EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2021
EMA/439844/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Spikevax

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

Procedure No. EMEA/H/C/005791/II/0021

Marketing authorisation holder (MAH) Moderna Biotech Spain, S.L.

Note

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

Table of contents

List of abbreviations

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AR	adverse reaction
bAb	binding antibodies
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMA	Conditional marketing authorisation
COP	correlate of protection
CoVs	Coronaviruses
COVID-19	Coronavirus disease 2019
DSMB	data safety monitoring board
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EUA	emergency use authorisation
FAS	full analysis set
FDA	Food and Drug Administration
GM	geometric mean
GMT	geometric mean titer
GMR	geometric mean ratio
IA	interim analysis
ID50	50% inhibitory dose
IgG	immunoglobulin
IP	investigational product
iPSP	investigational pediatric study plan
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MAAE	medically-attended adverse events
MIS-C	multisystem inflammatory syndrome in children
mITT1	modified intent-to-treat 1

mRNA	messenger ribonucleic acid
MSD	MesoScale Discovery
MSD-ECL	MesoScale Discovery electrochemiluminescence
MSSR	monthly safety summary report
NAAT	nucleic acid amplification test
nAb	neutralising antibody
NIAID	National Institute of Allergy and Infectious Diseases
NIM	noninferiority margin
NP	nasopharyngeal
PIP	paediatric investigation plan
PP	per-protocol
PSP	paediatric study plan
PsVNA	pseudotyped virus neutralising assay
PT	preferred term
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SMQ	standard Medical Dictionary for Regulatory Activities queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULOQ	upper limit of quantification
UTR	untranslated region
VE	vaccine efficacy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain, S.L. submitted to the European Medicines Agency on 5 June 2021 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include use in adolescents from 12 to 17 years of age for Spikevax; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance.

The variation requested amendments to the Summary of Product Characteristics and the Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 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 MAH 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.

Scientific advice

The MAH requested scientific advice at the CHMP on the clinical proposals for extending the indication under the conditional marketing authorisation, down to 12 years of age and the clinical development plan for variant vaccines of Spikevax. The scientific advice was ongoing at the time when this application was received.

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

Timetable	Actual dates
Submission date	5 June 2021
Start of procedure	8 June 2021
CHMP Rapporteur Assessment Report	15 July 2021
CHMP members comments	21 July 2021
ETF meeting	22 July 2021
Updated CHMP Rapporteur Assessment Report	22 July 2021
Opinion	23 July 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

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.

State the claimed therapeutic indication

The proposed indication and dosing administration for Spikevax are:

- **Proposed indication:** Active immunisation to prevent COVID-19 disease caused by SARS-CoV-2 virus, in individuals ≥12 years of age (extension including 12-17 year olds)
- **Dosing administration:** single 0.5-mL intramuscular (IM) dose followed by a second 0.5-mL dose 28 days later

Epidemiology and risk factors, screening tools/prevention

As of week 23 in 2021, there have been over 33 million confirmed cases of SARS-CoV-2 infection in the EU/EEA with approximately 734,000 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. Pre-existing medical conditions have also been suggested as a risk factor for severe disease and ICU admission in children and adolescents.

Increasing age is another risk factor for severe disease and death due to COVID-19. Individuals with high risk of exposure to SARS-CoV-2 due to occupation include healthcare and frontline workers.

There are currently several vaccines approved for prevention of COVID-19 in adults and elderly, but only one for the use in adolescents 12-17 years old. COVID-19 in adolescents is mostly a mild disease although severe cases also occur rarely.

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.

Clinical presentation, 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.

2.1.2. About the product

Spikevax (also referred to in this report as COVID-19 Vaccine Moderna or mRNA-1273) is a vaccine approved for the 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).

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.

Spikevax is administered intramuscularly in two 100 µg doses given 28 days apart. The vaccine is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH has applied for CHMP scientific advice on clinical proposals for extending the indication for this CMA down to 12 years of age and the clinical development plan for variant vaccines of Spikevax, which is currently under evaluation.

A PIP has been agreed (PIP P/0481/2020) and the current study is part of the PIP.

2.1.4. General comments on compliance with GCP

The MAH states that all clinical studies were performed in accordance with GCP. The current application is based on study P203 and the initial adult study P301, which was the pivotal phase 3 study included in the application for initial approval.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH 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.

- **Tabular overview of clinical studies**

With this submission, an extension of the indication of Spikevax is requested to include adolescents aged ≥ 12 to < 18 years based on the following: 1) safety and efficacy data, which includes a median of 53 days follow-up after dose 2, from the Phase 2/3 study mRNA-1273-P203 (Study P203); and 2) immunogenicity data from study P203 and from age group of the ≥ 18 to ≤ 25 years old from study mRNA-1273-P301 (Study P301) to infer vaccine effectiveness.

Table 1 Overview of the ongoing clinical studies with mRNA-1273 relevant for this submission

Study Number (Country)/ Status	Participants/Age Groups / Dose (Planned Participants)	Study Design	Vaccine Dose and Schedule	CSR Data Cutoff Points
mRNA-1273-P301 (US) Ongoing	Healthy adults Age groups: ≥18 years (n = 30,000) Dose groups: Placebo (n = 15,000) mRNA-1273 100 µg (n = 15,000)	Phase 3, randomized, stratified, observer-blind, placebo-controlled	100 µg mRNA-1273 or placebo 2 IM doses, 28 days apart	Interim CSR: Efficacy: -Interim efficacy analysis (11 Nov 2020 data cutoff/ DS1) - Primary efficacy analysis (25 Nov 2020 data cutoff/ DS2) - Supplemental efficacy results from the final blinded efficacy analyses for the primary and secondary efficacy endpoints based on the blinded phase. Immunogenicity: - bAb and nAb in a subset of participants Safety: - Safety data from the final blinded analyses based on the blinded phase will be included in the CSR.
mRNA-1273-P203 (US)/ Ongoing	Healthy adolescents Age group: ≥12 to <18 years N = 3,000 planned mRNA-1273 n = ~2000 placebo n = ~1000	Phase 2/3, randomized, observer-blind, and placebo-controlled	100 µg mRNA-1273 or placebo (2:1) 2 IM doses, 28 days apart	Safety: Day 57 (1-month post dose 2) for full cohort (2:1) Efficacy/Immunogenicity: Day 57 serum antibody (Ab) response in a subset of 550 participants (2:1)

2.3.2. Pharmacodynamics

Immunogenicity results are presented together with the efficacy analysis in section 2.4.

2.4. Clinical efficacy

2.4.1. Main study

Study mRNA-1273-P203

Study P203 is an ongoing, two-part (Part A and Part B), Phase 2/3, randomised, observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, and efficacy of Spikevax (also referred to as mRNA-1273 vaccine) in healthy adolescents aged ≥ 12 to < 18 years. Vaccine efficacy is inferred based on demonstrating non-inferiority of both the (a) geometric mean (GM) value of serum antibody (Ab) and (b) the seroresponse rate from adolescent participants - with both measures compared with those obtained from young adults (≥ 18 to ≤ 25 years of age) enrolled in the ongoing adult study (Study P301). Additionally, secondary study endpoints assessed the effect of Spikevax on COVID-19 and asymptomatic infection as measured by RT-PCR testing of mucosal samples and serologic assessment of SARS-CoV-2 infection. For this study, baseline SARS-CoV-2 status was determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1.

To support the use of the Spikevax in adolescents (aged ≥12 to <18 years), immunogenicity data from young adults (aged ≥18 to ≤25 years) from study P301, based on a database lock date of 04 May 2021, were used as a comparator group to infer vaccine efficacy to adolescents aged ≥12 to <18 years. Study P301 is the ongoing pivotal randomised, observer-blind, placebo-controlled study that supported the indication of Spikevax in adults ≥ 18 years of age. In study P301, more than 30,000 participants were randomised and >96.7% participants received dose 2 of mRNA-1273.

Methods

Study participants

Part A of study P203

Inclusion criteria:

Each participant must meet all of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

- Male or female, 12 to < 18 years of age at the time of consent (Screening Visit, Day 0) who, in the opinion of the investigator, is in good general health based on review of medical history and screening physical examination.
- Investigator assessment that the participant, in the case of an emancipated minor, or parent(s)/legally acceptable representative(s) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures and provides written informed consent/assent.
- Body mass index (BMI) at or above the third percentile according to World Health Organization (WHO) Child Growth Standards at the Screening Visit (Day 0).

- Female participants of non-childbearing potential may be enrolled in the study.
- Non-childbearing potential is defined as premenarche or surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy).
- Female participants of childbearing potential may be enrolled in the study if the participant fulfils all the following criteria:
    - Has a negative pregnancy test at Screening (Day 0), on the day of the first injection (Day 1), and on the day of the second injection (Day 29)
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1)
    - Has agreed to continue adequate contraception or abstinence through 3 months following the second injection (Day 29).

Exclusion Criteria:

Participants who meet any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

- Travel outside of the United States in the 28 days prior to the Screening Visit (Day 0).
- Pregnant or breastfeeding.
- Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
- Prior administration of an investigational CoV (eg, SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus [SARS-CoV], Middle East Respiratory Syndrome coronavirus [MERS-CoV]) vaccine.
- Current treatment with investigational agents for prophylaxis against COVID-19.
- Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
- Current use of any inhaled substance (e.g. tobacco or cannabis smoke, nicotine vapours).
- History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).
- History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of screening.
- History of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - Congenital or acquired immunodeficiency, including human immunodeficiency virus (HIV) infection
    - Suspected active hepatitis
    - Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - Dermatologic conditions that could affect local solicited AR assessments

- History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine
- Diagnosis of malignancy within the previous 10 years (excluding non-melanoma skin cancer)
- Febrile seizures.

- Receipt of:
  - Any licensed vaccine within 28 days before the first dose of investigational product (IP) or plans for receipt of any licensed vaccine through 28 days following the last dose of IP.
  - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrolment (for corticosteroids, ≥ 20 mg/day prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the day of enrolment. Participants may have visits rescheduled for enrolment if they no longer meet this criterion within the Screening Visit window.
  - Inhaled, nasal, and topical steroids are allowed.
  - Intravenous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrolment.
- Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.
- Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.
- Is an immediate family member or has a household contact who is an employee of the research centre or otherwise involved with the conduct of the study.

Study Eligibility Criteria (Part B):

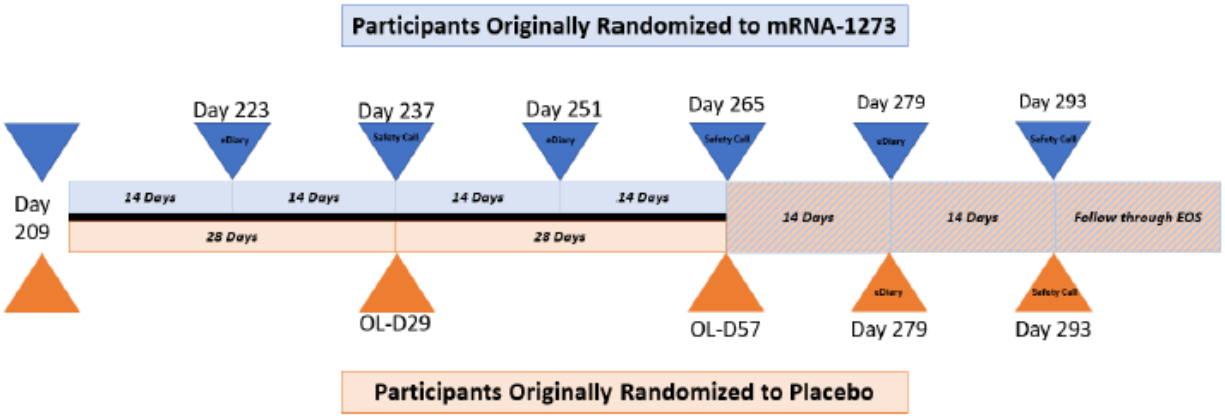
- Participants must have been previously enrolled in the mRNA-1273 P203 study.
- Female participants of childbearing potential may be enrolled in the study if the participant has a negative pregnancy test on the day of the first injection (OL-Day 1) and on the day of the second injection (OL-Day 29).

The CHMP considered the inclusion and exclusion criteria to be acceptable. There is good concordance with the adult population included in study P301 which is paramount for the immunobridging strategy.

Treatments

In Part A, the blinded phase of the study, each participant received either two doses of 0.5mL of Spikevax (100 µg) or placebo (0.9% sodium chloride) by intramuscular injection 28 days apart (i.e. Day 1 and Day 29). The protocol specified a window of +7 days for administration of the second dose.

In part B the open-label phase of the study, mRNA-1273 vaccine will be administered intramuscularly following the injection schedule for each group based on the product received in Part A. Participants who received placebo in Part A will receive 2 doses of mRNA-1273 (100 µg) on open-label (OL) – Day 1 and OL-Day 29 of Part B (see schedule below).



Objectives

Primary objectives

- To evaluate the safety and reactogenicity of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart
- To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart), serum Ab responses obtained 28 days after the second injection of mRNA-1273 (Day 57) will be either:
  - Evaluated against an accepted Ab threshold of protection against COVID-19 (if established in study P301)
  - Compared in primary vaccine response as measured by GM values of serum Ab and seroresponse rate in study P203 with those obtained from young adult recipients (18-25 years of age) of mRNA-1273 in the clinical endpoint efficacy trial (Study P301).

Secondary objectives

- To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of SARS-CoV-2 S2P-specific bAb through 1 year after Dose 2
- To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of nAb through 1 year after Dose 2
- To evaluate the effect of mRNA-1273 on the incidence of SARS-CoV-2 infection compared with the incidence among placebo recipients
  - To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo
  - To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with SARS-CoV-2 infection AND positive RT-PCR for SARS-CoV-2.

Exploratory Objectives

- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence
- To describe the ratio or profile of specific bAb relative to nAb in serum

- To characterise the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline.

The CHMP endorsed the study objectives.

Outcomes/endpoints

Primary Safety Endpoints

- Solicited local and systemic ARs through 7 days after each injection
- Unsolicited AEs through 28 days after each injection
- MAAEs through the entire study period
- SAEs through the entire study period
- AESI of MIS-C through the entire study period
- ≥Physical examination findings.

Primary Immunogenicity Endpoints

- The proportion of participants with a serum Ab level at Day 57 ≥ an Ab threshold of protection

  (Note: If an accepted serum Ab threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy)

- The primary vaccine response as measured by GM value of serum Ab level and seroresponse rate from study P203 vaccine recipients at Day 57 compared with those obtained from young adult recipients (≥18-<25 years of age) at Day 57 in the clinical endpoint efficacy trial (Study P301).

  (Note: If an accepted serum Ab threshold is not available, efficacy will be inferred based on establishing noninferiority of adolescent (≥12 to < 18 years; this clinical study) to adult GM values of serum Ab and seroresponse rate obtained in Study P301 (GM value ≥12 to < 18 years / GM value ≥18 to <25 years).

Seroresponse due to vaccination at a subject level may be defined as a change from below the LLOQ to equal to or above LLOQ, or a z-fold rise if baseline is equal to or above LLOQ. The definition of seroresponse may depend on assay-specific performance characteristics, and Table 2 lists the assay-specific definition of seroresponse for each assay/test of interest.

