safety data, including post-marketing data emerging from use in the US, the experience with biological products and other vaccines leads to the conclusion that anaphylaxis is an important identified risk for COVID-19 Vaccine Moderna. This safety concern will be followed up via routine pharmacovigilance activities and in the planned and ongoing safety studies and reported in the monthly summary safety reports and PSURs.

Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine-associated enhanced disease including vaccine-associated enhanced respiratory disease) should be taken into account. The applicant has included VAED/VAERD as an important potential risk and will further investigate it in the ongoing pivotal study and post-authorisation safety studies.

Missing information

Since pregnant and breast-feeding women were excluded from the study, no information is available for those populations. It is agreed to include use in pregnancy and while breast-feeding as missing information in the RMP and collect information via the EU safety study and the Pregnancy Outcome Study.

At the data cut-off of 21 December 2020, 9 weeks safety data are available (median study follow-up after the second injection). Thus, long-term safety is included as missing information and will be characterised as part of the continuation of the pivotal clinical trial and the phase 1 trial and the PASS.

Interaction with other vaccines has not been evaluated in clinical trials and may be of interest to prescribers. As elderly individuals will be one target group for vaccination, and they often may need vaccination with other vaccines such as influenza vaccines, further data is requested. The applicant commits to study concomitant use with other vaccines as part of the EU PASS study and the effectiveness study.

in frail subjects with unstable health conditions and co-morbidities is limited, and it is desirable to gather further data in these groups. Therefore, use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) has been included as missing information in the RMP. Furthermore, information is limited on the use in subjects with autoimmune or inflammatory disorders, as well as in immunocompromised subjects. Therefore, these groups are also included as missing information. Such missing information will be collected in the post-authorisation safety and effectiveness studies included in the pharmacovigilance plan.

Risks not considered important for inclusion in the summary of safety concerns

The reactogenicity is in line with what can be expected from a vaccine. Additionally, no adverse reactions were reported in clinical trials due to aspects related to the pharmaceutical formulation. The mRNA degradation products are not expected to represent functionally active mRNA molecules and they are naturally metabolised and are considered pharmacologically inactive. It is therefore considered acceptable to not include those events in the list of safety specifications.

Pharmacovigilance plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond the receipt and review and submission of ADRs include:

- **Signal detection** activities for the lifecycle of vaccines consist of individual AE assessment at case receipt, regular aggregate review of cases for trends and statistically disproportionately reported product-adverse event pairs. The MAH will perform ongoing monitoring of individual cases of Suspected Unexpected Serious Adverse Reaction, safety concerns, and Adverse Events of Special Interest and weekly aggregated review of AE cases for trend analyses. This will be complemented by review of disproportionate reporting of preferred terms during a time interval as compared to all data prior to the period. The MAH will perform biweekly review of

  reports in the EudraVigilance data analysis system using available reports and review of data from US Vaccine Adverse Event Reporting System together with the generation of disproportionality scores using Empirical Bayesian Geometrical Mean and its 90% confidence intervals.

- Routine signal detection activities for COVID-19 Vaccine Moderna will include routine and specific review of AEs **consistent with the AESI list** provided in the RMP.

- In addition, **observed versus expected analyses** will be conducted as appropriate as part of pharmacovigilance activities.

- In addition, published **literature** will be reviewed weekly for individual case reports and broader signal detection purposes.

- Ongoing review of **data for the product and similar products published on the Safety Web Portals of selected major regulatory agencies** to detect and further investigate potential signals being raised in other areas outside the EU.

- Specific adverse reaction **follow-up questionnaires** intended to capture clinical details about the nature and severity of COVID-19 illness or in relation to potential cases of vaccine lack of effect or VAED and/or AESI associated with COVID-19 disease, and to gather detailed information on cases of anaphylaxis.

- In addition to routine 6-monthly PSUR submission, **monthly summary safety reports** will be compiled and submitted to EMA, to support timely and continuous benefit risk evaluations during the pandemic. Minimum data to be submitted include:

    - Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately)
    - Interval and cumulative number of reports, overall and by age groups and in special populations (e.g., pregnant women)
    - Interval and cumulative number of reports per HLT and SOC
    - Summary of the designated medical events
    - Reports per EU country
    - Exposure data (lot distribution data total and per country)
    - Changes to reference safety information in the interval, and current CCDS
    - Ongoing and closed signals in the interval
    - AESI and RMP safety concerns: reports - numbers and relevant cases, including O/E analyses
    - Fatal reports -numbers and relevant cases, including O/E analyses
    - Risk/benefit considerations
- The need and frequency of submission of the summary safety reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 submissions).

- The proposed routine pharmacovigilance activities are considered appropriate for the safety profile of the product and the pandemic circumstances.

Traceability

Full traceability is crucial for pharmacovigilance purposes should assessment of a safety signal need to be performed by batch/lot.

The applicant's proposal to ensure traceability include:

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

- vaccine carton labelling containing a scannable 2D barcode that provides the batch/lot

- number and expiry date

- additional tools for vaccinators to record manufacturer and lot/batch information at the time of vaccination including a Traceability and Vaccination Reminder Card provided printed to vaccinators (as well as available electronically), and peel-off labels (stickers with brand name and lot/batch numbers as well as a scannable 2D code with this information), acknowledging that each Member State will decided if and how the tools will be used, in accordance with the national provisions for pharmacovigilance.

Each shipment to a vaccination site should be accompanied with a sufficient number of corresponding vaccinee traceability and vaccination reminder cards; the lot/batch numbers will be for the first batches distributed copied manually by the vaccinators, with the applicant's commitment that by 28 February 2021 all batches shipped will be accompanied at the receipt point in the Member States by sufficient peel-off labels to facilitate the recording of brand name and lot/batch number both in the vaccinators' records and the vaccinee traceability and vaccination reminder cards, where the Member States will require it.

The Traceability and Vaccination Reminder will include:

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

Additional pharmacovigilance activities

The applicant proposed eight studies to identify and characterise the risks of the product – six in the US, one in the EU and one in the EU, US and Canada. Four studies are interventional, including the three ongoing clinical trials and a study in immunocompromised subjects and four studies are non-interventional by design, including 3 for safety and 1 on effectiveness.

Study Title and categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances				
Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Study Status: Ongoing	Evaluate long term safety data and durability of vaccine effectiveness (VE)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Long term safety	Interim CSR Final CSR	30 June 2021 31 December 2022
Category 3 – Required pharmacovigilance activities				
Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults Study status: Ongoing	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses. Follow up period extended by an additional 12 months for 24 months follow up total after the second dose. Assessment of a booster dose	Anaphylaxis Long term safety	Interim CSR Final CSR	1 March 2021 01 November 2022
Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in	Anaphylaxis	Interim CSR Final CSR	1 March 2021 18 November 2021

Study Title and categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
CoV-2 Vaccine in Adults ≥18 Years Study status: Ongoing	those that receive vaccine/booster			
Safety and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Immunocompromised Adults Aged 18 Years and Older Study status: Planned	Evaluate the safety and reactogenicity of the vaccine in immunocompromised adults Evaluate the immunogenicity of the vaccine in immunocompromised adults	Anaphylaxis Use in immunocompromised subjects	Protocol submission Interim Report Final CSR	05 Feb 2021 31 March 2022 31 Jan 2023
Post-Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US Study status: Planned	Enhanced pharmacovigilance study to provide additional evaluation of AESI and emerging validated safety signals. The study has three core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety AESI and emerging validated safety signals.	Protocol submission Interim updates Final study report	31 January 2021 30 Apr 2021, 31 July 2021, 31 October 2021, 31 Jan 2022, 30 Apr 2022, 31 July 2022, 31 October 2022, 31 December 2022 30 June 2023

Study Title and categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Study status: Planned	Enhanced pharmacovigilance study to provide additional evaluation of AESI and emerging validated safety signals in European populations. Electronic database assessment of use in pregnant women	Anaphylaxis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Use in pregnancy and while breast-feeding Long-term safety Interaction with other vaccines Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders	Feasibility assessment Protocol submission Interim Updates Final study report	31 January 2021 31 March 2021 30 June 2021, 30 September 2021, 31 December 2021, 31 March 2022, 30 June 2022, 30 September 2022, 31 December 2022, 31 March 2023, 30 June 2023 31 December 2023
Moderna mRNA-1273 Observational Pregnancy Outcome Study Study status: Planned	Evaluate outcomes of pregnancies in females exposed to mRNA-1273 vaccine during pregnancy	Use in pregnancy and while breast-feeding	Protocol submission Interim updates Final study report	31 Jan 2021 31 July 2021, 31 Jan 2022, 31 July 2022, 31 Jan 2023, 3, 31 July 2023, 31 Jan 2024 30 June 2024

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

Non-Interventional Post-Approval Safety Studies (4)

- The applicant proposed 4 studies of real-world safety and effectiveness of COVID-19 mRNA vaccine that use multiple data sources and study designs.