Table 2: Serological assays for immunogenicity assessment

Assay Name	Category	Test Name/ Description	Definition of Seroresponse
Pseudovirus (PsVNT)	nAb	PsVNT50 (ID 50)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 3.3-fold rise
		PsVNT80 (ID 80)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 2.3-fold rise

Anti-Spike ELISA	bAb	Anti-Spike VAC65 Spike IgG Antibody	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 4.6-fold rise
MSD multiplex	bAb	Anti-Spike	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 1.9-fold rise

Among the two pseudovirus tests, PsVNT50 and PsVNT80, PsVNT50 is considered the most appropriate measure of subject response because it falls in the middle of the dynamic range of the dilution response curve while PsVNT80 is close to the plateau and thus subject to restriction.

The GM and seroresponse rate comparisons between adolescents in study P203 and young adults (≥18-<25 years of age) in study P301 will be compared for the bAb and nAb measures listed in Table 2, with Pseudovirus nAb PsVNT50 (ID50) considered as the primary assay for the immunobridging.

Secondary Efficacy/Immunogenicity endpoints

The secondary objective will be evaluated by the following endpoints:

- The GM values of SARS-CoV-2 S2P-specific bAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2).
- The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2).
- The incidence of SARS-CoV-2 infection counted starting 14 days after the second dose of IP. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:
    - bAb levels against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive starting at Day 57 or later. OR
    - Positive RT-PCR counted starting 14 days after the second dose of IP.
- The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) counted starting 14 days after the 2nd dose of IP in participants with negative SARS-CoV-2 at baseline.
- The incidence of the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria:
    - The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥38ºC/≥ 100.4ºF), 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 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalised) positive for SARS-CoV-2 by RT-PCR.
- The incidence of the first occurrence of the secondary COVID-19 case starting 14 days after the first dose of IP, and the secondary COVID-19 case starting 14 days after the second dose of IP.
- The secondary case definition of COVID-19 is defined by the following criteria:

- One of the following systemic or respiratory symptoms: fever (temperature >38ºC/≥100.4ºF), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhoea, AND
- At least one positive RT-PCR test for SARS-CoV-2.

Exploratory Endpoints

The exploratory endpoints are the following:

- The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR test performed at least 14 days after first dose, and by bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) at Day 57.
- Alignment of genetic sequence of viral isolates with that of the vaccine sequence.
- Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum.
- Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19).
- GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x and 4x rise of bAb relative to baseline.

Laboratory tests

Besides the serological assays listed in Table 2 the following assays were employed to assess SARS-CoV-2 baseline status and efficacy endpoints

- RT-PCR
- anti-Nucleocapsid antibody assay by Elecsys.

Information on assay validation and the laboratories involved in the evaluation are available for all assays used.

The CHMP noted the evidence of acceptable assay control, assay validation and sample storage provided. Studies on sample stability are ongoing; the respective validation reports should be provided upon completion (**REC**). The full bioanalytical report is not available yet and should be provided upon completion of the study (**SOB**).

The CHMP considered the selection and definition, time point as well as the applied non-inferiority margin to be acceptable for the immunobridging concept and in line with provisions as per variant RP (indent on naïve population) with the definition of seroresponse being an exception (i.e. protocol stipulating other than 4-fold increases above BL and/or threshold crossing in case of <LLOQ instead of using nominal value replacement).

Sample size

The overall sample size of the study was driven by safety. Approximately 3,000 participants were to be randomly assigned in a 2:1 ratio to receive mRNA-1273 and placebo. With 2,000 participants exposed to mRNA-1273, the study was planned to have at least 90% probability to observe at least 1 participant with an AE at a true 0.25% AE rate.

Sample size for immunogenicity subset

Serum samples from all participants were to be collected and banked, a subset of participants was to be selected, and their samples were to be processed for immunogenicity testing (the Immunogenicity Subset). Approximately 362 participants who receive mRNA-1273 were to be selected for the Immunogenicity Subset, with a target of 289 participants in the PP Immunogenicity Subset (adjusting for approximately 20% of participants who may be excluded from the PP Immunogenicity Subset, as they may not have immunogenicity results due to any reason).

In case an acceptable Ab threshold of protection against COVID-19 was available for the primary immunogenicity objective, with approximately 289 participants in the PP Immunogenicity Subset, the study was considered to have > 90% power to rule out 70% with a 2-sided 95% CI for the percentage of mRNA-1273 participants exceeding the acceptable threshold if the true rate of participants exceeded the acceptable threshold is 80%.

If an acceptable Ab threshold of protection against COVID-19 was not available at the time of analysis, for the primary immunogenicity objective, non-inferiority tests of two null hypotheses based on two coprimary endpoints, respectively, were to be performed:

With approximately 289 participants in the PP Immunogenicity Subset in study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from study P301, there was to be 90% power to demonstrate non-inferiority of the immune response as measured by Ab GM in adolescents in study P203 at a 2-sided alpha of 0.05, compared with that in young adults (18-25 years of age) from study P301 receiving mRNA-1273, assuming an underlying geometric mean titers (GMR) value of 1, a non-inferiority margin of 1.5, and a point estimate minimum threshold of 0.8. The standard deviation (SD) of the log-transformed levels was assumed to be 1.5.

With approximately 289 participants in the PP Immunogenicity Subset in study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from study P301, there was to be at least 90% power to demonstrate non-inferiority of the immune response as measured by sero-response rate in adolescents in study P203 at a 2 sided alpha of 0.05, compared with that in young adults (18-25 years of age) from study P301 receiving mRNA 1273, assuming a true sero-response rate of 85% in young adults (18-25 years of age) from study P301, and a true sero-response rate of 85% in adolescents in study P203 (i.e., true rate difference is 0 compared to young adults from study P301), a non-inferiority margin of 10%, and a point estimate minimum threshold of -5% in sero-response rate difference.

Overall, the CHMP endorsed the sample size considerations, both for the overall trial size as well as for the immunogenicity subset. It is noted that even less frequent AEs are observable with > 90% probability at least once. The claimed probability of ≥ 90% to observe AEs which occur in 0.25% of subjects would even be achieved with around 1,000 participants, i.e., the study is overpowered for the claimed goal. Overall, the sample size is appreciated, however. The power for immunogenicity analysis was always estimated to be above 90% based on the assumptions provided. If a correlate of protection (COP) was established the power for the expected to be > 97%. Similarly, it seems that in case no COP was established, the power for the geometric mean titers (GMR) is around 97% given the assumptions made. Under the made assumptions, the power for sero-response was estimated to be about 92%. While both serologic endpoints were required, the power for this analysis was hence seemingly driving the sample size in the immunogenicity subset. The sample size is sufficient for the immunogenicity analysis.

- **Randomisation**

Random assignment of participants in a 2:1 ratio was based on a centralised interactive response technology, in accordance with pre-generated randomisation schedules. No strata for randomisation were defined in study P203.

Immunogenicity Sampling Plan for study P203

For the primary analysis of immunogenicity, and charactering immunogenicity of the vaccine, a simple, very pragmatic sampling method was to be used for measuring bAb and nAb data from a subset of trial participants. The first 550 participants enrolled in Part A were to be selected who met the following the criteria:

- The participant is in Full Analysis Set.
- Baseline SARS-CoV-2 status is not missing.

Hence, approximately only 362 participants who received mRNA-1273 were to be selected for the Immunogenicity Subset, with a target of 289 participants in the PP Immunogenicity Subset after adjusting for approximately 20% of participants not meeting inclusion criteria for PP Immunogenicity Subset, resulting in a set size of approximately 289 participants, which is endorsed.

The pragmatic sampling approach itself, however, might lead to a biased subset if the participant population was to change over time, which could be reasonably assumed. Upon review of side-by-side tables for the different analysis sets, which are discussed below, there might be slight imbalances (e.g. in age and race/ethnicity) between the FAS and the immunogenicity samples, which could affect the overall representativeness of the immunogenicity estimates for the overall population. As subgroup analyses were provided as well, this issue can however be considered minor.

The MAH further argued that due to a very quick enrolment in less than three months no marked time difference between the first 550 and the overall population existed. This argument is only partially shared as differences in the willingness to participate in such a trial might occur regardless of calendar time and hence the population might change.

Immunogenicity Sampling Plan for study P301

An immunogenicity subset of 340 young adults from study P301 was to be randomly selected from all participants (18-25 years of age) receiving mRNA-1273, with a target of 289 participants in the PP Immunogenicity Subset (using same definition as in study P203) after adjusting for approximately 15% of participants not meeting inclusion criteria for PP Immunogenicity Subset.

The CHMP endorsed the overall randomisation to treatment arms. The selection of immunogenicity subsets is not considered optimal and not well documented.

The random sampling took place prior to evaluating the blood samples and only the blood samples of the randomly selected subjects were evaluated in the laboratory. Hence, no data driven choices based on immunogenicity data could be made for study P301, while clinical efficacy data in principle might have been able to influence the choice. It is not assumed that this has happened and even if so, it is not expected that this would affect the results in a meaningful way.

The anticipated rates of participants in the immunogenicity subset who do not meet the PP definition were substantially higher than the observed rates. In study P203 the "dropout" rate was only ~9% (rather than the assumed 20%) and in study P301 ~10% (rather than the assumed 15%). Of note the assumed rates from the immunogenicity to the immunogenicity PP set were different for study P301 and study P203.

- **Blinding (masking)**

Part A of this study was to be observer-blind. The investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) were to be blinded to the IP administered until study end or initiation of Part B, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) was to be assigned to vaccine accountability procedures and was to prepare and administer mRNA-1273 (or placebo) to all participants.

- Unblinded study site monitors, not involved in other aspects of monitoring, were to be assigned as the IP accountability monitors.
- An unblinded statistical and programming team was to perform the pre-planned interim analyses (IA). Sponsor team members were to be pre-specified to be unblinded to the IA results and were not to communicate the results of IA to the blinded investigators, study site staff, clinical monitors, or participants. This was to be detailed in the study Data Blinding Plan.

In Part A, the dosing assignment was to be concealed by having the unblinded pharmacy personnel prepare the IP in a secure location that is not accessible or visible to other study staff. 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 to that of placebo. Access to the randomisation code was to be strictly controlled at the pharmacy.

A limited number of Sponsor and CRO personnel was to be unblinded for the interim analyses. The purpose of the unblinding was to enable the group to develop regulatory submission documents and to address questions from regulatory agencies during the regulatory review of the submission. After unblinding, this unblinded team was not to participate in the conduct or execution of the subsequent course of the study. The study Data Blinding Plan provides details of the blinding/unblinding process and personnel. The study site staff, investigators, study monitors, and participants were to remain blinded until the initiation of Part B.

Individual unblinding of participants was possible in specific situations (e.g. due to SAEs, medical emergencies, pregnancy). Unblinding was to be documented in a timely fashion.

Overall, the CHMP considered the blinding procedure to be reasonable. The laboratories who analysed the serum samples for immunogenicity analyses were blinded to the time-point when the sample was collected (baseline or follow up) and that samples from both studies were analysed at the same time. All lab analyses were conducted in the same labs (PsVNA was performed at Duke University, anti-S ELISA and MSD 3-plex at PPD Vaccine Laboratory) for all samples. It was further clarified that age was not "specifically provided to testing labs", but that subject IDs were provided to the labs. This means that identification of the study might have been possible, while otherwise some level of blinding at the laboratory can be reasonably assumed. From the reply and the display in the SAP and study protocol, it is assumed that blood samples were drawn from all of the first ~550 subjects enrolled in Study P203 but only the samples from vaccinated subjects were subsequently analysed. This is important to maintain the blinding of participants enrolled in the trial. Likewise, it is assumed that blood samples from all participants in study P301 were collected as otherwise the sampling approach described above would not have been possible. Although the timing of the unblinding of the study team is not entirely clear, this is not considered to impact the immunogenicity analysis in a meaningful way.

- **Statistical methods**

Analysis sets

The MAH defined in total 9 analysis sets, see Table 3. The most relevant analysis sets for immunogenicity was to be the PP immunogenicity set (a subset of subjects selected for immunogenicity testing [see Randomisation] who were observed and treated according to protocol). For efficacy, the PP efficacy set was planned to be used as primary analysis set, with supplementary analyses in the FAS, mITT set, and mITT1 set. For safety analyses, the safety set was to be used.

Table 3: Analysis sets

Analysis Set	Description
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least 1 injection of IP.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing.
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset who received planned doses of study vaccination per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise.
PP Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, had no immunologic or virologic evidence of prior COVID-19, and have no major protocol deviations that impact key or critical efficacy data.
Solicited Safety Set	The Solicited Safety Set consists of FAS participants who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Safety Set	All randomized participants who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline
Modified Intent-to-Treat-1 (mITT1) Set	All participants in the mITT Set excluding those who received the wrong treatment (ie, at least 1 dose received in Part A is not as randomized).

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID 19 = coronavirus disease 2019; FAS = full analysis set; IP = investigational product; mITT = modified intent-to-treat; PP = per protocol; RT-PCR = reverse transcription polymerase chain reaction.

Immunogenicity analyses

If an accepted serum Ab threshold of protection against COVID-19 was available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 were to be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group was > 70%, the primary immunogenicity objective of this study was to be considered met. The percentage of participants with serum Ab greater than or equal to the threshold with 95% CI were to be provided at each post-baseline time point.

If an accepted serum Ab threshold of protection against COVID-19 was not established, the non-inferiority of primary vaccine response as measured by Ab GM and sero-response rate in adolescents

compared with those in young adults (18-25 years of age) receiving mRNA-1273 was to be assessed as co-primary immunogenicity endpoints.

An analysis of covariance (ANCOVA) model was to be carried out with Ab value at Day 57 as a dependent variable and group (adolescents in Study P203 and young adults in study P301) as fixed variable. The GM values of the adolescents at Day 57 was to be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) was to be estimated by the ratio of GLSM from the model. A corresponding 2-sided 95% CI was to be provided to assess the difference in immune response for the adolescents in Study P203 compared to the young adults (18-25 years of age) in study P301 at Day 57. The non-inferiority of immune response to mRNA-1273 as measured by GM was considered to be demonstrated if the lower bound of the 95% CI of the GMR was > 0.67 based on the non-inferiority margin of 1.5, and the GMR point estimate was > 0.8 (minimum threshold).

The difference of sero-response rates between adolescents receiving mRNA-1273 in Study P203 and young adults (18-25 years of age) receiving mRNA-1273 in study P301 was to be calculated with 95% CI. The non-inferiority in seroresponse rate of adolescents in study P203 compared to young adults (18-25 years of age) in study P301 was to be considered demonstrated if the lower bound of the 95% of the sero-response rate difference is > -10%, based on the non-inferiority margin of 10%, and the sero-response rate difference point estimate > -5% (minimum threshold).

In addition, the GM level of specific nAb and bAb with corresponding 95% CI was to be provided at each time point. The 95% CIs were to be calculated based on the t-distribution of the log transformed values then back transformed to the original scale. The geometric mean fold-rise (GMFR) of nAb and bAb with corresponding 95% CI was to be provided at each time point with Day 57 as the primary time point of interest.

Interim analyses

- The first interim analysis for *safety and efficacy* was to be performed after at least 1,500 participants (1,000 participants receiving mRNA-1273) completed Day 57 (one month after dose 2, Part A).
- The second interim analysis for *immunogenicity, safety and efficacy* was to be performed after Day 57 immunogenicity data were available for the immunogenicity subset. This interim analysis was to be considered as the primary analysis of immunogenicity.
- The final analysis of all applicable endpoints is planned to be performed after all participants have completed all planned study procedures. Results of this analysis are planned to be presented in an end of study CSR, including individual listings.

Analysis sets

Overall, the CHMP considered the primary analysis sets to be acceptable. The huge amount of defined analysis sets suggests more "sensitivity analyses" and – if these are in line – more robustness than actually supported by the data. E.g. the PP efficacy set and the mITT set were almost identically defined and only differed in the exclusion of patients with major protocol deviations, which might affect efficacy endpoints, from the former set. The mITT1 set is even closer to the PP efficacy set by excluding subjects who were not treated as randomised. Actually, this definition is considered to be very close to a PP set.

Immunogenicity analyses

Overall, the CHMP endorsed the planned immunogenicity analyses. The comparison of immunogenicity data with external controls from Study s301 is considered a pragmatic and acceptable approach.

The primary comparison in case no COP was established (the current situation) was not planned to be adjusted for any potential confounders. This is not considered optimal for a formal proof of non-

inferiority. Comparisons of baseline characteristics between the analysis sets and studies provided some reassurance that the data was collected in overall comparable populations (see below). However, it cannot be fully excluded that subjects differ "immunologically" between studies; see also the discussions on randomisation, choice of immunogenicity subsets and blinding. In the light of the obtained results, this can however be considered negligible.

No methodological details on the analyses of sero-response rate were provided with the protocol and SAP. The definition of sero-response was only defined in the SAP version 2. It is noted, however, that only the definition of seroresponse for sero-positive patients was critical. For the majority of subjects in the sero-negative population of primary interest sero-response was defined as change from Ab levels below the LLOQ to levels equal to or above the LLOQ. Only very few subjects had measurable Ab levels at baseline. Hence, this is not considered a critical issue for this procedure.

It was noted that the SAP Version 2 defined the visit windows applicable to immunogenicity analysis (as well as safety and efficacy) very liberal and wide. The relevant Day 57 visit window for the primary immunogenicity analysis spans from Day 44 post the first injection to Day 133, i.e., from roughly 6 weeks to as much as 19 weeks with a target of 8 weeks. Per the SAP visit schedule, however, immunogenicity blood samples were to be collected only at Day 1 (prior to vaccination, no tolerance window) and Day 57 (+7 days). The provided information is at least unclear or even contradictory. The PP immunogenicity subset was defined as all subjects who complied with the immunogenicity testing schedule.

Efficacy analyses

For vaccine efficacy analyses, SARS-CoV-2 infection, asymptomatic SARS-CoV-2 infection, COVID-19 and COVID-19 per secondary case definition, were to be analysed. For these analyses VE was to be defined as 1 – ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio was to be calculated using the exact method conditional upon the total number of cases adjusted by the total person-time. Person-time was to be defined as the total time from randomisation date to the date of event, last date of study participation, censoring time, or efficacy data cut-off date, whichever was earlier.

Interim analyses

The timing and nature of interim analyses was changed from SAP version 1 to version 2. The first interim for efficacy and safety was newly introduced with version 2 and replaces an interim analysis for safety, which was previously planned after approximately 250 participants (16-17 years of age) have completed Day 57.

At the EMA/Rapporteur meeting held on 7th May 2021, the MAH presented interim analyses results for efficacy. These were not pre-planned in SAP version 1 and also do not match the first interim analysis planned in SAP version 2. While efficacy data were anyway not under type 1 error control this however leaves some uncertainty as regards the blinding of the MAH during the conduct of trial. Of note, SAP version 2 was prepared on 7th May 2021, i.e., at the very same day as the EMA/Rapporteur meeting was held. During the meeting the MAH was asked for the document which defined the presented interim analysis and could not refer to the updated SAP. It is hence likely that the SAP was finalised after the meeting and after the analyses were conducted, i.e. post hoc. A request for further information on the conducted interim analyses did not provide further clarity. It appears that several "descriptive analyses" were conducted.

The timing and order of interim analyses 1 and 2 as defined in SAP version 2 remain somewhat unclear. Interim analysis 1 was to be conducted after at least 1,500 participants (over both arms) had completed Day 57. Interim analysis 2 was to be conducted after immunogenicity data were available for the immunogenicity subset, and this was planned to happen earlier, already after ~550 participants (over both arms) had had their Day 57 visit. The only reason for interim analysis 2 to happen later is potentially

the "availability" of the immunogenicity data, which is driven by the lab analyses. This unspecific timing of analyses for efficacy and safety theoretically leaves room for data-driven approaches.

Importantly and the above notwithstanding, the efficacy analyses are only considered as supportive in the trial, while the immunobridging approach serves as the main and acceptable basis for inferring efficacy.

Results

Participant flow

In study mRNA-1273-P203 subjects ≥12 to <18 years of age were enrolled. The disposition of subjects enrolled is detailed in Table 4 below.

Table 4: Subject disposition

	mRNA-1273 n (%)	**Placebo n (%)**	**Total n (%)**
Randomized	N=2489	N=1243	N=3732
Completed 1 dose	2486 (99.9)	1240 (99.8)	3726 (99.8)
Completed 2 doses	2480 (99.6)	1222 (98.3)	3702 (99.2)
Discontinued from study	57 (2.3)	188 (15.1)	245 (6.6)
Reason for discontinuation			
Adverse event	1 (<0.1)	0	1 (<0.1)
Withdrawal by participant	27 (1.1)	102 (8.2)	129 (3.5)
COVID-19 Non-infection related	2 (<0.1)	13 (1.0)	15 (0.4)
Other	25 (1.0)	89 (7.2)	114 (3.1)
Lost to follow-up	3 (0.1)	6 (0.5)	9 (0.2)
Protocol deviation	8 (0.3)	14 (1.1)	22 (0.6)
Physician decision	1 (<0.1)	0	1 (<0.1)
Other	17 (0.7)	66 (5.3)	83 (2.2)
Safety Set[a]	N=2486	N=1240	N=3726
Completed 2 doses	2479 (99.7)	1222 (98.5)	3701 (99.3)
Median follow-up post dose 2 (days)[b]	53.0	51.0	53.0
Completed at least 1 month follow-up post dose 2	2452 (98.6)	1173 (94.6)	3625 (97.3)
Completed at least 2 months follow-up post dose 2	1087 (43.7)	474 (38.2)	1561 (41.9)
Solicited Safety Set[c]	N=2485	N=1240	N=3725
First Dose Solicited Safety Set	2482 (99.8)	1238 (99.8)	3720 (99.8)
Second Dose Solicited Safety Set	2478 (99.7)	1220 (98.4)	3698 (99.2)
Full Analysis Set[d]	N=2486	N=1240	N=3726
mITT Set[e]	N=2167	N=1075	N=3242
mITT1 Set for Efficacy[f]	N=2163	N=1073	N=3236
Excluded from mITT1 Set for Efficacy	326 (13.0)	170 (13.68)	496 (13.29)
Reason for exclusion			
Randomized but not dosed	3 (0.12)	3 (0.24)	6 (0.16)
Positive or missing baseline SARS-CoV-2 status	319 (12.82)	165 (13.27)	484 (12.97)
Received incorrect vaccination	4 (0.16)	2 (0.16)	6 (0.16)

PP Set for Efficacy[g]	N=2139	N=1042	N=3181
Excluded from PP Set for Efficacy	350 (14.06)	201 (16.17)	551 (14.76)
Reason for exclusion			
Randomized but not dosed	3 (0.12)	3 (0.24)	6 (0.16)
Positive or missing baseline SARS-CoV-2 status	319 (12.82)	165 (13.27)	484 (12.97)
Discontinued study treatment or participation without receiving dose 2	2 (0.08)	13 (1.05)	15 (0.40)
As of cutoff date[h], not received dose 2 and passed window of +14 days	1 (0.04)	0	1 (0.03)
Received incorrect vaccination	4 (0.16)	2 (0.16)	6 (0.16)
Received dose 2 out of window	21 (0.84)	18 (1.45)	39 (1.05)
Immunogenicity Subset[i]	N=374	–	–
PP Immunogenicity Subset[j]	N=340	–	–
Excluded from PP Immunogenicity Subset[k]	34 (9.1)	–	–
Reason for exclusion			
Positive baseline SARS-CoV-2 status	26 (7.0)	–	–
Received dose 2 out of window	8 (2.1)	–	–

Abbreviations: Ab = antibody; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; FAS = Full Analysis Set; IP = investigational product; mITT = modified intent-to-treat; PP = per-protocol; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
Note: Percentages are based on the number of participants (N) for each analysis set, except for exclusions from mITT1 Set for Efficacy and PP Set for Efficacy where N is based on the Randomized Set.

a The Safety Set consists of all randomized participants who received any study injection.
b Study duration from second injection is 0 day for participants who did not receive dose 2.
c The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). Numbers are based on actual treatment group and percentages are based on the number of safety participants.
d The FAS consists of all randomized participants who received at least 1 dose of IP. Numbers are based on planned treatment group.
e The mITT Set consists of all participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) before the first dose of IP, ie, all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline. Numbers are based on planned treatment group.
f The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (ie, at least 1 dose received in Part A was not as randomized). Numbers are based on planned treatment group.
g The PP Set for Efficacy consists of all participants in the FAS who meet all the following criteria: received planned doses of study vaccination; complied with the timing of dose 2; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; and had no major protocol deviations that impacted key or critical efficacy data. Numbers are based on planned treatment group.
h For Study P203, data cutoff refers to the data snapshot date (08 May 2021).
i The Immunogenicity Subset consists of participants in the FAS who had baseline SARS-CoV-2 status available and had baseline and at least 1 post-injection antibody assessment for the analysis endpoint.
j The PP Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of dose 2; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data.
k A participant who has multiple reasons for exclusion is listed under the reason that appears earliest. Percentages are based on the number of participants in the Immunogenicity Subset.

Of the 374 mRNA-1273 participants in study P203 selected for the Immunogenicity Subset, 34 were excluded from the PP Immunogenicity Subset for the following reasons: baseline SARS-CoV-2 positive or missing (26 participants), or received dose 2 outside of [21, 42] days after dose 1 (8 participants).

Table 5: Summary of Reasons for Exclusion from Per-Protocol Immunogenicity Subset (Immunogenicity Subset)

P203 mRNA-1273			
	≥12 to <16 Years	≥16 to <18 Years	Overall
Immunogenicity Subset	N=265	N=109	N=374
Per-Protocol Immunogenicity Subset, n (%)	239 (90.2)	101 (92.7)	340 (90.9)
Excluded from Per-Protocol Immunogenicity Subset, n (%)	26 (9.8)	8 (7.3)	34 (9.1)

Reasons for Exclusion, n (%) [1]			
Received Incorrect Vaccination	0	0	0
Received Dose 2 Out of Window	5 (1.9)	3 (2.8)	8 (2.1)
Did not Receive Dose 1 per Schedule	0	0	0
Did not Receive Dose 2 per Schedule	0	0	0
Positive Baseline SARS-CoV-2 Status	21 (7.9)	5 (4.6)	26 (7.0)
Missing Baseline SARS-CoV-2 Status	0	0	0
Had no Immunogenicity Data at Day 57	0	0	0
Had Other Major Protocol Deviations	0	0	0

As comparator arm for the immunogenicity subset, 340 subjects aged ≥18 to ≤25 years were randomly selected from all participants in that age group enrolled in the mRNA-1273 group of study P301. Of the 340 selected, 35 were excluded from the PP Immunogenicity Subset for the following reasons: baseline SARS-CoV-2 positive or missing (17 participants), did not receive dose 2 per schedule (16 participants), or received dose 2 outside of [21, 42] days after dose 1 (2 participants).

Conduct of the study

Timing of the Application

A data snapshot for this submission was triggered on 08 May 2021 based on the availability of immunogenicity data from Study P203, resulting in a median study follow-up duration of 53 days after dose 2. This analysis included a total of 3,732 participants (3,726 participants randomised and received study treatment, with 1,240 participants randomised to placebo and 2,486 participants randomised to mRNA-1273).

Changes in primary immunogenicity endpoint(s) and evaluation:

- In case a protective threshold was established, the response rate based on **SARS-CoV-2 S protein (S2P)** serum Abs was initially to be compared against a response rate of ≤ 60%. This was changed to a serum Ab threshold which was to be compared against a response rate of **≤ 70%**.
- In case no protective threshold was established, the GM serum **neutralising** Ab level was replaced by GM serum Ab level **and sero-response rate.** The lower bound for GMR was changed from 0.5 to 0.67 (equivalently the NI margin was changed from 2 to 1.5). The definition of sero-response was to be defined in the SAP only based on outstanding information about assay performance. The lower margin was newly defined as -10%.
- Comparison was initially planned against study P301 subjects ≥ 18 years and changed to subjects 18 to 25 years.
- The immunogenicity subset (mRNA-1273 subjects only) was increased from 210 to 362 and the PP immunogenicity subset was increased from 178 to 289 subjects.
- mITT and mITT1 sets were newly defined.
- An additional safety interim analysis was introduced after 250 subjects in the cohort of subjects 16-17 years of age.
- The immunogenicity and safety analysis was planned earlier, already after the immunogenicity subset and an undefined number of subjects in the safety set has completed Day 57 assessments.

With the SAP version 2 additional changes were introduced:

- For Ab GM values an additional success criterion on point estimate has been added requiring the GMR point estimate > 0.8 (minimum threshold).

- For sero-response an additional success criterion on point estimate has been added requiring the sero-response rate difference point estimate > -5% (minimum threshold).
- New sero-response definition (Sec. 3.1) added.
- Clarification that COVID-19 cases 14 days after *first* dose were to be analysed in the mITT1 set.
- New secondary COVID-19 definition.
- Interim analyses changed again:
    - First interim analysis for safety was dropped and replaced by an interim analysis for *safety and efficacy* in all age groups after 1500 participants have completed Day 57
    - Second interim analysis dropped the specification of "a subset of all participants having completed Day 57" but this might be still included due to the time it takes to analyse the immunogenicity samples.

The CHMP noted the numerous changes from protocol version 1 to 2 and from SAP version 1 to 2 in the conduct of study affecting the immunogenicity endpoints and their analysis. Most of these changes were indeed considered to be conservative in nature, e.g. an increase in the lower acceptance bounds, the addition of a further primary endpoint "sero-response" if no COP was established, the addition of a lower threshold for the point estimates of both GMR and sero-response and the change of the population to be used as comparator from all adults to adults between 18 and 25 years of age. Although the timing and type of interim analyses was changed in a non-transparent manner twice, first with Protocol version 2 and later with the second SAP, this is considered to have negligible consequences on the interpretability of safety and immunogenicity data.

Demographics and baseline characteristics

The demographics and baseline characteristics of the FAS, Immunogenicity Subset, PP Immunogenicity Subset, mITT1 Set, and PP Efficacy Set is presented in Table 6. For parameters such as age, gender, race and ethnicity, the PP Immunogenicity Subset is generally representative of the FAS as well as other subsets.