- **Post Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US**
  US non-interventional active safety surveillance study for individuals who receive the Moderna mRNA-1273 SARS-CoV-2 Vaccine. The study will use secondary medical and pharmacy claims data from individuals insured under providers participating in several large US medical and pharmacy insurance claims submission systems. The three core objectives are: estimation of background rates for AESI prior to and during the pandemic, assessment of observed versus expected rates, and estimation of the relative risk for specific AESIs continuing to meet pre-specified evaluation threshold. The proposed milestones include interim reporting every three months. The final evaluation of the proposed studies will take place in a separate procedure once study protocols are submitted for review.

- **Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU**
  A Post-Authorisation Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the COVID-19 Vaccine Moderna in the EU. Secondary database analysis of observational data to estimate incidence rates of safety events of interest and other clinically significant events in cohorts of COVID-19 vaccine recipients in the EU.

- **Moderna mRNA-1273 Observational pregnancy outcome study**
  The use of mRNA vaccine in pregnant women is considered Missing Information in the RMP. The study will evaluate pregnancy outcomes among women exposed to mRNA-1273 vaccine during pregnancy. This is a prospective observational study and will evaluate pregnancy and birth outcomes among women exposed to mRNA-1273 vaccine during pregnancy based on data from US, Canada and EU. Pregnant women will be recruited from the general population and followed from enrolment until the end of pregnancy (live birth, stillbirth, termination of pregnancy, or spontaneous abortion); live-born infants will be followed from birth until 1 year of age. Data from EU countries will be included in the study.

- **Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S.** will evaluate mRNA-1273 effectiveness and long- term effectiveness. Primary objectives of the study are to evaluate the effectiveness of 2 doses of COVID-19 Vaccine Moderna in preventing COVID-19 and severe COVID-19 disease. Secondary objectives include effectiveness estimates stratified by age, sex, race/ethnicity, comorbid conditions, and concomitant receipt of another adult vaccine. Durability of one or two doses of Moderna's COVID-19 vaccine against COVID-19 and severe COVID-19 disease will also be assessed.

Interventional studies (4)

- The applicant proposed 4 interventional studies, of which 3 are ongoing and 1 is planned.

- **Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults, Protocol No. 20-0003**
  The purpose of this study is to study the safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses. Follow up period extended by an additional 12 months for 24 months follow up total after the second dose.

- **Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARSCoV-2 Vaccine in Adults ≥18 Years, Protocol No. mRNA-1273-P201**
  The study objective is to study the safety and reactogenicity and immunogenicity of 2 dose

levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster.

- **Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARSCoV-2 Vaccine in Adults Aged 18 Years and Older, Protocol No. mRNA-1273 P301**
  The primary objectives of study P301 are to demonstrate the efficacy of mRNA-1273 to prevent COVID-19 and to evaluate the safety and reactogenicity of 2 injections of mRNA-1273 given 28 days apart. The study has secondary and exploratory objectives.
- A planned interventional study '**Safety and Immunogenicity of mRNA-1273 SARSCoV-2 Vaccine in Immunocompromised Adults Aged 18 Years and Older'** in order to study the safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in immunocompromised adults.

Overall conclusions on the Pharmacovigilance Plan

The proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

None proposed.

Risk minimisation measures

Routine Risk Minimisation Measures

Potential Medication Errors

The applicant included a discussion on potential medication errors which is endorsed:

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, including instructions in SmPC (section 6.6) contains instructions for preparation and administration, vaccination scheme, and storage conditions of the vaccine. Additionally, a Traceability and Vaccination Reminder card will be provided with the pre-printed MAH name and fields for entry of dates of vaccination, batch/lot as a mitigation effort for potential confusion between vaccines, as well as peel-off labels with lot/batch number to document the doses administered.

These available resources will inform healthcare providers on the proper preparation and administration of the vaccine and reduce the potential for medication errors in the context of a mass vaccination campaign. Additionally, the patient information leaflet and, in those member states where applicable, a Traceability and Vaccination Reminder card informs patients of the vaccine received so that a series is completed with the same product.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Anaphylaxis	Routine risk communication : SmPC Sections 4.3 Contraindications 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects PL Sections 2 and 4 Ensure appropriate medical treatment and supervision to be always readily available in case of an anaphylactic reaction following administration of the vaccine. Recommendations for close observation for at least 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 vaccine Moderna (SmPC section 4.4). Patients to get urgent attention in case of signs and symptoms of allergic reactions is included in the PL section 4. Contraindication in subjects with prior hypersensitivity to any component of the vaccine is included in section 4.3 and PL section 2. Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of anaphylactic reactions including anaphylaxis in individuals who have received mRNA-1273 vaccine. Additional pharmacovigilance activities (final CSR due date): • Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US (final CSR: 30 June 2023) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023) • Phase 3 P301 (final CSR: 31 December 2022) • Phase 2a P201 (final CSR: 18 November 2021) • Phase 1 20-0003 (final CSR: 01 November 2022) • Safety and Immunogenicity in Immunocompromised Adults (final CSR: 31 January 2023)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine and enhanced pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of COVID-19 disease in individuals who have received mRNA-1273 vaccine. The intent is to provide insight into potential cases of vaccine lack of effect or VAED. Additional pharmacovigilance activities (final CSR due date): • Post Authorisation Safety of SARS-CoV-2 mRNA-1273 vaccine in the US (final CSR: 30 June 2023) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023) • Phase 3 P301 (final CSR: 31 December 2022)
Use in pregnancy and while breast-feeding	Routine risk communication: SmPC Sections 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data PL Section 2 Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023) • Moderna mRNA-1273 Observational Pregnancy Outcome Study (final CSR: 30 June 2024)
Long-term safety	Routine risk communication: None Additional risk minimisation: None	Additional routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Post Authorisation Safety of SARS-CoV-2 mRNA-1273

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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	Routine risk minimisation measures: SmPC section 5.1. Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. (final CSR: 30 June 2025) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023)
Use in subjects with autoimmune or inflammatory disorders	Routine risk minimisation measures: None PL Section 2 Additional risk minimisation: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. (final CSR: 30 June 2025) • Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU (final CSR: 31 December 2023)

Summary of additional risk minimisation measures

None proposed.

The applicant stated that Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. This is acceptable.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Summary of the risk management plan

The public summary of the RMP is acceptable.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. Furthermore, during the duration of the COVID-19 pandemic situation, the MAH shall submit summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18.12.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that CX-024414 (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) has not been previously authorised in a medicinal product in the European Union.

CX-024414 is the mRNA that encodes for the pre-fusion stabilised Spike protein of 2019-novel Coronavirus (SARS-CoV-2). The full-length SARS-CoV-2 spike (S) protein is modified with 2 proline substitutions (K986P and V987P) within the heptad repeat 1 domain (S 2P) to stabilise the S protein into the pre-fusion conformation. All uridines in the mRNA are replaced by 1-methylpseudouridine. A highly similar chemical active substance encoding for the same vaccination antigen was previously authorised in a medicinal product for human use in the European Union. Although, CX-024414 as active substance exposes patients to the same vaccination antigen as the already authorised active substance in the European Union, the respective mRNAs of both vaccines are not identical. Structural elements of the mRNA, including the sequence control elements and codon usage of the open reading frame of the vaccination antigen are different. This can lead to an increased mRNA stability and to an improved translation efficacy.

In conclusion, the active substance CX-024414 provides a unique sequence in the UTRs that can influence the stability and translational behaviour of the active substance. These sequences are not present in any authorised medicinal product in the EU. Therefore, the new active substance claim is supported.

The CHMP, based on the available data, considers CX-024414 (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) to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable, given the current urgent public health need for rapid development and approval of vaccines to prevent the global burden of disease associated with SARS-CoV-2 infection and COVID-19 disease, and because the product will always be administered by a healthcare professional.

The applicant is expected to thoroughly review and update the package leaflet in the light of the results from the user testing, especially as regards the section 'Information about storage and handling'.

2.10.2. Labelling exemptions

The following exemptions from labelling and serialisation requirements have been granted on the basis of article 63.3 of Directive 2001/83/EC. In addition, the derogations granted should be seen in the context of the flexibilities described in the *Questions and Answers on labelling flexibilities for COVID-19 vaccines* (EMA/689080/2020 rev.1, from 16 December 2020)[3] document which aims at facilitating the preparedness work of COVID-19 vaccine developers and the associated logistics of early printing packaging activities. The ultimate goal is to facilitate the large scale and rapid deployment of COVID-19 vaccines for EU citizens within the existing legal framework.

EU packaging specific derogations

a. From start of supply to beginning of February '21 the following exemptions are agreed for the outer and immediate labelling:

Outer carton

- (Invented) name: 'Moderna COVID-19 Vaccine'
- Pharmaceutical form: 'suspension for injection' instead of 'dispersion for injection';
- Inclusion of a strength (0.20 mg/ml);
- Inclusion of non-standard pictograms.
- common name: covid-19 mRNA vaccine

Immediate label (vial)

- (Invented) name: 'Moderna COVID-19 Vaccine';
- Pharmaceutical form: 'suspension for injection' instead of 'dispersion for injection'
- common name: covid-19 mRNA vaccine

b. From beginning of February '21 until end of March '21 the following has been agreed with respect to the (invented) name:

It has been allowed to deviate from the (invented) name containing the BWP approved common name (for the Product Information (PI) Annexes/Opinion documents) by omitting the 'mRNA' and '(nucleoside modified)' parts, i.e. **COVID-19 ~~mRNA~~ Vaccine ~~(nucleoside-modified)~~ Moderna**. This derogation is valid until a proper invented name is granted or until a WHO INN is approved and used

[3] Available at https://www.ema.europa.eu/en/documents/other/questions-answers-labelling-flexibilities-covid19-vaccines_en.pdf, last consulted on 21 December 2021.

for an INN+MAH name. This will result in the following text for the PI annexes/Opinion documentation:

(Invented) name: **COVID-19 Vaccine Moderna**

Common name: **COVID-19 mRNA Vaccine (nucleoside modified)**

The above decision is justified on the grounds of clarity and consistency between the printed materials produced for the batches released from February to March '21 and PI annexes/Opinion documents plus company website (QR code content). It will also minimise confusion amongst vaccine users and reduce the number of changes needed post-marketing. Moderna shall continue working closely with EMA to define an appropriate strategy to switch to a proper invented name or INN + MAH name within the above-mentioned period and possibly even from the beginning of February '21.

c. Outer and immediate labelling will be provided in English only for all EU Member States, as well as Norway and Iceland. Country/language specific outer/immediate labelling will be developed late 2021 with implementation starting Q2 2022.

Production of different vaccine packs in different languages will significantly reduce the supply chain efficiency. The multiple changes on packaging lines will result in significant time and capacity losses and would slow down the rapid deployment of COVID-19 vaccines. Moreover, English only labelling will better help to manage a shortage situation in one country by using immediately the supply from another country.

d. From the beginning of supply and until March 2021 no printed package leaflet (PL) in the national language(s) will be supplied to EU MSs, including Norway and Iceland. During this time access to the national version of the PL will be ensured via a QR code printed on the outer and immediate labels. MAH shall supply as of March 2021 printed PLs in the national language(s) of all MSs, including Norway and Iceland. Moreover, a reduced number of 5 printed PLs per 1,200 doses will be provided. A QR code will be printed on the PL and on the Patient Reminder Card to ensure in parallel access to the national versions of the PL.

e. The Blue Box will be omitted for the initial batches. The MAH shall provide the Blue Box via a QR code at a later stage following agreement on exact timing of implementation with the National Competent Authorities in each MS.

f. The inclusion of the EU Marketing Authorisation number in the labelling will be implemented with the switch to EU compliant packs in Q2 2022, as the labels used until the end of 2021 are covering regions other than EU.

Exemption from the obligation of serialisation

- All EU Member States have accepted a temporary derogation from serialisation for the EU pack from beginning of supply until the end of March 2021.

- The MAH shall provide two progress reports on the serialisation: a first by 1st of February '21 and a second by 1st of March '21 referring to details on the progress achieved in terms of ensuring compliance, e.g. the proof of contract to connect to the European Medicines Verification Organisation.

- The MAH shall provide additional mitigating measures, e.g. immediate reporting of any stolen product during the period of exemption, reporting of any counterfeit or falsified vaccine in the EU or third countries in the legal supply or internet, reconciliation of product distributed and used in the respective territory.

2.10.3. Quick Response (QR) code

A request to include a QR code in the labelling and the package leaflet for the purpose of providing information to Healthcare Professionals and vaccine recipients has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

- The Summary of Product Characteristics
- The Package Leaflet
- Storage & Handling guide
- Reminder card
- Local telephone numbers for medical information and safety reporting

2.10.4. Additional monitoring

Pursuant to Article 23(1) of Regulation (EC) No 726/2004, COVID-19 Vaccine Moderna (COVID-19 mRNA Vaccine (nucleoside-modified), CX-024414 (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)) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication of COVID-19 Vaccine Moderna is the prevention of COVID-19 in adults. COVID-19 is the disease caused by a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2). COVID-19 is primarily recognised as febrile respiratory illness. While the majority of cases subsides without specific treatment in a subgroup of patients the disease progresses to severe disease characterised by oxygen requirement. Still fewer patients progress to critical disease with respiratory failure, ARDS, multiorgan failure and/or thromboembolic complications. Age is the major risk factor for severe COVID-19 and death; other described risk factors are adiposity, pre-existent diabetes, cardiovascular disease, lung disease, immuno-deficiency and pregnancy. COVID-19 can be considered confirmed by the existence of the above clinical signs and proof of the presence of the virus by RT-PCR.

3.1.2. Available therapies and unmet medical need

Only a couple of medicinal products have received marketing authorisation for the treatment of COVID-19. These encompass antiviral therapy (remdesivir) and anti-inflammatory therapy (dexamethasone). A number of products are in clinical development, either antivirals such as monoclonal antibodies

directed to spike protein, convalescent plasma/hyperimmune immunoglobulins or anti-inflammatory medicinal products. Other widely used treatments of hospitalised patients include anticoagulants. These therapies have shown variable efficacy depending on the severity and duration of illness.

While care for individuals with COVID-19 has improved with clinical experience gained over time, there remains an urgent and unmet need for vaccines able to prevent or mitigate COVID-19 during the ongoing pandemic. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. Although a first vaccine for prevention of COVID-19 was approved recently (Comirnaty), there is still an important need for additional vaccines to meet global demand or specific subpopulations.

3.1.3. Main clinical studies

Three studies were conducted with mRNA-1273, of which two dose finding immunogenicity and safety phase 1 and phase 2a studies and one large phase 3 efficacy and safety trial, which is the pivotal study for this application.

Phase 3 Study mRNA-1273-P301 is a pivotal randomised, observer-blind, placebo-controlled, stratified, efficacy, immunogenicity, and safety study in adults ≥ 18 years of age, being conducted in 99 sites across the United States. The overall study duration will be approximately 26 months for each participant. The participant's final scheduled visit will be on Day 759.

In this trial, 30,420 subjects were randomised 1:1 to receive either 100µg of mRNA-1273 vaccine (n=15,210) or placebo (n=15,210) on Day 1 and on Day 29 (cut-off date for this application was 25 November 2020). Randomisation was stratified by age and health risk into one of three strata, i.e. ≥65 years of age or 18 to <65 years of age with or without the presence of risk factors for severe COVID-19 based on CDC recommendation as of March 2020. The trial design has been revised recently after EUA in the US, unblinding participants to offer vaccination with mRNA-1273 within the trial (for participants who had received placebo).

3.2. Favourable effects

The main favourable effect is the ability to prevent COVID-19. The primary endpoint in the pivotal trial is vaccine efficacy (VE) defined as 1- HR (vaccine vs. placebo) with cases counted 14 days after the second dose of the vaccine. A dosing window of −7 to +14 days was allowed for inclusion in the PPS, therefore subjects included in the primary efficacy analysis had an interval between doses ranging from 3 to 6 weeks. COVID-19 cases were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT PCR) and by a Clinical Adjudication Committee. Vaccine efficacy (final analysis, 196 cases overall, per protocol set) to prevent COVID-19 in subjects aged 18 years and older, with or without underlying chronic disease and without prior evidence of SARS-CoV-2 infection, was 94.1% (95% CI 89.3%, 96.8%).