Table 6: Demographics and Other Baseline Characteristics for Study mRNA-1273-P203, Participants 12 to <18 Years (FAS, Immunogenicity Subset, PP Immunogenicity Subset, mITT1 Set, PP Efficacy Set)

Characteristic	Full Analysis Set (FAS)[a]	Immunogenicity Subset[b]	Per-Protocol Immunogenicity Subset[c]	mITT1 Set[d]	PP Efficacy Set[e]
	mRNA-1273 (N=2486) n (%)	mRNA-1273 (N=374) n (%)	mRNA-1273 (N=340) n (%)	mRNA-1273 (N=2163) n (%)	mRNA-1273 (N=2139) n (%)
Sex					
Female	1204 (48.4)	176 (47.1)	162 (47.6)	1049 (48.5)	1037 (48.5)
Male	1282 (51.6)	198 (52.9)	178 (52.4)	1114 (51.5)	1102 (51.5)
Age					
16 to <18 years	649 (26.1)	109 (29.1)	101 (29.7)	572 (26.4)	566 (26.5)
12 to <16 years	1837 (73.9)	265 (70.9)	239 (70.3)	1591 (73.6)	1573 (73.5)
Race					
American Indian or Alaska Native	12 (0.5)	0	0	11 (0.5)	11 (0.5)
Asian	142 (5.7)	16 (4.3)	15 (4.4)	127 (5.9)	127 (5.9)
Black or African American	83 (3.3)	6 (1.6)	4 (1.2)	61 (2.8)	59 (2.8)
Native Hawaiian or Other Pacific Islander	2 (<0.1)	0	0	2 (<0.1)	2 (<0.1)
White	2085 (83.9)	314 (84.0)	285 (83.8)	1813 (83.8)	1792 (83.8)
Other	27 (1.1)	8 (2.1)	7 (2.1)	22 (1.0)	22 (1.0)

Multiracial	118 (4.7)	20 (5.3)	19 (5.6)	113 (5.2)	112 (5.2)
Not reported	11 (0.4)	6 (1.6)	6 (1.8)	8 (0.4)	8 (0.4)
Unknown	6 (0.2)	4 (1.1)	4 (1.2)	6 (0.3)	6 (0.3)
Ethnicity					
Hispanic or Latino	280 (11.3)	29 (7.8)	26 (7.6)	240 (11.1)	235 (11.0)
Not Hispanic or Latino	2188 (88.0)	335 (89.6)	304 (89.4)	1905 (88.1)	1886 (88.2)
Not reported	17 (0.7)	9 (2.4)	9 (2.6)	17 (0.8)	17 (0.8)
Unknown	1 (<0.1)	1 (0.3)	1 (0.3)	1 (<0.1)	1 (<0.1)
Race and Ethnicity Group[f]					
White non-Hispanic	1857 (74.7)	293 (78.3)	267 (78.5)	1621 (74.9)	1605 (75.0)
Communities of Color	625 (25.1)	77 (20.6)	69 (20.3)	538 (24.9)	530 (24.8)
Missing	4 (0.2)	4 (1.1)	4 (1.2)	4 (0.2)	4 (0.2)
Body Mass Index					
<30 kg/m2	2316 (93.2)	344 (92.0)	316 (92.9)	2026 (93.7)	2005 (93.7)
≥30 kg/m2	170 (6.8)	30 (8.0)	24 (7.1)	137 (6.3)	134 (6.3)
Positive baseline SARS-CoV-2 status[g]	147 (5.9)	27 (7.2)	0	0	0
Negative baseline SARS-CoV-2 status[h]	2167 (87.2)	347 (92.8)	340 (100)	1073 (100)	2139 (100)
Missing baseline SARS-CoV-2 status	172 (6.9)	0	0	0	0

Abbreviations: Ab=antibody; bAb=binding antibody; COVID-19=coronavirus disease 2019; FAS=full analysis set; mITT=modified intent to treat; PP=per-protocol; RT-PCR=reverse transcription polymerase chain reaction SARS-CoV-2=severe acute respiratory syndrome coronavirus-2.

[a] Percentages are based on the number of participants in FAS (N). The FAS consists of all randomized participants who received any study injection.

[b] Percentages are based on the number of participants in the Immunogenicity Subset.

[c] Percentages are based on the number of participants in the PP Immunogenicity Subset (N). The PP Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of second dose of injection; had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data.

[d] Percentages are based on the number of participants in the mITT1 Set (N). The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (ie, at least 1 dose received in Part A is not as randomized).

[e] Percentages are based on the number subjects in the Per-Protocol Set for Efficacy.

[f] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.

[g] Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1.

[h] Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1

Immunogenicity subset

In the PP Immunogenicity Subset including study P203 and study P301 participants, proportions of males and females were comparable (Table 7). The mean and median ages were 14.4 years and 14.0 years, respectively, for Study P203 participants and 22.3 years and 23.0 years, respectively, for study P301 young adults.

In the PP immunogenicity subset of study P203 a total of 20.3% of the participants were from communities of colour (78.5% were non-Hispanic white) (Table 7). Of note, 51.8% of young adults enrolled in study P301 were from communities of colour, which was numerically higher than in all study P301 mRNA-1273 participants who received at least one dose (37.1%, FAS, PA, 25 Nov 2020).

The percentages of participants with ≥30 kg/m^2 BMI were 7.1% in study P203 and 23.3% in study P301 young adults.

Table 7: Demographic and Baseline Characteristics in Study mRNA-1273-P203 (Participants Aged≥12 to < 18 Years) and Study mRNA-1273-P301 (Participants Aged ≥ 18 to ≤25 Years) (PP Immunogenicity Subset)

Characteristic	P203 mRNA-1273 (N = 340) n (%)	P301 mRNA-1273 (N = 305) n (%)
Sex		
Female	162 (47.6)	157 (51.5)
Male	178 (52.4)	148 (48.5)
Age		
16 to <18 years	101 (29.7)	–
12 to <16 years	239 (70.3)	–
Race		
American Indian or Alaska Native	0	3 (1.0)
Asian	15 (4.4)	30 (9.8)
Black or African American	4 (1.2)	34 (11.1)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
White	285 (83.8)	211 (69.2)
Other	7 (2.1)	8 (2.6)
Multiracial	19 (5.6)	14 (4.6)
Not reported	6 (1.8)	3 (1.0)
Unknown	4 (1.2)	0
Ethnicity		
Hispanic or Latino	26 (7.6)	81 (26.6)
Not Hispanic or Latino	304 (89.4)	222 (72.8)
Not reported	9 (2.6)	0
Unknown	1 (0.3)	2 (0.7)
Race and ethnicity group[a]		
White non-Hispanic	267 (78.5)	147 (48.2)
Communities of colour	69 (20.3)	158 (51.8)
Missing	4 (1.2)	0
Body mass index		
<30 kg/m^2	316 (92.9)	233 (76.4)
≥30 kg/m^2	24 (7.1)	71 (23.3)
Positive baseline SARS-CoV-2 status[b]	0	0
Negative baseline SARS-CoV-2 status[c]	340 (100)	305 (100)

Abbreviations: COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
Note: Percentages are based on the number of participants in the Immunogenicity Subset (N).
a White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.
b Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1.
c Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1.

Source: Study P203, Table 1.3.2.

The CHMP noted that the immunogenicity subset and PP immunogenicity subset differ slightly from the FAS/mITT sets e.g. with respect to age, and race and ethnicity group with a higher proportion of older subjects and a higher proportion of white non-Hispanics in the immunogenicity subset. As the immunogenicity subsets were defined based on the first 550 enrolled subjects, this shows that some changes over time might exist in the enrolled subject population, which could slightly affect the results in the immunogenicity (PP) subset in comparison to the overall population.

The study was conducted in the US only. This is considered acceptable and no concerns arise from lack of European data as there are no major intrinsic/extrinsic differences seen between regions to question applicability of main results to the EU.

The demographic characteristics of the two immunogenicity subsets of study P203 and study P301 differ as regards ethnicity and body mass index with a higher proportion of white non-Hispanic participants and a higher number of participants with a BMI of <30 kg/m^2 in the PP immunogenicity subset in study P203. No subjects with comorbidities such as diabetes or other risk factors were randomised in the immunogenicity subsets of studies P203 and P301, respectively.

Interestingly, differences between the safety set and the PP immunogenicity population also occurred in study P301, where a random sample was to be drawn. Of interest, patients with BMI < $30kg/m^2$ and white non-Hispanics were even slightly enriched in the PP immunogenicity subset as compared to the safety set.

Overall, this could affect immunogenicity data and hence the comparison of the two age cohorts to an unknown but most likely to a minor extent.

Outcomes and estimation

- **Non-inferiority of the immune response (nAb levels and seroresponse rates)**

At the time the immunogenicity/efficacy analyses were performed no correlate of protection has been established. Therefore, the primary efficacy objective to infer efficacy of mRNA-1273 in adolescents (≥ 12 to < 18 years of age; Study P203) was evaluated by comparing the immune response to mRNA-1273 as measured by GM values/titers of serum Ab and seroresponse rates 28 days after dose 2 (Day 57) with those obtained from young adults (≥ 18 to ≤ 25 years of age; study P301) and establishing non-inferiority.

The seroresponse criteria were 1) Number of subjects with baseline <LLOQ and ≥LLOQ at D57 and 2) Number of subjects with baseline ≥LLOQ and ≥3.3-fold rise at D57. Numbers of subjects meeting the respective criteria are shown in the Table 8. The MAH also provided 3) the number of subjects with baseline <LLOQ and ≥3.3-fold rise from baseline 0.5xLLOQ at D57.

Table 8 Summary of seroresponse at Day 57 by baseline antibody titer level (<LLOQ or ≥LLOQ) for PsVNT (ID50) in studies P203 and P301, Per-Protocol immunogenicity subset

Seroresponse at Day 57	**P203** **n/N (%)**	**P301** **n/N (%)**
Overall	336/340 (98.8)	292/296 (98.6)
By Baseline titer		
Number of subjects with baseline <LLOQ:	338	294
Number of subjects with seroresponse	334/338 (98.8)	291/294 (99.0)

(≥LLOQ at D57) Number of subjects with ≥3.3-fold rise from baseline 0.5xLLOQ at D57	334/338 (98.8)	291/294 (99.0)
Number of subjects with baseline ≥LLOQ: Number of subjects with seroresponse (≥3.3-fold rise)	2 2/2 (100)	2 1/2 (50)

N: number of participants in the Per-Protocol immunogenicity subset who have PsVNT (ID50) assay data available for both baseline and Day 57 in the specified baseline category.

Descriptive results depicting PsVNT (ID50) are shown in Table 9.

Table 9: Summary of Pseudovirus Neutralising Antibody ID50 Titers by Age Group (PP Immunogenicity Set)

Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ:18.5, ULOQ:45118)

Timepoint Data Category Statistic	P203 mRNA-1273 >=12 and <16 Years (N=239)	 >=16 and <18 Years (N=101)	 Overall (N=340)	 P301 mRNA-1273 (N=305)
Baseline (Day 1)				
n [1]	239	101	340	305
GMT	9.250	9.827	9.418	9.634
95% CI [2]	(NE,NE)	(9.029,10.696)	(9.185,9.657)	(9.135,10.160)
Median	9.250	9.250	9.250	9.250
Min, Max	9.25, 9.25	9.25, 248.80	9.25, 248.80	9.25, 9650.19

Timepoint Data Category Statistic	P203 mRNA-1273 >=12 and <16 Years (N=239)	 >=16 and <18 Years (N=101)	 Overall (N=340)	 P301 mRNA-1273 (N=305)
Day 57				
n [1]	239	101	340	296
GMT	1390.980	1427.294	1401.670	1301.312
95% CI [2]	(1237.627,1563.335)	(1250.120,1629.577)	(1280.121,1534.760)	(1172.324,1444.492)
Median	1496.850	1292.793	1404.373	1213.391
Min, Max	9.25, 12917.07	159.48, 14851.52	9.25, 14851.52	9.25, 31206.69
N1	239	101	340	296
GMFR	150.376	145.242	148.832	136.896
95% CI [2]	(133.798,169.009)	(126.226,167.123)	(135.789,163.129)	(122.266,153.276)
>= 2-fold Increase from Baseline [3]				
n (%) [4]	235 (98.3)	101 (100)	336 (98.8)	292 (98.6)
95% CI [5]	(95.8,99.5)	(96.4,100.0)	(97.0,99.7)	(96.6,99.6)
>= 3-fold Increase from Baseline [3]				
n (%) [4]	235 (98.3)	101 (100)	336 (98.8)	292 (98.6)
95% CI [5]	(95.8,99.5)	(96.4,100.0)	(97.0,99.7)	(96.6,99.6)
>= 4-fold Increase from Baseline [3]				
n (%) [4]	235 (98.3)	101 (100)	336 (98.8)	292 (98.6)
95% CI [5]	(95.8,99.5)	(96.4,100.0)	(97.0,99.7)	(96.6,99.6)

The CHMP considered that the criteria specified in the SAP 2.0 based on PsVNT (ID50) allow the following classification of seroresponse: (1) baseline <LLOQ >=LLOQ or (2) baseline >=LLOQ: 3.3-fold rise). Numbers were provided for each outcome separately and also for the number of subjects with "(3) baseline <LLOQ and 3.3-fold-rise for PsVNT (ID50) with imputed baseline value = 0.5xLLOQ" (PP Immunogenicity Set)". The majority of subjects (in both studies) could be classified into both categories (1) and (3) (approx. 99 % each), which rules out the possibility that "seroresponse" might have been attributed to titers merely above the LLOQ. In addition, an analysis employing the more commonly used "4-fold increase" criterion was provided for the PP immunogenicity subset (PsVNT (ID50), PP Immunogenicity Set), which does not suggest a different outcome compared to the MAH's primary "3.3-fold rise" criterion (based on assay-specific considerations).

Table 10 summarises the analysis of the differences in immune response at Day 57 for adolescents without evidence of prior SARS-CoV-2 infection in Study P203 compared to young adults aged ≥18 to ≤25 years in study P301 for serum nAb level (PsVNA ID50 assay) and seroresponse.

The GMR of adolescent (Study P203) to young adult (study P301) nAb titers at Day 57 was 1.077 (95% CI: 0.939, 1.236), meeting the 1.5-fold non-inferiority criterion (ie, lower bound of the 95% CI for GMR is > 0.67). The difference in adolescent to young adult nAb seroresponse rates at Day 57 was 0.2% (95% CI: -1.8%, 2.4%), meeting the 10% non-inferiority criterion (lower bound of the 95% of the seroresponse rate difference is > -10%). Non-inferiority for the primary endpoints (neutralising antibody level and seroresponse) was demonstrated.