From the experience with other vaccines it is expected that prevention of severe COVID-19 will be achieved by preventing COVID-19 overall. Currently no adjudicated severe COVID-19 cases were found in the vaccine group while 30 cases were found in the placebo group resulting in a VE of 100% (95%CI 87.0%, NE). Of the 30 participants with severe disease, 9 were hospitalised, of which 2 were admitted to an intensive care unit, one of which died. The majority of the remaining severe cases fulfilled only the SpO2 criterion for severe disease.

Vaccine efficacy was very similar irrespective of whether individuals with prior evidence of SARS-CoV-2 infection were included in analysis or not. Efficacy regardless of prior SARS-CoV-2 infection

(determined by baseline serology and NP swab sample testing) from 14 days after Dose 2 was 93.6% (95% CI 88.5%, 96.4%.

In addition, all subgroup analyses based on age, ethnicity, race and comorbidities gave consistent estimates for vaccine efficacy. Specifically, efficacy against confirmed COVID-19 regardless of severity starting 14 days after the 2nd dose in the Per-Protocol Set was 95.6% (95% CI 90.6%, 97.9%) in individuals aged 18 to <65 YOA and 86.4% (95% CI 61.4%, 95.2%) in individuals aged 65 years and older. Individuals having a higher risk for severe COVID-19 disease due to comorbidities were allowed to participate. Overall, 2775 (18.3%) subjects in the mRNA-1273 vaccine group had a higher risk for severe COVID-19, of them 624 subjects (4.1%) had 2 or more risk factors. This included: chronic lung disease, significant cardiac disease, severe obesity (body mass index ≥ 40 kg/m2), diabetes (Type 1, Type 2 or gestational), and liver disease. It should be noted, that the individuals must have been in a stable health condition. In subjects with comorbidities, efficacy against COVID-19 14 days after dose 2 (primary efficacy analysis in the PPS) was:

- 90.9% (95% CI 74.7%, 96.7%; 4 cases vs. 43 cases in vaccine vs. placebo group) in individuals at high risk (N=~3200 each arm), defined as subjects at increased risk of severe COVID-19 due to at least one pre-existing medical condition (chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease or HIV infection), regardless of age;
- 94.4% (95% CI 76.9%, 98.7%; 2 cases vs. 35 cases in vaccine vs. placebo group) in individuals at high risk aged 18 to <65 years (N=~2100 each arm, same definition as above).

3.3. Uncertainties and limitations about favourable effects

Data on vaccine efficacy is available for approximately 9 weeks starting 14 days after dose 2. Data on long-term protection are expected, however the extent and quality of data that can be anticipated from the ongoing phase 3 study is uncertain because participants in the placebo arm will be offered vaccination under the FDA EUA hence the study will be unblinded. Alternative plans to determine duration of protection should be discussed post-authorisation.

The efficacy was demonstrated in a general population aged 18 years and older. Case numbers in the very old patient population (i.e. 75 and older) at highest risk of severe COVID-19 are limited. Only ~1300 subjects across study arms were aged 75 years and older.

No data are available on certain populations such as patients under immune suppressive therapy and immune deficient patients. Data are also lacking from pregnant and breast-feeding women.

The definition of severe COVID-19 (as per protocol) follows a list of clinical categories (e.g. low oxygen saturation, transfer to ICU) with pronounced difference in severity, and of which at least one category needs to be fulfilled. This complicates interpretation of efficacy estimates for severe disease prevention and the most frequent component driving severe case counts appears to be SPO2 below 93%. One currently unadjudicated severe case was reported as SAE in vaccine group.

The case-driven readout and high VE translates into limited case numbers at present and resulting limited precision for estimating VE in several substrata including elderly, people with comorbidities and efficacy against severe COVID-19.

Protection against asymptomatic infection is currently unknown, however data will be generated during the ongoing phase 3 trial on antibodies against the nucleocapsid protein. In addition, the pivotal study was not designed to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals experiencing asymptomatic infections after vaccination. The efficacy of the vaccine in

preventing SARS-CoV-2 shedding and transmission, in particular from individuals with asymptomatic infection, can only be evaluated post-authorisation in epidemiological or specific clinical studies

The extent of cross-neutralisation of circulating and newly emerging strains of SARS-CoV-2 is not known, however more data will be generated post-authorisation with sera from the ongoing trials.

There seems to be at least a partial onset of protection after the first dose, but this remains unconfirmed at this stage.

Available data do not suffice to establish efficacy in subjects seropositive for SARS-CoV-2 at baseline, and subjects with a known history of COVID-19. However, efficacy is anticipated in this group, to the extent that they are not naturally protected against re-infection, which is presently incompletely characterised.

The process from incident COVID-19 symptom occurrence during study to final decision as to whether or not a 'case' was declared (and considered for primary efficacy analyses) leaves some uncertainty for the final VE estimate.

The data from the phase 3 study currently presented as basis of the conditional MA are based on data snapshots from an ongoing study rather than on database locks with fully monitored, cleaned and adjudicated data. Due to the speed of events not all COVID-19 cases reported could be adjudicated so far. While adjudication of events starting 14 days after the second dose were prioritised even for the primary endpoint not all potential events could be adjudicated at the time of the data cut-off leading to potentially lower numbers of cases in this endpoint.

Concomitant administration with other vaccines was not studied and will be investigated post-authorisation by means of a PASS and an effectiveness study.

The timing and number of interim analyses was modified very late in the study and strong overrunning was observed. While it seems very unlikely, potentially data driven choices cannot be excluded. Given the large treatment effect a potential impact was considered negligible.

3.4. Unfavourable effects

In the phase 3 trial, the analysis of solicited local and systemic adverse reactions was performed within the Solicited Safety Set that consisted of randomised participants who received at least one injection of the vaccine and contributed to any solicited adverse reaction data. The solicited safety set overall included 15,179 subjects in the mRNA-1273 vaccine group and 15,163 subjects in the saline placebo group. Of the 15,179 subjects in the solicited safety set of the vaccine group, 15,168 subjects received 1 dose and 14,677 received 2 doses. In the placebo group, the numbers were 15,155 and 14,566 (as of 25 November 2020). At the 25 November 2020 data cut, 9,406 (61.9%) subjects in the mRNA-1273 group of the pivotal trial were followed for ≥56 days since the second injection. The median study duration from the second injection was 63.0 days.

Solicited local and systemic reactions were reported at a higher incidence in the mRNA-1273 group than in the placebo group after each injection. Any solicited local injection site reaction of any grade after any dose was reported by 29.3% of subjects in the placebo group and by 92.4% of subjects in the vaccine group. Any solicited systemic AR after any dose was reported by 53.5% of subjects in the placebo group and by 84.1% in the vaccine group. Pain at the injection site was the most common solicited local AR in the mRNA-1273 group (92%), followed by lymphadenopathy (axillary swelling/tenderness; 19.8%), injection site swelling (14.7%), and injection site erythema (10%). The most frequent reported solicited systemic ARs in the m-RNA-1273 vaccine group after each dose were fatigue (70%), and headache (64.7%). This was followed by myalgia (61.5%), arthralgia (46.4%), and

chills (45.4%). Local and systemic reactogenicity increased from dose 1 to dose 2. The increase was more evident for systemic solicited ARs compared with local solicited ARs. The majority of solicited systemic and local ARs was mild to moderate.

Any grade 3 or 4 solicited systemic AR was reported from 3.0% of subjects in the vaccine group after dose 1 and by 15.9% after dose 2. No local AE grade 4 were reported and the majority of grade 3 local AEs was pain at the injection site. After the first injection, grade 4 solicited systemic ARs were reported by 5 participants in the vaccine group vs. 6 participants in the placebo group. After the second injection, grade 4 events occurred in 14 vs. 3 subjects. Nearly all grade 4 events were fever >40°C, except for single reports of fatigue, arthralgia and nausea/vomiting in the mRNA-1273 group.

Solicited local ARs persisted longer after dose 2 (median 3 days) than after dose 1 (median 2 days). Solicited systemic ARs generally persisted for a median of 2 days after each dose.

Unsolicited adverse events occurred in a similar rate in both placebo and vaccine group. Related were 8.2% in the vaccine and 4.5% in the placebo group of which severe were 0.5% (vaccine) and 0.2% (placebo). The most common events are similar to events seen with any vaccine, e.g. fatigue, headache, myalgia and arthralgia. Urticaria and rash were the most commonly seen skin and tissue events, most of them a continuation of solicited events reported but some also starting a week after vaccination.

The incidences of severe, serious and medically-attended unsolicited AEs were similar between vaccine and placebo recipients. However, there were some imbalances for events such as facial swelling, acute peripheral facial paralysis, or certain hypersensitivity events (injection site urticaria, rash).