Table 10: Analysis of Serum Antibody Level and Seroresponse at Day 57 by Pseudovirus Neutralisation Assay (ID50): ANCOVA Model (Per-Protocol Immunogenicity Subset for SARS-CoV-2-specific nAb)

Serum antibody level Pseudovirus Neutralization (ID50)	Study P203: ≥ 12 to < 18 Years GLSM 95% CI N= 340	Study P301: ≥18 to ≤ 25 Years GLSM 95% CI N= 305	GMR Study P203 vs. Study P301 95% CI	Met Success Criteria[a]?
	1401.670 1276.300, 1539.355	1301.312 1176.979, 1438.780	1.077 0.939, 1.236	Yes
Seroresponse by Pseudovirus Neutralization (ID50)	Study P203: ≥12 to <18 Years n (%) 95% CI N1= 340	Study P301: ≥18 to ≤25 Years n (%) 95% CI N1= 296	Difference in Seroresponse Rate 95% CI	Met Success Criteria[b]?
	N1=340 336 (98.8) 97.0, 99.7	N1=296 292 (98.6) 96.6, 99.6	0.2 -1.8, 2.4	Yes

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least square; N1=number of participants with non-missing data at baseline and the corresponding timepoint; n = number of subjects with non-missing data at the corresponding timepoint; ULOQ = upper limit of quantification

a The lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, and the GMR point estimate > 0.8 (minimum threshold).

b The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

Notes:

- The ULOQ for selected P301 participants tested previously was different.
- Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
- The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resultant LS means, difference of LS means, and 95% CI were back-transformed to the original scale for presentation.

Analysis according to a 4-fold increase of nAb levels from Day 1 to Day 57 as measured by Pseudovirus Neutralisation (ID50) based on the PP immunogenicity subset confirmed the seroresponse rates obtained with the criterion of a 3.3-fold rise in neutralising antibody levels as shown in Table 10 above.

Employing the pseudo neutralisation assay and the read out of a 80% inhibitory dose (ID80) a GMR (study P203 vs. study P301) of 1.117 (95% CI: 0.991, 1.260) and a difference of the seroresponse rate of 0.2 (95% CI: -1.8, 2.4) were obtained meeting the non-inferiority.

Table 11: Analysis of Serum Antibody Level and Seroresponse at Day 57 by Pseudovirus Neutralisation Assay (ID80): ANCOVA Model (Per-Protocol Immunogenicity Subset for SARS-CoV-2-specific nAb)

Serum antibody level Pseudovirus Neutralization (ID_{80})	Study P203: ≥ 12 to < 18 Years GLSM 95% CI N= 340	Study P301: ≥18 to ≤ 25 Years GLSM 95% CI N= 305	GMR Study P203 vs. Study P301 95% CI	Met Success Criteria[a]?
	474.468 437.151, 514.970	424.678 388.984, 463.647	1.177 0.991, 1.260	Yes
Seroresponse by Pseudovirus Neutralization (ID_{80})	Study P203: ≥ 12 to < 18 Years n (%) 95% CI	Study P301: ≥ 18 to ≤ 25 Years n (%) 95% CI	Difference in Seroresponse Rate 95% CI	Met Success Criteria[b]?
	N= 340 336 (98.8) 97.0, 99.7	N1= 296 292 (98.6) 96.6, 99.6	0.2 -1.8, 2.4	Yes

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least square; N1 = Number of subjects with non-missing data at baseline and the corresponding timepoint ULOQ = upper limit of quantification

a The lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, and the GMR point estimate > 0.8 (minimum threshold).

b The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

Notes:

- The ULOQ for selected P301 participants tested previously was different.
- Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available.
- The log-transformed antibody levels are analysed using an ANCOVA model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resultant LS means, difference of LS means, and 95% CI were back-transformed to the original scale for presentation.

Neutralising antibody responses by age stratification

Stratification according to age group ≥12 to <16 years and ≥16 to <18 years indicates no difference in the GMR of the nAb response at day 57 as measured by Pseudovirus Neutralisation Assay (ID50) when compared to the age group of young adults in study P301. The seroresponse rates are slightly lower in younger participants (≥12 to <16 Years) than in young adults.

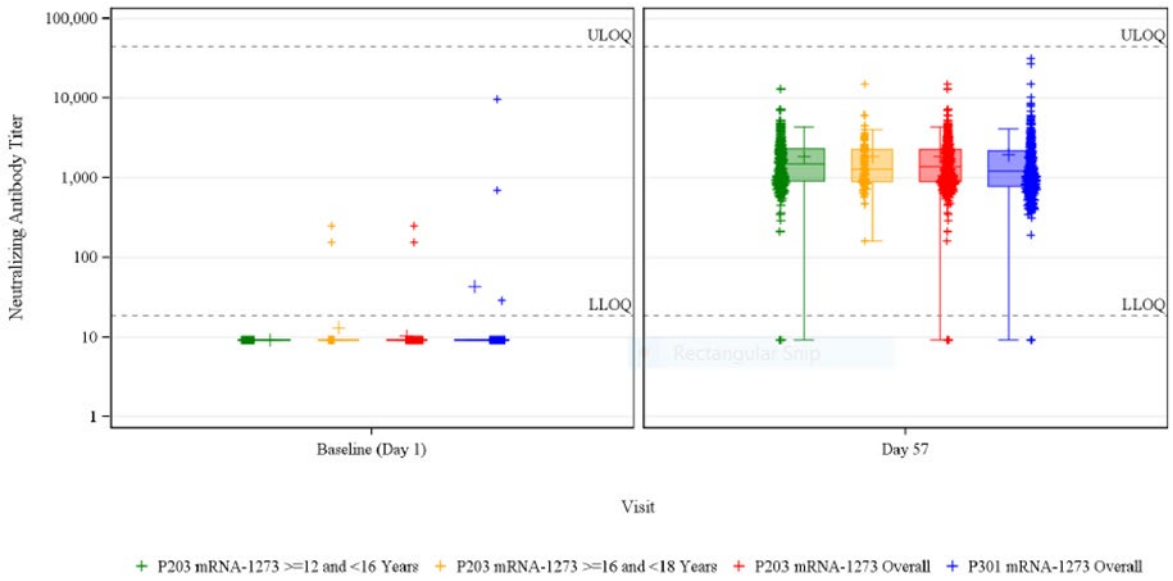
Table 12: Analysis of Pseudovirus Neutralising Antibody ID50 Titers and seroresponse rates by Age Group (Per-Protocol Immunogenicity Subset)

Serum antibody level Pseudovirus Neutralization (ID_{50})	Study P203: ≥ 12 to < 16 Years GLSM 95% CI N= 239	Study P203: ≥ 16 to < 18 Years GLSM 95% CI N= 101	Study P301: ≥18 to ≤ 25 Years GLSM 95% CI N= 305
	1390.980 1243.796, 1555.581	1427.294 1201.700, 1695.238	1301.312 1176.891, 1438.887
GMR Study P203 vs. P301 95% CI	1.069 0.920, 1.242	1.097 0.899, 1.339	
Seroresponse by Pseudovirus Neutralization (ID_{50}) [1, 2]	Study P203: ≥ 12 to < 16 Years GLSM 95% CI N= 239	Study P203: ≥ 16 to < 18 Years GLSM 95% CI N= 101	Study P301: ≥18 to ≤ 25 Years GLSM 95% CI N= 296
	235 (98.3) 95.8, 99.5	101 (100) 96.4, 100.0	292 (98.6) 96.6, 99.6
Difference (P203 vs. P301) 95% CI [3]	-0.3 -3.0, 2.0	1.4 -2.3, 3.4	

[1] Seroresponse due to vaccination specific to pseudovirus neutralizing antibody ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
[2] 95% CI is calculated using the Clopper-Pearson method.
[3] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

As shown in Figure 1 Box Plot analyses presented for nAb responses at day 1 and day 57 reveals that very few participants without evidence of prior SARS-CoV-2 infection in study P203 and in study P301 had neutralising antibody titers at day 1 and almost all participants had neutralising antibodies at day 57.

Figure 1: Box Plot of Pseudovirus Neutralising Antibody ID50 (Per-Protocol Immunogenicity Set)



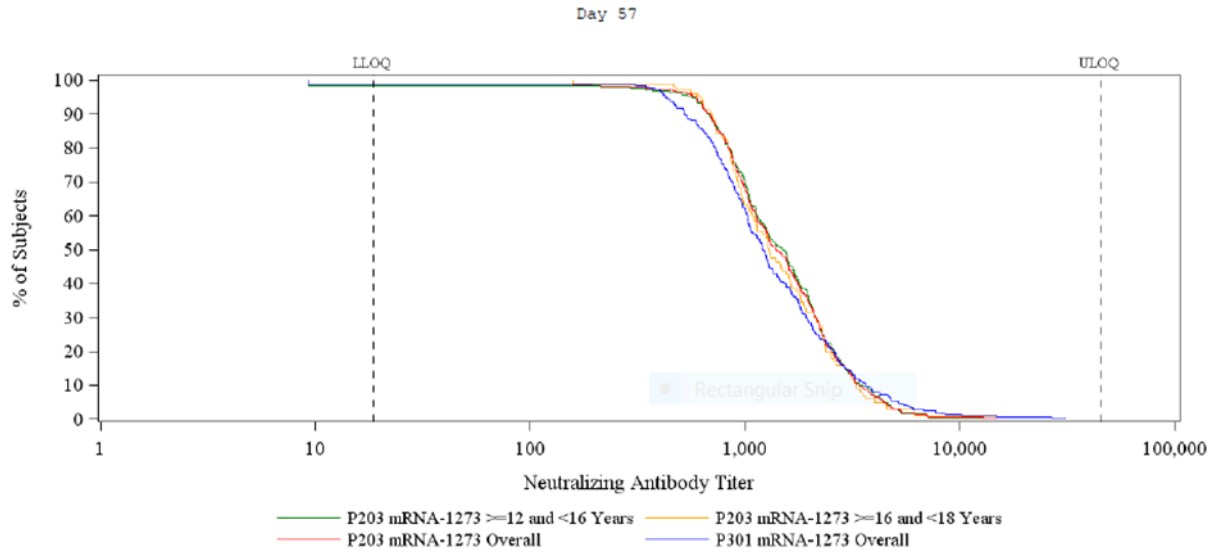
Abbreviations: LLOQ = lower limit of quantification; P203 = Study mRNA-1273-P203; P301 = Study mRNA-1273-P301
ULOQ = upper limit of quantification.
Note: Antibody values reported as below the LLOQ (18.5) are replaced by 0.5 x LLOQ. Values greater than the ULOQ (45118) are replaced by the ULOQ if actual values are not available.

Reverse cumulative distribution curves

Figure 2 displays the reverse cumulative distribution curves of neutralising antibodies titers as measured by Pseudovirus Neutralising Assay (ID50) of participants assessed in the PP immunogenicity subset of study P203 and study P301 and stratified according to age group. Overall, the distribution of neutralising antibody titers as well as the distribution of bAb titers (figures not shown) between the study population of studies P203 and P301 are comparable. No difference in the nAb distribution between the two age strata in study P201 is observed. There is however a slightly broader distribution of antibody titers in study P301 particularly with a higher proportion of subjects having lower nAb titers.

Figure 2: Reverse Cumulative Distribution Function of Pseudovirus Neutralising Antibody Titers (ID50) at day 57 by Age Group (Per-Protocol Irnmunogenicity Subset)

Antibody: Pseudovirus Neutralising Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)



Neutralising antibody responses by baseline status and other characteristics

In general, comparable antibody levels and response rates were found across different subgroups except for some ethnicities (e.g. Hispanic). The analyses by baseline SARS-CoV-2 status based on the immunogenicity subset showed that higher antibody levels were elicited in baseline seropositive subjects in the adolescents than in young adults and that the GMR and seroresponse rates are in the same range as for the non-inferiority analyses on the PP immunogenicity subset.

Table 13: Subgroup Analysis of CoPrimary Immunogenicity Endpoints at Day 57 Based on Pseudovirus nAb ID50, Participants ≥12 to <18 Years (Per-Protocol Immunogenicity Subset)

Characteristic	**GMT (95% CI) P203 ≥12 to <18 years**	**GMT (95% CI) P301 ≥18 to <25 years**	**GMT Ratio (95% CI) P203 vs. P301**
Age			
12 to <16 years	n=239 1390.980 (1243.796, 1555.581)	n=296 1301.312 (1176.891, 1438.887)	1.069 (0.920, 1.242)
16 to <18 years	n=101 1427.294 (1201.700, 1695.238)	n=296 1301.312 (1176.891, 1438.887)	1.097 (0.899, 1.339)
Sex			
Male	n=178 1493.460 (1321.525, 1687.764)	n=143 1352.322 (1179.823, 1550.041)	1.104 (0.919, 1.326)
Female	n=162 1307.306 (1132.635, 1508.913)	n=153 1255.378 (1083.133, 1455.014)	1.041 (0.848, 1.279)
Ethnicity groups			
Black or African American	n=4 1159.565 (463.298, 2902.216)	n=29 1478.961 (1051.917, 2079.369)	0.784 (0.295, 2.086)
White	n=285 1385.232 (1248.333, 1537.144)	n=207 1314.601 (1163.501, 1485.324)	1.054 (0.898, 1.237)
Others	n=51 1519.619 (1211.981, 1905.344)	n=60 1181.128 (958.794, 1455.019)	1.287 (0.946, 1.750)
Hispanic or Latino	n=26 1260.223	n=79 1505.890	0.837 (0.567, 1.235)

	(899.119, 1766.353)	(1240.720, 1827.733)	
Not Hispanic or Latino	n=304 1422.479 (1287.132, 1572.058)	n=215 1235.102 (1096.652, 1391.030)	1.152 (0.986, 1.345)
White non-Hispanic	n=267 1415.535 (1271.839, 1575.465)	n=145 1220.052 (1055.103, 1410.788)	1.160 (0.969, 1.390)
Communities of Color	n=69 1350.461 (1099.490, 1658.719)	n=151 1384.433 (1204.794, 1590.857)	0.975 (0.761, 1.250)
High risk conditions			
Body Mass Index: <30 kg/m^2	n=316 1378.486 (1263.875, 1503.489)	n=227 1221.832 (1102.892, 1353.598)	1.128 (0.986, 1.290)
Body Mass Index: ≥30 kg/m^2	n=24 1745.892 (1032.401, 2952.476)	n=68 1621.957 (1187.099, 2216.113)	1.076 (0.584, 1.983)
Baseline SARS-CoV-2 positive[b,c]	n=27 2866.606 (1690.348, 4861.382)	n=15 1216.205 (595.968, 2481.938)	2.357 (0.961, 5.779)
Baseline SARS-CoV-2 negative[b,c]	n=347 1413.105 (1284.851, 1554.161)	n=300 1263.337 (1140.455, 1399.460)	1.119 (0.973, 1.286)
Characteristic	**Seroresponse[e] n (%) (95% CI[f]) P203 ≥12 to <18 years**	**Seroresponse[e] n (%) (95% CI[f]) P301 ≥18 to <25 years**	**Difference in Seroresponse rate % (95% CI[g]) P203 vs. P301**
Age			
12 to <16 years	N1=239 235 (98.3) (95.8, 99.5)	N1=296 292 (98.6) (96.6, 99.6)	-0.3 (-3.0, 2.0)
16 to <18 years	N1=101 101 (100) (96.4, 100.0)	N1=296 292 (98.6) (96.6, 99.6)	1.4 (-2.3, 3.4)
Sex			
Male	N1=178 177 (99.4) (96.9, 100.0)	N1=143 141 (98.6) (95.0, 99.8)	0.8 (-1.9, 4.5)
Female	N1=162 159 (98.1) (94.7, 99.6)	N1=153 151 (98.7) (95.4, 99.8)	-0.5 (-4.2, 3.0)
Ethnicity groups			
Black or African American	N1=4 4 (100) (39.8, 100.0)	N1=29 29 (100) (88.1, 100.0)	0 (NA, NA)
White	N1=285 281 (98.6) (96.4, 99.6)	N1=207 204 (98.6) (95.8, 99.7)	0.0 (-2.3, 2.9)
Others	N1=51 51 (100) (93.0, 100.0)	N1=60 59 (98.3) (91.1, 100.0)	1.7 (-5.5, 8.9)
Hispanic or Latino	N1=26 25 (96.2) (80.4, 99.9)	N1=79 78 (98.7) (93.1, 100.0)	-2.6 (-17.8, 3.7)
Not Hispanic or Latino	N1=304 301 (99.0) (97.1, 99.8)	N1=215 212 (98.6) (96.0, 99.7)	0.4 (-1.7, 3.1)
White non-Hispanic	N1=267 264 (98.9)	N1=145 143 (98.6)	0.3 (-2.1, 3.9)