Of the SAEs seen in the vaccine group some are also attributable to the activation of the inflammatory system (e.g. colitis, cholecystitis, arthritis). Until the data cut-off, there were 7 subjects with treatment-related SAEs in the vaccine group, compared to 5 subjects in the placebo group as judged by the Investigator, however based on the information available to date no conclusion on relatedness could be drawn. The event of facial swelling in the vaccine group occurred in subjects that received dermal filler injections (hyaluronic acid, hyaluronic acid / Botox combination) prior to vaccination and was included in section 4.8 of the SmPC due a reasonable possibility of causal relationship.

A numerical imbalance is observed for acute peripheral facial paralysis with three cases in the vaccine vs. one case in the placebo arm. All cases in the vaccine arm showed an onset in close temporal relationship to second injection. A reasonable possibility of a causal relationship to the vaccine cannot be excluded with certainty and this AE should therefore be reflected in the SmPC section 4.8.

At the time of the latest data cut-off (25 November 2020), there were single events of anaphylaxis in each treatment group, but without a temporal connection to the injection. Additionally, there was one report of anaphylaxis in an individual with a severe shellfish allergy occurring after vaccination in the context of the emergency use authorisation. This is reflected in the SmPC (sections 4.4, 4.8).

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety data are not yet available. Participants in the clinical trials will be followed until 24 months after the second dose (study P301) or 12 months after the second dose (studies P201, P101). Long-term safety is considered as missing information in the RMP and will be characterised as part of the continuation of the pivotal clinical trial, other trials and a PASS.

No difference was observed with regards to incidence and severity of reactogenicity in subjects who were seropositive for SARS-CoV-2 at baseline compared with subjects who were seronegative for SARs-CoV-2 at baseline. The proportion of seropositive subjects was small with 343 subjects SARS-

CoV2 positive at baseline who received mRNA-1273 vaccine (2.3%) and 337 seropositive placebo subjects (2.2%), however no specific concerns arise in the observed safety profile so far.

The safety and reactogenicity data in a limited number of HIV infected individuals with stable antiviral therapy did not reveal any concern. Limited safety data are available in individuals with autoimmune disorders and individual under immune-suppressive treatment. An immunogenicity and safety trial in immunosuppressed/immunodeficient people will be conducted post-authorisation as reflected in the RMP.

Very limited clinical safety data are available for use of the vaccine during pregnancy and lactation that do not allow any conclusions. A PASS and a pregnancy exposure registry are planned in the RMP to generate data post-authorisation.

Whereas individuals having a higher risk for severe COVID-19 disease due to comorbidities were included in the study, these were required to be stable at baseline. No safety data are available for frail individuals with unstable comorbidities. Plans to gather data post-authorisation are laid down in the RMP.

Reactogenicity was lower in individuals of 65 years of age and older compared with the younger population 18 to 65 years of age. Approximately 24.8% (3763) of subjects older than 65 years of age were included in the vaccine group of the phase 3 trial. However, there were limited participants for the age group ≥85 years and above. It is however not anticipated, that reactogenicity will increase by age.

The available data (non-clinical, clinical, neutralising capacity of antibodies) do not raise a concern regarding vaccine-enhanced respiratory disease at the time being. However, the possibility of enhanced disease cannot be excluded with certainty. The current version of the RMP lists vaccine-associated enhanced respiratory disease as a safety concern and an important potential risk and plans for monitoring are included.

COVID-19 Vaccine Moderna contains lipid nanoparticles that include two novel lipid components (SM-102, PEG2000-DMG). The distribution, metabolism and PK of SM-102 has not been extensively studied but submitted data on a close structural analogue show efficient hydrolysis and clearance. Currently the involvement of PEG as an antigen triggering allergic reactions is increasingly being recognised. Anaphylaxis has been recognised as an established risk, but the responsible antigen is currently unknown and non-IgE mediated allergic reactions remain a possibility. The low molecular weight of the PEG, the small amount contained in the vaccine and the administration of only few doses do not raise concerns regarding possible accumulation.

Interaction with other vaccines has not been evaluated in clinical trials. Safety of concomitant use with other vaccines will be investigated post-authorisation as part of a PASS study included in the RMP.

3.6. Effects Table

Table 22 - Effects Table for COVID-19 Vaccine Moderna intended for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older

Effect	Short Description	Unit	mRNA-1273 (100 µg, 2 doses)	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	mRNA-1273 (100 µg, 2 doses)	Placebo	Uncertainties/ Strength of evidence	References
Vaccine efficacy overall	First COVID-19 (any severity) occurring 14 days after Dose 2, without prior evidence of SARS-COV-2 infection	VE % (95% CI) COVID-19 cases	94.1 % (89.3%, 96.8%) 11	 185	Robust data with similar VE across different analysis sets and in important subgroups, especially all age strata Vaccine group N=13,934 Placebo N=13,883	Study mRNA-1273-P301 (PP set)
Vaccine efficacy against severe COVID-19	First COVID-19 (severe) occurring 14 days after Dose 2, without prior evidence of SARS-COV-2 infection	VE % (95% CI) COVID-19 cases	100% (87.0%, NE) 0	 30	One (currently) unadjudicated severe case reported as SAE in vaccine group.	
Vaccine efficacy in individuals aged >65 years	First COVID-19 (any severity) occurring 14 days after Dose 2, without prior evidence of SARS-COV-2 infection	VE % (95% CI) COVID-19 cases	86.4% (61.4, 95.2) 4	 29		

Unfavourable Effects

	Unit	Post-dose 1	Post-dose 2	Post-dose 1	Post-dose 2	Transient events, majority mild to moderate intensity	Study mRNA-1273-P301 (Solicited safety set) Placebo (N= 15,162) mRNA-1273 (N=15,179)
Injection site pain	% of individuals reporting the AE	83.7%	88.2%	17.5	17.0%		
Injection site swelling/induration		6.1%	12.2%	0.3%	0.3%		
Axillary swelling/tenderness (lymphadenopathy, ipsilateral)		10.2%	14.2%	4.8%	3.9%		
Headache		32.7%	58.6%	26.6%	23.4%		
Fatigue		37.2%	65.3%	27.3%	23.4%		
Myalgia		22.7%	58.0%	13.7%	12.4%		
Arthralgia		16.6%	42.8%	11.8%	10.8%		
Nausea/vomiting		8.3%	19.0%	7.1%	6.4%		
Chills		8.3%	44.2%	5.8%	5.6%		

Effect	Short Description	Unit	mRNA-1273 (100 µg, 2 doses)	Placebo	Uncertainties/ Strength of evidence		References
Fever		0.8%	15.5%	0.3%	0.3%		
Bell`s palsy	n. of cases		3	1		Limited evidence for causality	

Abbreviations: VE: vaccine efficacy; AE: adverse event; CI: confidence interval

Notes: for a full summary of the adverse reactions please see the Summary of Product Information section 4.8.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In a large pivotal phase 3 trial, overall excellent efficacy in preventing COVID-19 of any severity has been demonstrated in individuals aged 18 years and older. The results are considered robust based on the study design and are further supported by the different secondary endpoints and analyses. Subgroup analyses indicate similar vaccine efficacy in those individuals that are considered to be at a higher risk of severe COVID-19 including elderly subjects and those with underlying health conditions known to increase the risk of severe disease and death following SARS-CoV-2 infection, which is considered as the population at highest need for preventative strategies.

In addition, preliminary and encouraging VE has also been estimated for the prevention of severe COVID-19.

Despite the limitations in the characterisation and control of the active substance and finished product, the available data and the proposed specifications for product related impurities are considered scientifically justified and acceptable in the context of a CMA in an emergency situation.

The main shortcoming of the current efficacy dataset is the unusually short follow up of approx. 9 weeks, but data will be submitted post-authorisation as detailed in the specific obligations, RMP, and recommendations. More data will be generated post-authorisation to further characterise longer term protection. In the current situation this gap in knowledge is outweighed by urgent need, high COVID-19 disease burden, and lack of or limited availability of preventative and therapeutic remedies.

It would be desirable to understand if this vaccine also has an effect on asymptomatic infection and viral transmission. Based on the current data this aspect is not answered yet, therefore the possibility for achieving herd immunity has not been demonstrated at the present time.