	(96.8, 99.8)	(95.1, 99.8)	
Communities of Color	N1=69 68 (98.6) (92.2, 100.0)	N1=151 149 (98.7) (95.3, 99.8)	-0.1 (-6.5, 3.5)
High risk condition			
Body Mass Index: <30 kg/m^2	N1=316 313 (99.1) (97.3, 99.8)	N1=227 225 (99.1) (96.9, 99.9)	-0.1 (-2.0, 2.3)
Body Mass Index: ≥30 kg/m^2	N1=24 23 (95.8) (78.9, 99.9)	N1=68 66 (97.1) (89.8, 99.6)	-1.2 (-17.6, 6.9)
Baseline SARS-CoV-2 positive[b,c]	N1=27 27 (100) (87.2, 100.0)	N1=15 13 (86.7) (59.5, 98.3)	13.3 (-0.5, 38.2)
Baseline SARS-CoV-2 negative[b,d]	N1=347 343 (98.8) (97.1, 99.7)	N1=300 296 (98.7) (96.6, 99.6)	0.2 (-1.8, 2.4)

Note: The assay used for these data was the pseudovirus neutralizing antibody ID50 titer. N1=number of participants with non-missing data at baseline and the corresponding timepoint. The Immunogenicity Subset consists of participants in the FAS who had baseline SARS-CoV-2 status available and had baseline and at least 1 post-injection antibody assessment for the analysis endpoint. The Per-Protocol Immunogenicity Subset consists of all participants in the Immunogenicity Subset who meet all of the following criteria: received planned doses of study vaccination per schedule; complied with the timing of second dose of injection; had negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by Roche Elecsys
Anti-SARS-CoV-2 assay) at baseline; had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint; and had no major protocol deviations that impact key or critical data. Antibody values reported as below the LLOQ are replaced by 0.5 x LLOQ. Values greater than the ULOQ are replaced by the ULOQ if actual values are not available. The log-transformed antibody levels are analyzed using an ANCOVA model with the group variable (adolescents in P203 and young adults in P301) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.

[a] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.

[b] Results by baseline SARS-CoV-2 status were based on the Immunogenicity Subset

[c] Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1.

[d] Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

[e] Seroresponse due to vaccination specific to pseudovirus neutralizing antibody ID50 titer at a participant level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.

[f] 95% CI is calculated using the Clopper-Pearson method.

[G] (score) confidence limits.

- **Non-inferiority of the immune response (bAb levels and seroresponse rates *as measured by Spike IgG Antibody ELISA and MSD Multiplex Assay*)**

Non-inferiority of the binding antibody response was demonstrated by employing the Spike IgG Antibody ELISA and the MSD Multiplex Assay (Table 14 and Table 15).

Table 14: Analysis of Serum Antibody Level and Seroresponse at Day 57 by ELISA: ANCOVA Model (Per-Protocol Immunogenicity Subset

Serum antibody level for Spike IgG Antibody (AU/mL)	Study P203: ≥ 12 to < 18 Years GLSM 95% CI N= 340	Study P301: ≥18 to ≤ 25 Years GLSM 95% CI N= 305	GMR Study P203 vs. Study P301 95% CI	Met Success Criteria?
	n=340 806.920 729.592, 892.445	n=295 739.928 664.080, 824.440	1.091 0.941, 1.264	Yes
Seroresponse by Spike IgG Antibody ELISA	Study P203: ≥ 12 to < 18 Years n (%) 95% CI N= 340	Study P301: ≥ 18 to ≤ 25 Years n (%) 95% CI N= 295	Difference in Seroresponse Rate 95% CI	Met Success Criteria?

	335 (98.5) 96.6, 99.5	293 (99.3) 97.6, 99.9	-0.8 -2.8, 1.1	Yes

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least square; n = number of subjects with non-missing data at the corresponding timepoint; ULOQ = upper limit of quantification

a The lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, and the GMR point estimate > 0.8 (minimum threshold).

b The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

(LLOQ: 1, ULOQ: 2052)

Table 15: Analysis of Serum Antibody Level and Seroresponse at Day 57 by Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD: ANCOVA Model (Per-Protocol Immunogenicity Subset

Serum antibody level by Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD (AU/mL)	Study P203: ≥ 12 to < 18 Years GLSM 95% CI N= 340	Study P301: ≥18 to ≤ 25 Years GLSM 95% CI N= 305	GMR Study P203 vs. Study P301 95% CI	Met Success Criteria[a]?
	n=340 331274.010 295992.773, 370760.639	n= 280 257131.438 227124.041, 291103.381	1.288 1.090, 1.523	Yes
Seroresponse by Binding Antibody Specific to SARS-CoV-2 Spike Protein Measured by MSD (AU/mL)	Study P203: ≥ 12 to < 18 Years n (%) 95% CI n=340	Study P301: ≥ 18 to ≤ 25 Years n (%) 95% CI n=280	Difference in Seroresponse Rate 95% CI	Met Success Criteria[b]?
	336 (98.8) (97.0, 99.7	279 (99.6) (98.0, 100.0)	-0.8 (-2.7, 0.9)	Yes

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GLSM = geometric least squares mean; GMR = geometric mean ratio; ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least square; n = number of subjects with non-missing data at the corresponding timepoint; ULOQ = upper limit of quantification

a The lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5, and the GMR point estimate > 0.8 (minimum threshold).

b The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10% and the seroresponse rate difference point estimate > -5% (minimum threshold).

SARSCOV2S2P IgG Antibody (AU/mL) by MSD MULTIPLEX (LLOQ: 23, ULOQ: 1400000)

The CHMP considered that non-inferiority of antibody responses (nAb/bAb titers and seroresponse rates) following a two doses vaccine regimen in baseline SARS-CoV-2 negative participants was demonstrated regardless of the serological assay used indicating a comparable immune response in children and adolescents from 12 years onwards to that of young adults. Neutralising antibody levels across various age groups (≥12 to <16, ≥16 to <18, ≥18 to <25 years of age) were found to be generally of the same magnitude and no substantial difference in antibody distribution was observed. The seroresponse rates measured by pseudo neutralisation assay across the different age strata of the ≥12 to <16, ≥16 to <18, and ≥18 to <25 years old were 98.3%, 100% and 98.6% respectively. Results from additional analyses applying different criteria for seroresponse (e.g. 4-fold increase instead of 3.3-fold increase) are reassuring that immune response is comparable between young adults and adolescents and all predefined success criteria were met regardless the definition of seroresponse.

Subgroup analysis suggests that the immune response in subjects with a higher BMI (≥30 kg/m^2) is lower in adolescents than in young adults as the non-inferiority criteria for the neutralising antibody levels and response rates were not met. The actual antibody levels in adolescents were higher than that in young adults. However, there is an imbalance in participant rates with higher BMI in the two immunogenicity subsets with a substantial lower number of subjects included in the immunogenicity

subset of study P203 (n=24, 7.1%) compared with study P301 (n=71, 23.3%). No subjects with comorbidities other than obesity were included in the immunogenicity subsets of study P203 and study P301.

A similar observation applies to the ethnicity 'Hispanic' and Black or African American with lower antibody levels and seroresponse rates reported in adolescents. Again, a substantially lower number of subjects were included in the immunogenicity subset in study P203 than in study P301 and it is not known whether any other cofactors impact these results.

Additional analyses (descriptive statistics including PsVNT50/80, ELISA, MSD read-outs and analyses related to e.g. GMFR, RCDC) are in good agreement with the primary read-out. Considerably higher PsVNT (ID50) titers were induced by Spikevax in adolescents who were SARS-CoV-2 positive at baseline compared to their young adult counterparts (Immunogenicity Subset; GMT approx. 2.5-fold higher and median titer approximately 1.5-fold higher in younger subjects). This may, however, be an artefact driven by the low numbers of subjects contributing to this analysis (n=27 adolescents vs. n= 17 young adults).

In summary, results of this subgroup analysis should be interpreted with caution. The subgroup analyses do not show a meaningful heterogeneity between considered subgroups.

Vaccine efficacy (Secondary endpoints)

In addition to the primary immunobridging analysis, VE was assessed against COVID-19 and SARS-CoV-2 infections (asymptomatic and with or without symptoms). Methods used were the same as those employed for adults ≥18 years (Study P301). The secondary endpoint analysis results for vaccine efficacy are summarised in Table 16. All VE analyses are descriptive.

For the descriptive analysis of VE in Study P203 employing the COVID-19 "P301 case definition" used in the pivotal adult efficacy study, the observed VE against confirmed cases occurring 14 days or more after dose 2 was 100.0% (95% CI: 28.9%, NE). There were no case in the mRNA-1273 group and 4 cases in the placebo group (Table 16). These results are consistent with results obtained in the pivotal efficacy study.

Using the COVID-19 "CDC case definition" with requiring only one symptom and reflecting the symptoms more common in adolescence VE against COVID-19 occurring 14 days or more after dose 2 was 93.3% (95% CI: 47.9%, 99.9%).

VE against asymptomatic SARS-CoV-2 infection occurring at least 14 days after dose 2 (PP Set for Efficacy) was 39.2% (95% CI, -0.247, 0.697).

Table 16: Summary of Key Secondary Efficacy Endpoint Analysis Results in Study mRNA-1273-P203

Set	Endpoint	mRNA-1273 (N = 2,162)	Placebo (N = 1,073)
PP[a]	**P301 case definition[b] starting 14 days after dose 2**		
	Cases, n	0	4
	Incidence rate per 1,000 person-years (95% CI)[c]	0 (NE, 7.149)	16.525 (4.503, 42.311)
	VE based on incidence rate (95% CI)[d]	1.00 (0.289, NE)	
mITT1[e]	**CDC case definition[f] of COVID-19 starting 14 days after dose 1**		
	Cases, n	2	13
	Incidence rate per 1,000 person-years (95% CI)[c]	3.828 (0.464, 13.830)	52.473 (27.939, 89.730)
	VE based on incidence rate (95% CI)[d]	0.927 (0.678, 0.992)	

	CDC case definition[f] of COVID-19 starting 14 days after dose 2		
PP[a]	Cases, n	1	7
	Incidence rate per 1,000 person-years (95% CI)[c]	1.940 (0.049, 10.808)	28.981 (11.652, 59.711)
	VE based on incidence rate (95% CI)[d]	0.933 (0.479, 0.999)	
	SARS-CoV-2 infection[g] starting 14 days after dose 1		
mITT1[e]	Cases, n	27	42
	Incidence rate per 1,000 person-years (95% CI)[c]	51.922 (34.217, 75.543)	172.120 (124.049, 232.656)
	VE based on incidence rate (95% CI)[d]	0.698 (0.499, 0.821)	
	SARS-CoV-2 infection[g] starting 14 days after dose 2		
PP[a]	Cases, n	22	23
	Incidence rate per 1,000 person-years (95% CI)[c]	42.856 (26.857, 64.884)	96.649 (61.267, 145.021)
	VE based on incidence rate (95% CI)[d]	0.557 (0.168, 0.764)	
	Asymptomatic SARS-CoV-2 infection[h] starting 14 days after dose 1		
mITT1[e]	Cases, n	25	29
	Incidence rate per 1,000 person-years (95% CI)[c]	48.076 (31.112, 70.969)	118.828 (79.581, 170.657)
	VE based on incidence rate (95% CI)[d]	0.595 (0.284, 0.773)	
	Asymptomatic SARS-CoV-2 infection[h] starting 14 days after dose 2		
PP[a]	Cases, n	21	16
	Incidence rate per 1,000 person-years (95% CI)[c]	40.908 (25.323, 62.532)	67.230 (38.428, 109.178)
	VE based on incidence rate (95% CI)[d]	0.392 (-0.247, 0.697)	

Abbreviations: bAb = binding antibody; CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; FAS = Full Analysis Set; n = number of events; N = number of participants; NE = not evaluable; mITT1 = Modified Intent-to-Treat-1; PP = Per-Protocol Efficacy Set; RT-PCR = reverse transcription polymerase chain reaction; VE = vaccine efficacy.

[A] The PP Set for Efficacy is defined as all participants in the FAS who meet all the following criteria: received planned doses of study vaccination, had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by *Roche Elecsys* Anti-SARS-CoV-2 assay) at baseline, and had no major protocol deviations that impact key or critical efficacy data.

[b] Defined as symptomatic disease and positive RT-PCR results.

[c] 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.

[d] Vaccine efficacy 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.

[e] mITT1 Set for Efficacy defined all participants in the mITT Set (defined as all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline), excluding those who received the wrong treatment.

[f] Defined as the presence of at least one symptom from a list of COVID-19 symptoms using the CDC case definition (CDC 2020b), and a positive nasopharyngeal swab or saliva sample for SARS-CoV-2 RT-PCR, in baseline negative SARS-CoV-2 participants.

[g] SARS-CoV-2 infection defined in participants with negative SARS-CoV-2 at baseline as bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys)* counted starting at Day 57 or later, OR positive RT-PCR counted starting 14 days after the second dose of investigational product.

[h] Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and as bAb levels against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) counted starting at Day 57 or later, OR positive RT-PCR.

The CHMP considered that the exploratory vaccine efficacy results after 14 days post dose 2 indicate that Spikevax is efficacious in preventing laboratory confirmed COVID-19 in adolescents from 12 to 17 years, although only a low number of cases were observed using the same stringent case definition as in the

pivotal study P301 in adults. A VE of 100.0% (95% CI: 28.9%, NE) was estimated. Analysis of VE based on the FAS population (starting 14 days after dose 1) confirmed the results with a comparable number of cases observed in both groups.

Using the less stringent CDC definition amended to reflect the clinical course in adolescents a VE of 93.3% (95% CI: 47.9%, 99.9%) is reported starting 14 days post dose 2 with 1 case reported in the vaccine group and 7 cases observed in the placebo group confirming the initial VE results in adults ≥ 18 years of age. The low number of confirmed COVID-19 cases regardless of the case definition is not surprising given the low number of subjects enrolled, the time of follow-up and the normal course of infection in this age group where most SARS-CoV-2 infections are expected to cause no (asymptomatic) or mostly mild symptoms. As regards prevention of SARS-CoV-2 infection or asymptomatic SARS-CoV-2 infections 14 days following the second dose lower VE was observed with 55.7% (95% CI:16.8, 76.4) and 39.2% (95% CI: -24.7, 69.7), respectively.

As can be expected, no severe cases occurred in the study. The risk of severe disease increases with increasing age.

The data further suggest that the protection against asymptomatic disease may be (substantially) lower. This may be indicative of a shift in disease severity on individual vaccinee level rather than complete infection prevention explaining part of the pronounced efficacy observed for symptomatic endpoints. It should be noted, however, that sensitivity for estimating asymptomatic case prevention is likely limited due to operational constraints. No firm conclusions regarding prevention of asymptomatic infection can be drawn for the time being. Final study results should be submitted as soon as available.

No information is currently available on the virus variants causing COVID-19 or asymptomatic SARS-CoV-2 infections in study P203. As the study was solely conducted in the USA between December 2020 and May 2021 it is unclear whether the circulating variants in the US at the time of study conduct are representative of the variants observed and currently spreading in Europe. From virus variant distribution data available from US CDC it can be assumed that the main virus variants circulating at the time of study conduct were the alpha, followed by the iota and gamma variants. The delta variant, which is expected to become the predominant variant in Europe with an anticipated 90% infection rate by end of August, was not substantially circulating in the USA until early May 2021.

Summary of main study

Table 17 summarises 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 17 Summary of key efficacy/immunogenicity results for study P203

Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age		
Study identifier	mRNA-1273-P203	
Design	Phase 2/3 randomized, observer-blind, placebo-controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	<time> <time> <not applicable> <time> <not applicable>
Hypothesis	Non-inferiority of nAb response younger (P203) vs older age groups (P301) Efficacy was measured and reported with 95% CI	
Treatments groups	Active arm	Spikevax (mRNA1273, 100µg), 2 doses, 28 days apart, 2,489 subjects randomized
	Control arm	Placebo (Saline), 2 doses, 28 days apart, 1,243 subjects randomized

	Comparator group P301 immunogenicity subset		Spikevax (mRNA1273, 100µg), 2 doses, 28 days apart, 340 young adults randomly selected
Endpoints and definitions	Primary endpoint (Immuno-genicity)	GM value of serum nAb level	geometric least square mean (GLSM) at 28 days post dose 2 (day 57)
		seroresponse rate by nAb	percentage of participants with a 3.3-fold rise in neutralizing antibody levels from day 1 prior first dose to 28 days post dose 2
		GM value of serum bAb level by Spike IgG ELISA	geometric least square mean (GLSM) at 28 days post dose 2 (day 57)
		seroresponse rate by Spike IgG ELISA	percentage of participants with a 4.6-fold rise in binding antibody levels from day 1 prior first dose to 28 days post dose 2
		GM value of serum bAb level by MSD	geometric least square mean (GLSM) at 28 days post dose 2 (day 57)
		seroresponse rate by MSD	percentage of participants with a 1.9-fold rise in binding antibody levels from day 1 prior first dose to 28 days post dose 2
	Secondary endpoints	VE	The incidence of the first occurrence of COVID-19 starting 14 days after the second dose with participants experiencing at least two systemic symptoms or one respiratory symptom and having at least 1 positive SARS-CoV-2 RT-PCR result
		VE	The incidence of the first occurrence of COVID-19 starting 14 days after the second dose with participants experiencing at least one systemic or respiratory symptoms (CDC definition) and having at least 1 positive SARS-CoV-2 RT-PCR result
		VE	The incidence of SARS-CoV-2 infection starting 14 days after the second dose in SARS-CoV-2 negative subjects at baseline
Database lock	04 May 2021		

Results and Analysis

Analysis description	**Immunogenicity Analysis (Primary Analysis):**			
Analysis population and time point description	Per-Protocol Immunogenicity subset, D57 Per-Protocol Efficacy Set			
Descriptive statistics and estimate variability	Treatment group	12-18 years	18-25 years	
	Number of subjects	340	305	GMR (95% CI), non-inferiority (yes/no)
	GLSM (95% CI) by pseudo neutralization (ID50)	**1401.670** (1276.300, 1539.355)	**1301.312** (1176.979, 1438.780)	**1.077** (0.939, 1236) Yes
	Number of subjects	340	296	Difference in seroresponse rates (95% CI) (yes/no)

	Seroresponse rate n, **%** (95% CI) by pseudo neutralization (ID50)	336 **98.8** (97.0, 99.7)	292 **98.6** (96.6, 99.6)	**0.2** (-1.8, 2.4) Yes
	Number of subjects	340	295	GMR (95% CI), non-inferiority (yes/no)
	GLSM (95% CI) for Spike IgG antibody (AU/ml)	**806.920** (729.592, 892.445)	**739.928** (664.080, 824.440)	**1.091** (0.941, 1264) Yes
	Number of subjects	340	295	Difference in seroresponse rates (95% CI) (yes/no)
	Seroresponse rate n, **%** (95% CI) for Spike IgG antibody (AU/ml)	335 **98.5** (96.6, 99.5)	293 **99.3** (97.6, 99.9)	**-0.8** (-2.8, 1.1) Yes
	Number of subjects	340	280	GMR (95% CI), non-inferiority (yes/no)
	GLSM (95% CI) for Spike specific antibody by MSD (AU/ml)	**331274.010** (729.592, 892.445)	**257131.438** (664.080, 824.440)	**1.288** (1.090, 1523) Yes
	Number of subjects	340	280	Difference in seroresponse rates (95% CI) (yes/no)
	Seroresponse rate n, **%** (95% CI) for Spike specific antibody by MSD (AU/ml)	336 **98.8** (97.0, 99.7)	279 **99.6** (98.0, 100)	**-0.8** (-2.7, 0.9) Yes
Effect estimate per comparison	Secondary endpoints	VE against confirmed COVID-19 (P301 definition) starting 14 days post dose, PP set	Cases in mRNA-1273 group N= 0/2,163 0 per 1000 person-years Cases in Placebo group N=4/1,073 16.525 per 1000 person-years	
		VE, 1-ratio of incidence rate	**100**	
		95% CI	28.9, NE	
		VE against confirmed COVID-19 (CDC definition) starting 14 days post dose, PP set	Cases in mRNA-1273 group N= 1/2,163 1.940 per 1000 person-years Cases in Placebo group N=7/1,073 28.981 per 1000 person-years	
		VE 1-ratio of incidence rate	**93.3**	
		95% CI	47.9, 99.9	

		VE against SARS-CoV-2 infection starting 14 days post dose 2, PP set	Cases in mRNA-1273 group N= 22/2,163 42.856 per 1000 person-years Cases in Placebo group N=23/1,073 96.649 per 1000 person-years
		VE 1-ratio of incidence rate	**55.7**
		95% CI	16.8, 76.4

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Immunogenicity and vaccine efficacy of Spikevax in adolescents aged ≥12-<18 years was assessed in an interim analysis of the study P203, which is a multicentre, randomised, placebo-controlled (2:1 randomised in favour of IP), observer blind study conducted in the US. The study is ongoing and currently immunogenicity and (exploratory) efficacy data are available from a median duration of follow-up of 57 days after the second dose. The planned study duration is 14 months, 12 months after the second dose to collect long-term efficacy, immunogenicity and safety data.

The choice of the comparator arm consisting of the immunogenicity set of young adults aged 18 to 25 years enrolled in the pivotal study P301 is acceptable as COVID-19 vaccine efficacy was convincingly demonstrated in this adult study.

The study population comprised adolescents ≥12 to< 18 years of age including individuals with higher BMI. No individuals with comorbidities were included in the immunogenicity subset. There are no major intrinsic/extrinsic differences seen between regions to question applicability of main results to the EU. Pregnant and breastfeeding adolescents were excluded from the studies. The selection of immunogenicity subsets is considered not optimal due to slight imbalances (e.g. in age and race/ethnicity) between the FAS and the immunogenicity samples, which could affect the overall representativeness of the immunogenicity estimates for the general population.

The primary 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 for immunobridging to young adults. However, the chosen criteria for defining seroresponse are not fully in line with established criteria generally used for vaccines. Therefore, additional analyses were requested, for details see below.

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.

As regards the comparative primary immunogenicity assessments, the co-primary endpoints are agreed in definition and respective sample sourcing. It was noted during the assessment (partly based on interaction with the MAH) that for finalisation of SAP version 2, prior availability/access to immunogenicity reads cannot be conclusively ruled out based on described timelines (and unclear masking of study origin). This is relevant insofar, as some specifics of the co-primary immunogenicity endpoints were left open in version 1 of the SAP. Additional analyses were requested to address the robustness of results across ('candidate') immunogenicity endpoint specifications as per SAP version 1. More generally, and questions regarding pre-specification in protocol/SAP aside, the specifications eventually considered for primary inference are supported from a regulatory perspective.

In addition, various exploratory efficacy endpoints (largely aligned with those from the adult pivotal study P301) were specified to evaluate 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. Two different COVID-19 case definitions were employed to identify probable cases, one being identical to the case definition used in study P301 and the second following the CDC case definition.

As noteworthy additions, *asymptomatic COVID-19 infection* and (related to that) *COVID-19 infection* (combining symptomatic and asymptomatic cases) have been included as efficacy endpoints. Respectively reported study P203 data are the first obtained from any Spikevax study. Available interim results are, however, limited and do not allow firm conclusions regarding prevention of asymptomatic infection.

Overall, the analysed/reported efficacy endpoints only warrant consideration as supportive and for consistency (across studies, endpoint definitions and with immune response) but do not *per se* enable reliably estimating vaccine efficacy in adolescents. For that purpose, primary reference is made to immunogenicity data (see above).

A protocol amendment split up study P203 into part A (db RCT) and part B (OLE) to enable subjects to seek unblinding by choice and elect to go for IP (or other vaccine) if initially allocated to placebo upon EUA of COVID-19 vaccine for younger cohorts (in the US). This will impair developing long-term controlled data (safety) and meaningful efficacy readout at later time points.

Overall, the design and conduct of the study were appropriate for the intended purpose of showing comparable immunogenicity and safety.

Assessment of paediatric data on clinical immunogenicity/ efficacy

Immunogenicity to infer vaccine efficacy

Inferring efficacy by immunobridging from adults to adolescents is an accepted strategy for vaccines and has been applied previously. Since no serological correlate of protection is currently established, non-inferiority analyses based on antibody levels and response rates following vaccination are recommended. Antibody responses in adolescents and young adults following vaccination with Spikevax were assessed using three different serological assays to measure anti-spike binding and neutralising antibodies. As demonstrated in *in vitro studies* and *in vivo* using monoclonal antibodies, neutralising antibodies against the spike protein play a crucial role in the prevention of COVID-19. Hence, results of the analyses of neutralising antibody responses are key to establish non-inferiority and to conclude on the acceptability of immunobridging.

The immunobridging strategy to infer vaccine efficacy was based on a non-inferiority approach employing ratios of geometric mean titers (GMR) and seroresponse rates between young adults 12-17 years of age from study P203 (n=340) and adolescents 18-25 years of age from study P301 (n=296). Evaluations were based on neutralising antibody (nAb) titers measured via PsVNT (ID50) at day 57 post-vaccination (Per-Protocol Immunogenicity Subset). The criteria specified in the SAP version 2 based on PsVNT (ID50) allow the following classification of seroresponse: (1) baseline <LLOQ >=LLOQ or (2) baseline >=LLOQ: 3.3-fold rise). To allow for a more granular analysis, the MAH provided numbers for each outcome separately and also provide the number of subjects with "(3) baseline <LLOQ and 3.3-fold-rise for PsVNT (ID50) with imputed baseline value = 0.5xLLOQ" (PP Immunogenicity Set). The majority of subjects (in both studies) could be classified into both categories (1) and (3) (approx. 99 % each), which rules out the possibility that "seroresponse" might have been attributed to titers merely above the LLOQ. In addition, an analysis employing the more commonly used "4-fold increase" criterion was provided for the PP immunogenicity subset (PsVNT (ID50), PP Immunogenicity Set), which does not suggest a different outcome compared to the MAH's primary "3.3-fold rise" criterion (based on assay-specific considerations).

An increase in neutralising antibodies was reported in adolescents aged 12-17 years of age 4 weeks after the recommended adult vaccination schedule of 2 doses given 28 days apart. In SARS-CoV-2 baseline negative individuals the neutralising antibody (nAb) levels were in the same range as the nAb levels observed in young adults included in the PP immunogenicity set in the pivotal efficacy study P301 (1401.670 and 1301.312, respectively). Seroresponse rates (per defined criteria as stated above) was detected in almost all subjects in both age groups (12-17 years of age: 98.8% and 18-25 years of age: 98.6%). These results indicate that the neutralising antibody levels (1.077; 95%CI: 0.939, 1.236) and the seroresponse rates (0.2; 95%CI: -1.8, 2.4) are non-inferior in adolescents compared to young adults. Results of additional analyses provided upon request (see also paragraph above) are reassuring that immune response is comparable between young adults and adolescents and all predefined success criteria were met regardless the definition of seroresponse. Analyses based on two different binding anti-Spike antibody assays confirmed these results, i.e. non-inferiority of bAb responses and response rates were established.

Overall, comparable immunogenicity in young adults 12-17 years of age and adolescents 18-25 years of age to infer vaccine efficacy is considered to be adequately demonstrated.

Further analyses of the nAb responses stratified according to age group ≥12 to <16 years and ≥16 to <18 years indicates no difference in the magnitude of nAb levels at day 57. This is somewhat unexpected and in contrast to recent findings with another COVID-19 vaccine evaluated in adolescents. A possible explanation could be that the antibody responses achieved after vaccination with Spikevax reached a maximum level and plateau at that level. The vaccine dose initially chosen for the pivotal study was selected in view of the immune responses observed in elderly. As no dose-finding studies were conducted in subjects below 18 years of age, it is unclear whether the dose level evaluated is the most appropriate for this age group and whether lower doses would have triggered comparable responses in adolescents.

No immunogenicity data are available from subjects who received placebo. Predictors of immune response, apart from age and immune status remain uncertain. Likewise, the MAH stated that no immunogenicity data from study P203 from subjects counted as SARS-CoV-2 infection have been available to date. Availability of such data would have been considered of value, yet the lack thereof does not impact on the overall conclusion of the primary immunogenicity comparison.

Exploratory efficacy data

Based on a very low number of confirmed COVID-19 cases in adolescents tested SARS-CoV-2 negative at baseline and having received 2 doses 28 days apart, consistent vaccine efficacy across the different age groups (adolescents and adults) was reported. Using the same COVID-19 case definition as in the pivotal adult study P301 or a less stringent CDC case definition a VE of 100% (95% CI: 28.9, NE; 0/4 cases) and 93.3% (95% CI: 47.9, 99.9; 1/7 cases), respectively, was estimated. VE against SARS-CoV-2 infection was estimated to be 55.7% (95%CI: 16.8, 76.4).

As can be expected, no severe cases occurred in the study. The risk of severe disease increases with increasing age.

The data further suggest that the protection against asymptomatic disease may be (substantially) lower. This may be indicative of a shift in disease severity on individual vaccinee level rather than complete infection prevention explaining part of the pronounced efficacy observed for symptomatic endpoints. It should be noted, however, that sensitivity for estimating asymptomatic case prevention is likely limited due to operational constraints. No firm conclusions regarding prevention of asymptomatic infection can be drawn for the time being. Final study results should be submitted as soon as available.