The observed safety profile is considered well characterised and acceptable based on short term data. ADRs are generally mild to moderate and are self-limited, although local tolerability and systemic ADRs overall indicate that this vaccine appears more reactogenic than many of the standard vaccines in use. Long term safety has to be characterised further and it is important to analyse the full 2-year safety follow-up of the pivotal trial, which is ongoing. The current dataset gives no indication of vaccine-enhanced disease, a potential concern that is addressed in the RMP.

There are very limited data on use in pregnant women, but a protective effect is anticipated. In the light of the reassuring data from the DART study, noting that pregnancy as such is a risk factor for

severe COVID19, and that pregnant women may additionally belong to other risk groups, vaccination may be considered on a case by case basis.

There are no data for breast-feeding women. Based on biological plausibility no risk for the breastfed infant is anticipated.

There are no efficacy data in immunocompromised individuals. Such patients may not be protected as well as immunocompetent individuals by vaccination. While there are limited safety data too in the immunocompromised subjects (a broad and disparate category), no particular safety issues are anticipated, and the benefit/risk balance of vaccination of such subjects is deemed positive, also in light of the underlying excess risk of COVID-19. Nevertheless studies are planned in the post-authorisation phase as detailed in the RMP.

3.7.2. Balance of benefits and risks

Given the clearly demonstrated favourable effect and considering the overall characteristics of the unfavourable effects, a favourable B/R balance in the proposed indication is concluded. This conclusion is particularly relevant for individuals at elevated risk of severe COVID-19 disease, like the elderly (especially those older than 75 years of age) and those with comorbid conditions that have been described to increase the risk of severe disease.

Although only limited data are available on HIV infected individuals, immunosuppressed /immuno-deficient individuals in general have a high risk of developing severe COVID-19. No specific safety issues are expected in this group, hence the benefit/risk balance for vaccination is also regarded as favourable.

Pregnant women are likely to be at an increased risk of severe COVID-19. The overall data in this population are not sufficient to make a general recommendation for use of the vaccine but an individual benefit-risk appraisal appears appropriate given the reassuring data from the DART study.

3.7.3. Additional considerations on the benefit-risk balance

Given the current emergency situation, it is considered that the identified uncertainties can be addressed post-authorisation through specific obligations, including the continuation of the pivotal clinical study as long as possible, and post-approval effectiveness studies and routine disease surveillance.

Conditional marketing authorisation

Efficacy, safety and immunogenicity was demonstrated using clinical batches of vaccine manufactured at Scale A. The commercial batches are produced using an up-scale process (initial Scale B for the active substance, Scale B for the finished product), and the comparability of these processes rely on demonstration of comparable biological, chemical and physical characteristics of the active substance and finished product.

Although the data provided so far are not considered to be complete with respect to the requested characterisation of the product, comparability, process validation and stability, the quality of the product is deemed sufficiently assured. Nevertheless, the applicant is requested to review the specification of the active substance and finished product and provide additional stability data when further manufacturing experience is gained.

Based on the above, the following uncertainties are considered to be of importance for the benefit-risk assessment:

- Comparability between the product used in the clinical trials and the commercial product
- Validation of the commercial scale manufacturing process at the sites registered for EU production
- Quality control of the product at release and during storage

The agreed specifications in relation to the control of the active substance and finished product are subject to review once more batch analysis data from routine manufacturing at the sites registered for EU manufacture are available. While some of the characterisation data still need to be completed and taking into account the emergency situation, the characterisation of the active substance and finished product are considered acceptable, and the proposed specifications for RNA purity are considered scientifically justified and acceptable subject to specific obligations.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed in section 3.7.2.
- It is likely that the applicant will be able to provide comprehensive data.

Studies are underway to complete the characterisation of the active substance and finished product, and additional clinical data from batches currently in use in ongoing clinical studies, will complete the clinical qualification of these specifications. Based upon the applicant's justification and commitment, detailed plans have been agreed with the applicant and reflected in the quality part of this assessment regarding data to be generated and submitted with interim milestones for assessment by the CHMP in order to complete all proposed specific obligations. Based on the applicant's plans and documentation, it is expected that data to fulfil all quality SOs will be submitted gradually between January and June 2021.

Furthermore, the applicant will continue the ongoing pivotal Phase 3 randomised, placebo-controlled, observer-blind study P301 to obtain 2-year long-term data and to ensure sufficient follow-up in order to confirm the efficacy and safety of COVID-19 Vaccine Moderna. The completion of the Phase 3 study P301 will lead to comprehensive date on the efficacy and safety of COVID-19 Vaccine Moderna.

- Unmet medical needs will be addressed.

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. Comirnaty (COVID-19 mRNA vaccine (nucleoside-modified)) was approved in the EU on 21/12/2020, being the first approved vaccine against COVID-19. Despite the recent granting of a conditional marketing authorisation for Comirnaty, there is still an unmet medical need for further vaccines to be authorised in order to increase the supply and availability across the EU.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Convincing efficacy evidence, including in the elderly and those with comorbid conditions has been provided and long-term effectiveness and safety data will be provided post-authorisation. Taking all this into account, it would not be considered appropriate to withhold a highly beneficial vaccine considering the severity of COVID-19 disease and the current global pandemic situation, since the

demonstrated benefits in the current emergency setting clearly outweigh the uncertainties of the available data as outlined above.

3.8. Conclusions

The overall benefit-risk of COVID-19 Vaccine Moderna is positive.

Eligibility to a conditional marketing authorisation as well as requirements have been demonstrated in line with provisions of Article 14-a of Regulation (EC) No 726/2004.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of COVID-19 Vaccine Moderna is favourable in the following indication:

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

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions and specific obligations:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply this medicinal product is subject to a time-limited exemption allowing reliance on batch control testing conducted in the registered site(s) that are located in a third country. This exemption ceases to be valid on 31 January 2021. Implementation of EU based batch control arrangements, including the necessary variations to the terms of the marketing authorisation, has to be completed by 31 January 2021 at the latest, in line with the agreed plan for this transfer of testing.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data.	January 2021
In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the MAH should provide additional comparability and validation data.	April 2021 Interim reports will be provided monthly prior to that date.
In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience.	June 2021
In order to confirm the efficacy and safety of COVID-19 Vaccine Moderna, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P301.	December 2022

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that CX-024414 (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) is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Annex I – List of Recommendations

Note: The active substance is the mRNA CX-024414. However, in the submitted dossier, the information on lipids and the LNP have been included in 3.2.S. An update of the current dossier structure needs to be provided (see REC1.1). The references in the list of recommendations to sections of the dossier which have to be updated, are with regard to the current structure of the dossier to facilitate traceability, but all the information pertaining to LNP will have to be moved to section 3.2.P.

Area	Number	Description	Classification*	Due date
Quality	1	**Active substance, CX-024414 (mRNA)** 1) In line with EU definition of active substance, which corresponds to the 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 MAH is recommended to structure the Module 3 accordingly and ensure that the relevant GMP requirements are applied to the manufacturing sites involved in the production of the active substance and finished product. 2) S.2.2 Description of manufacturing process and process controls a) The applicant is requested to provide hold time qualification data for CX-024414 mRNA manufacture no later than 31-03-2021. b) The applicant should provide numerical values for IPC acceptance limits for CX-024414 manufacturing by 30-06-2021. 3) S.2.3 Control of material a) The applicant commits to provide further information on the medium used for MCB and WCB no later than 31-01-2021. b) The acceptance criteria for the linearised plasmid should be revised if appropriate to reflect process capability not later than 30-06-2021. c) The applicant commits to provide sources for all appropriate reference materials/assay controls for plasmid and linearised DNA plasmid manufacturing no later than 31-03-2021. d) Evidence as regards qualification/validation of methods used for release testing of the linear DNA plasmid should be provided no later than 31-03-2021.	REC	See description

		e) The nucleotide starting material specifications will be finalised with suitably tight limits for purity (and impurities and other parameters if relevant) that ensure consistent active substance quality. A flow chart and description of the manufacture of modified UTP should be included to support its proposed specifications, i.e. whether contamination by impurities that can be later incorporated into the mRNA is a risk no later than 31-03-2021. 4) S.2.4 Control of critical steps and intermediates a) The qualification report for the residual protein assay should be provided no later than 31-01-2021. 5) S.3 Characterisation a) The applicant is asked to provide data to elucidate the nature of the observed additional bands by *in vitro* translation assay. Furthermore, additional details should be provided for the *in vitro* translation method and the negative and positive controls used, since the number and intensity of unspecific bands observed still leaves place for uncertainties regarding the possible translation of additional proteins/peptides no later than 31-03-2021. Additional characterisation data may be needed, unless justified otherwise. 6) S.4 Control of active substance a) The information concerning mRNA sequencing for in-process monitoring of mRNA concentration should be provided no later than 31-01-2021. b) The applicant should provide a summary of the CX-024414 mRNA analytical method experiment summaries and results by 31-03-2021. c) The applicant should provide details of the control strategy for dsRNA. The control strategy should ensure that dsRNA levels will always be at a sufficiently low level when the manufacturing process is run within the registered process parameter ranges. Alternatively, an appropriate release specification for dsRNA should be registered. no later than 31-01-2021. 7) S.5 Reference standard a) The report for qualification of the CX-024414 reference material lot should be provided by 31-01-2021. 8) S.6 Container closure system		

		a) From OC 58: Results from extractables/leachables testing of storage bags should be provided by 30-04-2021. 9) <u>S.7. Stability</u> a) The applicant should provide a summary of the CX-024414 mRNA analytical method experiment summaries and results by 31-03-2021. 10) <u>Appendices</u> a) Dossier section 3.2.A.2 should be updated to include information as regards control of sterility no later than 31-03-2021. b) Dossier section 3.2.A.2 should be updated to include a TSE risk assessment (not only considering active substance and finished product manufacturing processes but also manufacture of the starting material) and a statement as regards compliance with EMEA/410/01 Rev.3 requirements. The update should be provided by 30-06-2021.		
Quality	2	**<u>LNP</u>** 1) <u>S.2 Manufacture</u> a) Section 3.2.S.2.2 {LNP - Lonza Visp} should be amended to provide example calculations no later than 31-01-2021. b) Some in-process controls in section S.2.2 LNP currently are listed as report results. Numerical ranges should be established after PPQ and after sufficient manufacturing history (30 batches). Numerical ranges for in-process controls should be submitted no later than 30-04-2021. c) Section S.2.2 {LNP – Lonza Visp} should be amended to include mixing duration time and speed during lipid stock solution preparation no later than 31-01-2021. d) The TFF process parameter PAR "membrane feed flowrate" is different for initial concentration / diafiltration and final concentration. However, in section S.2.2 only one PAR is given. Section S.2.2 {LNP – Lonza Visp} should be amended to provide PAR for both flowrates no later than 31-01-2021. e) Section S.2.2 {LNP – Lonza Visp} should be amended to include the target lipid concentration and buffer mixing duration time/speed, cryoprotectant mixing time/speed as well as cryoprotectant addition flow rate no later than 31-01-2021.	REC	See description

		f) A hold time of 24 hours has been established using laboratory-scale experiments; Section 3.2.S.2.4 {LNP- Lonza Visp} should be amended to reflect this. The storage temperature should be added to Section 3.2.S.2.2 {LNP- Lonza Visp}. These updates should be provided by 31-01-2021. g) The applicant should revise Section S.2.2 { LNP – Lonza Visp} to reflect the 168 hr (7 day) hold duration instead of the currently included 14 day. It should be added that the 7 day hold duration will be inclusive of the "pre-aliquot interim storage duration". This update should be provided by 31-01-2021. h) The applicant should provide information for DSPC in accordance with the Guideline on excipients (EMEA/CHMP/QWP/396951/2006) no later than 31-01-2021. i) A risk assessment concerning potential extractables and leachables from manufacturing components and container closure systems has been performed according to the applicant in S.2.3 LNP. However, no details are available on possible extractables. Leachables studies are necessary when extraction studies have resulted in one or several extractables. In these situations, it should be demonstrated that in conditions representative for the intended use, substances will not migrate in such quantities as to alter the efficacy and stability of the product or to present a toxicological risk. Respective data should be provided not later than 30-06-2021. j) The applicant should provide results from forced degradation studies no later than 31-03-2021. k) No filter validation and no further information (filter type, number, material, pore size, area) to any of the used filters has been provided. For every filtration step an appropriate solvent specific filter validation should be provided and all relevant information regarding the filters should be presented within the dossier. The respective validation data and information should be provided no later than 30-04-2021. l) Section S.2.2 {LNP - Lonza Visp} should be amended to include the target fill volume no later than 31-01-2021. m) Hold time qualification is being repeated for Scale B PPQ and results are expected in January 2021. These results should determine hold duration for processes at Lonza Visp and should be submitted by 31-03-2021. n) Section S.2.4 {LNP - Lonza Visp} should be amended no later than 31-01-2021 to describe characterisation of mRNA post-thaw interim storage duration and temperature.		

		o) The applicant should establish a consensus specification for Tromethamol HCl in section S.2.3 Control of materials LNP instead of the currently included three specifications and should submit the specification no later than 31-03-2021. p) The applicant is requested to establish numerical acceptance criteria for in-process controls on bioburden and bacterial by 30-04-2021 2) <u>S.2.5. Process validation</u> a) The applicant explained the appearance of an additional CPP in the PPQ protocol by an update of the control strategy of mRNA purity based on process characterisation results. The applicant is requested to update the respective section 2.4 by 21-03-2021. 3) <u>S.3. Characterisation</u> a) The applicant should provide a comprehensive summary on the investigations and process changes related to lipid-RNA species impurities, justify the control strategy for lipid-mRNA species and its implementation and plans for further improvement, and update the relevant Module 3 manufacturing development sections by 31-01-2021. b) The applicant should outline the differences between the routine RP-HPLC purity method and lipid-RNA species characterisation RP-HPLC method (as described in Figure 1 of Section 3.2.S.3.2.1.1.1) by 31-01-2021. c) The applicant should provide information to demonstrate that the detection wavelength is suitable for the quantification of lipid-RNA species and UV spectra for impurity-enriched fractions by 31-01-2021. 4) <u>S.4 Control of Active Substance</u> a) The applicant should provide information on method verification for bioburden testing of LNP at Lonza, CH no later than 31-03-2021. b) The applicant should provide the deviation report from Lonza AG related to bacterial endotoxin testing of LNP no later than 15-01-2021.		

		c) Cholesterol is stated to be non-compendial and compendial "Synthetic Cholesterol (Phytochol)", whereas compendial is not further defined. In the Ph. Eur two monographs are provided for cholesterol, monograph 0993 and monograph 2397. For parenteral use cholesterol has to be in compliance to monograph 2397. The applicant is advised to solely use cholesterol of this quality and to update the provided specification and related documentation accordingly, to use non-compendial cholesterol has to be sufficiently justified. d) The applicant should provide a summary of the LNP analytical method experiment summaries and results by 31-03-2021. e) Final analytical method validation reports from Lonza, Visp should be provided once available (REC). 5) <u>S.6 Container Closure System</u> a) Compliance for packaging materials of LNP to EU regulation 10/2011 should be submitted no later than 31-01-2021. b) The applicant is requested to perform an extractables data assessment, and if necessary, a corresponding leachables study no later than 30-04-2021. 6) <u>S.7 Stability</u> a) The applicant should provide any additional stability data for LNP (clinical and PPQ lots) no later than 31-01-2021. b) The applicant should include the PPQ batches manufactured by Lonza AG, CH into the stability program. The acceptance criteria should be identical for release and stability		
Quality	3	**<u>Finished product</u>** 1) <u>P.2 Pharmaceutical Development</u> a) The applicant commits to submit all relevant batches to Section 3.2.P.2.3 {Rovi} no later than 31-01-2021.	REC	See description

		2) P.3 Manufacture a) A brief summary the shipping validation for finished product should be provided and the dossier updated accordingly by 31-03-2021 3) P.4 Control of Excipients a) The applicant should provide evidence that the impurities and/or degradation products resulting from PEG2000-DMG, cholesterol and DSPC have been sufficiently investigated and do not result in the formation of lipid-RNA species by 31-01-2021. 4) P.5 Control of finished product a) As committed, the reference sequence should be added to the method description for the identity test no later than 31-03-2021. b) As committed, the applicant should provide the quantitative risk assessment on nitrosamine impurities by 30-06-2021. c) The acceptance criteria for osmolality and *in vitro* translation should be re-evaluated after substantial expansion of manufacturing experience (e.g. 30 lots as proposed by the applicant) d) The applicant commits to conduct a risk assessment with respect to the potential presence of elemental impurities in the finished product based on the general principles outlined in Section 5.1 of ICH Q3D. The risk assessment will be provided no later than 31-03-2021. e) The applicant provide evidence to confirm that the impurities and/or degradation products resulting from PEG2000-DMG, cholesterol and DSPC have been sufficiently investigated and do not result in the formation of lipid-RNA species by 31-01-2021. f) The applicant commits to provide the validation reports for *in vitro* translation and Identity no later than 31-01-2021. g) The applicant commits to revise the toxicology assessments to present only the total daily intake based on µg/dose and will be updated by 31-01-2021.		

		h) For the chlorobutyl stoppers/flip-caps, the cycle conditions for depyrogenation/sterilisation of vials and steam sterilisation of stopper will be provided in a revision to Section 3.2.P.3.5 {Rovi} no later than 31-01-2021. For the RTU, chlorobutyl stoppers, confirmation about the gamma sterilisation of the stoppers will be provided in a revision to Section 3.2.P.7 {Rovi} no later than 31-01-2021. 5) <u>P.8 Stability</u> a) The applicant commits to revising the stability studies such that the lipid impurities are aligned with the release specification with respect to the reporting of lipid impurities no later than 31-01-2021. b) The finished product acceptance criteria for individual and total lipid impurities should be tightened based on current data for mRNA-1273 finished Product by 31-01-2021. c) The formulated RNA LNPs have been shown to be sensitive to interfacial stress during mixing and filling steps, as concluded from the studies in section P.2.3.6.4. In order to gain more information on the possibility and conditions to perform (short distance) shipments of thawed vaccine (at 2°C - 8°C), the applicant is requested to perform further studies to evaluate the stability of the final product with regard to mechanical stress during potential transport at 2°C - 8°C. More in particular, since mechanical stress (vibrations, shocks,…) may increase mRNA degradation (and as such decrease mRNA purity), it should be investigated how long the thawed vaccine can be stored at 2°C - 8°C and remain within specifications after having been transported in the thawed condition and as such exposed to some degree of mechanical stress (cumulative scenario of thawing, mechanical stress at 2°C - 8°C and storage at 2°C - 8°C). Results should be provided as soon as possible but no later than 31-03-2021		
Quality	4	**<u>Novel Excipients</u>** **<u>SM-102</u>** 1) <u>Manufacture</u> a) The process description should be updated to include the inert gas overlay information no later than 31-01-2021.	REC	See description

		b) Some in-process controls for the manufacturing process of SM-102 currently are listed as report results. Numerical ranges should be established for these IPCs after manufacturing 30 batches and should be submitted no later than 30-06-2021. c) The specifications of the SM-102 starting materials partly contain "Report results" as acceptance criteria. Numerical acceptance criteria should be established after sufficient manufacturing history (30 batches) is gained and should be submitted no later than 30-06-2021. d) The dossier of the novel excipient SM-102 should be updated to include CQAs, CPPs and CMAs. This update should be provided no later than 30-03-2021. 2) <u>Control of SM-102</u> a) The applicant should take into account the principles of ICH Q3a and Q3b for the reporting of impurities on the specification for SM-102 and should provide preliminary identification and reporting limits no later than 31-01-2021. The applicant should provide an interim report for the impurities no later than 31-03-2021 and a final revision for the SM-102 lipid specification no later than 30-06-2021. b) The applicant should establish numerical limits for all elemental impurities currently included in the specification for SM-102 with the acceptance criterion "Report Results" by 30-06-2021. c) A risk assessment for the presence of benzene in SM-102 should be completed and the control strategy should be updated and submitted no later than 30-06-2021. d) Information concerning the in-house test procedures for SM-102 should be provided no later than 30-06-2021. e) Information concerning the validation reports for the in-house test procedures for SM-102 should be provided no later than 30-06-2021. f) Section 3.2.S.4.4 should be updated with batches of the excipient SM-102 that were included in the toxicological and the clinical studies. This information should be provided no later than 30-06-2021. g) Mutagenic impurities, including impurities originating from the starting materials, have not been discussed, discussion with regard to ICH M7 should be provided. Special attention should be set on the potential mutagenic primary halogens (i.e. starting material SM-102-11).		

		h) The assay limits and the purity limits in the specification of SM-102 are rather wide. A commitment should be provided to tighten the limits as appropriate as more experience is gained. The commitment should state the number of batches after which re-evaluation of the limits will be performed. Further investigation on the cause of the fluctuation in assay values should be performed. Assay and purity limits will be re-evaluated following production of 30 batches of SM-102 from Option B and revised specification will be submitted accordingly. 3) <u>Container Closure System</u> a) The SM-102 primary packaging information will be amended as agreed. All components are fully compliant with current international food contact regulations such as (EU) No 10/2011 This information will be provided no later than 31-03-2021. b) Specifications for the functional secondary packaging for SM-102 should be submitted no later than 31-01-2021. 4) <u>Stability</u> a) It should be clarified that the container closure systems as included in section S.6 and the commercial test procedures were used for the stability samples. A response no later than 31-01-2021 should be provided. b) The applicant should provide results from forced degradation studies for SM-102 no later than 31-03-2021. c) The applicant should provide post-approval stability protocol and stability commitments for SM-102 by 31-03-2021.		
Quality	5	**<u>PEG2000-DMG</u>** 1) <u>Manufacture</u> a) Details on the lyophilisation step of the manufacturing process should be provided no later than 30-06-2021. b) Information on the additional supplier(s) of starting material should be provided no later than 30-06-2021.	REC	See description

		c) The specifications for water content and high molecular weight in starting material should be stated with one decimal place. The information should be provided no later than 30-06-2021. d) A description of the analytical methods to control the starting materials should be provided no later than 30-06-2021. e) Information on analytical methods used for in-process testing should be provided no later than 30-06-2021. f) A justification for the starting materials should be provided including reactions schemes for the respective syntheses no later than 30-06-2021. 2) <u>Control of PEG2000-DMG</u> a) Polydispersity should be included in the specification for PEG2000-DMG. Additional data should be provided no later than 30-06-2021. b) The applicant should provide characterisation data for impurities, which are reported under 'content of unknown' by 30-06-2021. The specification and the reporting of impurities should be updated accordingly. c) Numerical limits for specified and unspecified impurities should be included in the PEG2000-DMG specification. The acceptance criteria for overall purity and moisture should be reported with one decimal place. This update should be provided no later than 30-06-2021. d) A risk assessment for the presence of benzene in PEG2000-DMG should be completed and the control strategy should be updated and submitted no later than 30-06-2021. e) Information on batches of the excipient PEG2000-DMG that were included in toxicological and clinical studies should be provided no later than 30-06-2021. f) In the description of the HPLC purity method information on the reporting threshold is missing and should be provided no later than 30-06-2021. g) Validation data for the analytical methods to control PEG2000 DMG are missing and should be provided no later than 30-06-2021.		

		h) Details with regard to the manufacturing data and the batch size should be provided for the batches provided in section '20 Batch analysis of GM-020' no later than 30-06-2021. i) Mutagenic impurities, including impurities originating from the starting materials, have not been discussed, discussion with regard to ICH M7 should be provided. 3) <u>Container Closure System</u> a) Information and specifications on the primary container used for the storage of PEG2000-DMG is missing and should be provided no later than 31-01-2021. 4) <u>Stability</u> a) The applicant should provide the post-approval stability protocol no later than 30-06-2021. b) The applicant should submit the results from the on-going PEG2000-DMG stability studies by 30-06-2021.		
Clinical	6	The applicant should thoroughly pre-plan analyses in a dedicated supplementary SAP (sSAP; to be submitted to EMA as soon as available), which allow to extract the best available information from the ongoing Phase 3 study with respect to duration of protection, correlate of protection, vaccine-enhanced disease, prevention of asymptomatic infection and other long-term safety data. This sSAP should be further discussed and agreed on with the EMA preferably in a scientific advice procedure.	REC	As soon as available
Clinical	7	Aside of the SOB above to provide the final CSR by end of 2022, it is recommended to prepare a separate CSR for part A of this study to be submitted as soon as available in 2021 (including outstanding results for prevention of asymptomatic infection).	REC	As soon as available
Non-clinical /Clinical	8	Provide data on cross-neutralisation for clinically relevant and emerging SARS-CoV-2 strains by testing both sera from vaccinated animals and human clinical trial participants in functional *in vitro* assays as well as conducting challenge/protection studies in animals.	REC	As soon as available
Clinical	9	Provide data on deep sequencing of virus breakthrough cases evaluated in the phase 3 trial to identify any potential gap in protection against mutant strains.	REC	As soon as available
Clinical	10	Provide interim updates on antibody persistence over time (Day 90, Day 180) evaluated in study mRNA-1273-P201.	REC	As soon as available

Clinical	11	Provide interim results of outstanding secondary & exploratory endpoints for study mRNA-1273-P301 as per protocol as soon as available	REC	As soon as available