Information on the virus variants causing COVID-19 or asymptomatic SARS-CoV-2 infections in adolescents was not provided (exploratory endpoint). As the study was solely conducted in the USA between December 2020 and May 2021 it is unclear whether the circulating variants in the US at the time

of study conduct are representative of the variants observed and currently spreading in Europe. From virus variant distribution data available from US CDC it can be assumed that the main virus variants circulating at the time of study conduct were the alpha, followed by the iota and gamma variants. The delta variant, which is expected to become the predominant variant in Europe with an anticipated 90% infection rate by end of August, was not substantially circulating in the USA until early May. Although no data is currently available on the duration of the immune response or protection, it is to be expected that the level of protection over time is similar to the adult population.

Concluding remarks

In summary, and mainly building on the co-primary immunobridging endpoints, efficacy against symptomatic COVID-19 can be inferred for adolescents 12-17 years of age. The effect size for efficacy endpoints was largely in agreement with that seen in adults overall, which supports immunogenicity results but respective analyses are hampered by low case counts.

The final clinical study report for study mRNA-1273-P203 including the full bioanalytical report will be submitted no later than September 2022 and is subject to a specific obligation laid down in the marketing authorisation, in order to provide long-term efficacy data in adolescents 12-17 years of age.

2.4.3. Conclusions on the clinical efficacy

From the data available, the CHMP concludes that Spikevax protects adolescents aged ≥12 to <18 years against symptomatic COVID-19 based on demonstration of non-inferior humoral immune responses compared to young adults ≥18 to <25 years old. This is supported by exploratory analyses of efficacy.

The CHMP considers the following measure (**SOB**) necessary to address the missing efficacy data:

- The final clinical study report for study mRNA-1273-P203 including the full bioanalytical report will be submitted no later than September 2022 and is subject to a specific obligation laid down in the marketing authorisation. This will provide long-term data.

In addition, the following recommendations (**REC**) are made:

- Since no dose finding trial in this population has been conducted it is not possible to conclude whether lower dose could have resulted in a lower reactogenicity with comparable immune response and efficacy. The MAH should further explore lower dose levels in adolescents 12-17 years of age given the high reactogenicity of Spikevax and the usually mild course of infection caused by SARS-CoV-2 in this age group.
- The CHMP noted the evidence of acceptable assay control, assay validation and sample storage provided. Studies on sample stability are ongoing; the MAH should provide the respective validation reports upon completion.
- The MAH should provide, on a regular basis and as soon as (interim) results are available, data from relevant endpoints, e.g. immunogenicity data over time, efficacy against variants, immunogenicity data from breakthrough cases.

2.5. Clinical safety

Introduction

On 6th of January 2021, mRNA-1273 (COVID-19 Vaccine Moderna) was granted a conditional marketing authorisation in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in

individuals 18 years of age and older. The present submission intends to extend the existing indication to individuals ≥12 years of age for the prevention of COVID-19. Route of administration, dose and schedule will be the same as for the adult indication, i.e. 100 µg IM, given as 2 injections, 28 days apart. To extend the indication the MAH submitted preliminary safety data from clinical trial mRNA-1273-P203. This trial is a two-part Phase 2/3, randomised, placebo-controlled trial to evaluate the safety, reactogenicity, immunogenicity and efficacy of mRNA-1273 in healthy adolescents 12 to < 18 years of age.

Participants in Part A, the blinded Phase of the study are randomly assigned to receive 2 injections (28 days apart) of either 100 µg of mRNA-1273 vaccine or placebo in a 2:1 randomisation ratio. The dosage and dosing schedule were identical to that used in adults in study P301.

Part B is an open-label observational phase of this study, designed to offer participants who received placebo in Part A of this study and who meet the EUA eligibility criteria an option to receive mRNA-1273 in an open-label fashion.

The safety data base of this submission includes data from the 08 May 2021 data snapshot with a median study follow-up duration of 53 days (approximately 2 months) after dose 2. Details are provided in the Patient disposition section below.

Patient exposure and disposition

As of 08 May 2021 (data snapshot date), 2,486 of 2,489 randomised participants (99.9%) in the mRNA-1273 group and 1,240 of 1,243 randomised participants (99.8%) in the placebo group had received dose 1. 2,480 (99.6%) and 1,222 (98.3%) in the 2 groups had received dose 2, respectively.

In the Safety Set population 2,480 of the 2,486 participants included in the mRNA-1273 group (99.8%) and 1,222 of 1,240 in the placebo group (98.5%) had received 2 doses. In the Solicited Safety Set population 2,478 participants of 2,485 included in the mRNA-1273 group (99.7%) and 1,220 of 1,240 (98.4%) participants included in the placebo group have received 2 doses, respectively. In the mRNA-1273 group, the median follow-up time was 83.5 days after dose 1, and 53 days after dose 2. In the placebo group, the follow-up period was 82.0 days after dose 1, and 51 days after dose 2.

The Safety Set consists of 1,838 subjects ≥12 and <16 years of age and of 648 subjects ≥16 and <18 years of age who received at least one dose of in the mRNA-1273 vaccine, and of 929 and 311 subjects in the two age cohorts who received placebo, respectively. The overall sample size of the Safety Set included 3,726 subjects, 2,486 who received mRNA-1273 and 1,240 who received placebo.

Overall 6.6% of subjects (245) of the 3,732 randomised subjects discontinued from study. 2.3% (57) of 2,489 randomised subjects randomised to the mRNA-1273 group, and 15.1% (188) of 1,243 subjects randomised to the placebo group. 3 subjects in the mRNA-1273 group discontinued due to an AE.

An overview of participant disposition in the safety Set is provided in Table 18 below.

Table 18 - Participant Disposition in Study mRNA-1273-P203 (amended from Table 3, clinical overview)

	mRNA-1273 n (%)	Placebo n (%)	Total n (%)
Randomized	N=2489	N=1243	N=3732
Completed 1 dose	2486 (99.9)	1240 (99.8)	3726 (99.8)
Completed 2 doses	2480 (99.6)	1222 (98.3)	3702 (99.2)
Discontinued from study	57 (2.3)	188 (15.1)	245 (6.6)
Reason for discontinuation			
Adverse event	1 (<0.1)	0	1 (<0.1)
Withdrawal by participant	27 (1.1)	102 (8.2)	129 (3.5)
COVID-19 Non-infection related	2 (<0.1)	13 (1.0)	15 (0.4)
Other	25 (1.0)	89 (7.2)	114 (3.1)
Lost to follow-up	3 (0.1)	6 (0.5)	9 (0.2)
Protocol deviation	8 (0.3)	14 (1.1)	22 (0.6)
Physician decision	1 (<0.1)	0	1 (<0.1)
Other	17 (0.7)	66 (5.3)	83 (2.2)
Safety Set[a]	N=2486	N=1240	N=3726
Completed 2 doses	2479 (99.7)	1222 (98.5)	3701 (99.3)
Median follow-up post dose 2 (days)[b]	53.0	51.0	53.0
Completed at least 1 month follow-up post dose 2	2452 (98.6)	1173 (94.6)	3625 (97.3)
Completed at least 2 months follow-up post dose 2	1087 (43.7)	474 (38.2)	1561 (41.9)
Solicited Safety Set[c]	N=2485	N=1240	N=3725
First Dose Solicited Safety Set	2482 (99.8)	1238 (99.8)	3720 (99.8)
Second Dose Solicited Safety Set	2478 (99.7)	1220 (98.4)	3698 (99.2)
Full Analysis Set[d]	N=2486	N=1240	N=3726

In the Safety Set 43.7% (1087) of the 2,486 subjects in the mRNA-1273 group and 38.2% (474) of the 1,240 subjects in the placebo group had a follow-up time-period of ≥56 days post dose 2. 54.9% (1,366) of subjects in the mRNA-1273 group and 56.4% (699) subjects in the placebo group had a follow-up between ≥28 and <56 days after dose 2. All subjects except of 12 in the mRNA vaccine group and 27 in the placebo group had a follow-up time of 7 days after dose 2 (99.5% and 97.8%, respectively). The follow-up duration by age cohort is provided in Table 19 below. In the mRNA-1273 vaccine group 801 subjects ≥12 to <16 years of age (43.6%) and 286 subjects ≥16 to <18 years of age (44.1%) had a follow-up period of ≥56 days after dose 2, and 1026 (55.8%) and 340 (52.5%) a follow-up period between ≥28 and <56 days after dose 2, respectively. In the placebo-group 388 subjects ≥12 to <16 years of age (41.8%) and 86 subjects >16 to <18 years of age (27.7%) had a follow-up period of ≥56 days after dose 2, and 582 (56.8%) and 171 (55.0%) a follow-up period between ≥28 and <56 days after dose 2, respectively.

Table 19: Summary of Study Duration by Age Group, Safety Set

	>=12 and <16 Years			>=16 and <18 Years			Overall		
	Placebo (N=929)	mRNA-1273 (N=1838)	Total (N=2767)	Placebo (N=311)	mRNA-1273 (N=648)	Total (N=959)	Placebo (N=1240)	mRNA-1273 (N=2486)	Total (N=3726)
Number of Subjects, n (%)									
Received First Injection	929 (100)	1838 (100)	2767 (100)	311 (100)	648 (100)	959 (100)	1240 (100)	2486 (100)	3726 (100)
Received Second Injection	920 (99.0)	1835 (99.8)	2755 (99.6)	302 (97.1)	645 (99.5)	947 (98.7)	1222 (98.5)	2480 (99.8)	3702 (99.4)
>= 7 Days Since First Injection	929 (100)	1838 (100)	2767 (100)	311 (100)	648 (100)	959 (100)	1240 (100)	2486 (100)	3726 (100)
>= 35 Days Since First Injection	928 (99.9)	1835 (99.8)	2763 (99.9)	300 (96.5)	645 (99.5)	945 (98.5)	1228 (99.0)	2480 (99.8)	3708 (99.5)
>= 56 Days Since First Injection	917 (98.7)	1830 (99.6)	2747 (99.3)	268 (86.2)	628 (96.9)	896 (93.4)	1185 (95.6)	2458 (98.9)	3643 (97.8)
>= 7 Days Since Second Injection	919 (98.9)	1832 (99.7)	2751 (99.4)	294 (94.5)	642 (99.1)	936 (97.6)	1213 (97.8)	2474 (99.5)	3687 (99.0)
>= 28 Days Since Second Injection	916 (98.6)	1827 (99.4)	2743 (99.1)	257 (82.6)	626 (96.6)	883 (92.1)	1173 (94.6)	2453 (98.7)	3626 (97.3)
>= 28 and < 56 Days Since Second Injection	528 (56.8)	1026 (55.8)	1554 (56.2)	171 (55.0)	340 (52.5)	511 (53.3)	699 (56.4)	1366 (54.9)	2065 (55.4)
>= 56 Days Since Second Injection	388 (41.8)	801 (43.6)	1189 (43.0)	86 (27.7)	286 (44.1)	372 (38.8)	474 (38.2)	1087 (43.7)	1561 (41.9)
Study Duration from Randomization (Days)									
Mean	87.5	88.0	87.9	76.9	87.7	84.2	84.9	87.9	86.9
(SD)	(16.29)	(15.76)	(15.94)	(23.11)	(17.76)	(20.28)	(18.80)	(16.30)	(17.23)
Median	83.0	83.0	83.0	75.0	85.0	81.0	82.0	83.5	83.0
Q1, Q3	74.0, 97.0	75.0, 97.0	75.0, 97.0	63.0, 90.0	75.0, 100.0	74.0, 97.0	74.0, 96.0	75.0, 99.0	74.0, 97.0
Min, Max	31, 151	30, 151	30, 151	9, 139	34, 144	9, 144	9, 151	30, 151	9, 151

Percentages are based on the number of safety subjects.
[1] Person-years is defined as the total years from the first dose date to the earlier date of study discontinuation or data cutoff.
[2] Study duration from second injection is 0 day for subjects who did not receive second injection.
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The CHMP noted that the follow-up period in the Safety Set of the mRNA-1273 vaccine group was comparable between the 2 age cohorts ≥12 and <16 years and ≥16 and <18 years, but differed for the 2 age cohorts in the placebo groups with regards to the follow up period of ≥56 days. In the Safety Set, in the mRNA-1273 group, 43.6% of subjects ≥12 to <16 years of age and 44.1% of subjects ≥16 to <18 years had a follow-up period of more than 56 days after dose 2. In the placebo group only 27.7% of subjects ≥16 to <18 years of age had a follow-up period more than 56 days post dose 2 (versus 41.8% of subjects >=12 and <16 years). Almost all subjects in the Safety Set received a second dose, i.e. 99.8% of subjects (2,480/2,486 subjects included in the Safety Set) in the mRNA-1273 group and 98.5% in the placebo group (1,220/1,240 included in the Safety Set).

Dropout rate was low in the mRNA-1273 vaccine group (overall 2.3% of subjects), but notably higher in the placebo group (overall 15.1%, respectively), because of the increasing availability of authorised mRNA-COVID-19 vaccines. Mainly adolescents between 16 to 18 years of age requested unblinding. This was confirmed by the sponsor. In the mRNA-1273 group 1.2% of subjects in the ≥12 to <16 years of age cohort, and 5.4% in the ≥16 to <18 years of age cohort discontinued from trial. In the placebo group the percentage was 45% in the ≥16 to <18 years of age cohort and 5.0% in the ≥12 to <16 years of age cohort.

There is a discrepancy between the disposition analysis in the table and the analysis for unsolicited AEs leading to discontinuation from study vaccine. Overall, 3 subjects in the mRNA-1273 vaccine group, and not only 1 as listed in the table, discontinued the trial due to AEs (COVID-19, eye swelling, drug-induced liver injury, all AEs considered being not related to study vaccine). Details for the 3 AEs that lead to discontinuation are provided in the corresponding section "Discontinuation due to adverse events".

Demography

In the Safety Set, 74.3% of subjects (2767) were enrolled in the younger age cohort (≥12 to <16 years of age). Of them, 1,838 subjects (73.9%) were enrolled in the mRNA-1273 group, and 929 (74.9%) in the placebo group. 25.7% (959 subjects) were enrolled in the older age cohort (≥16 to <18 years of age), 648 subjects in the mRNA-1273 group (26.1%), and 311 (25.1%) in the placebo group, respectively. Overall, 87.0% of subjects were seronegative at baseline, 87.2% (2167 subjects) in the mRNA-1273 group, and 86.7% (1075) in the placebo group. Overall, 51.4% of subjects (1915) were male, and 48.6% (1811) were female. 83.9% (3126 subjects) of all subjects in the Safety Set were White, 83.9% (2085 subjects) in the mRNA-1273 group, and 84.0% (1041) in the placebo group. Demographic and baseline characteristics for the Safety Set are provided in Table 20 below.

Table 20: Demographic and Baseline Characteristics in Study mRNA-1273-P203 (Safety Set)

Characteristic	mRNA-1273 (N=2486) n (%)	Placebo (N=1240) n (%)	Total (N=3726) n (%)
Sex			
Female	1203 (48.4)	608 (49.0)	1811 (48.6)
Male	1283 (51.6)	632 (51.0)	1915 (51.4)
Age			
16 to <18 years	648 (26.1)	311 (25.1)	959 (25.7)
12 to <16 years	1838 (73.9)	929 (74.9)	2767 (74.3)
Race			
American Indian or Alaska Native	12 (0.5)	7 (0.6)	19 (0.5)
Asian	142 (5.7)	79 (6.4)	221 (5.9)
Black or African American	83 (3.3)	42 (3.4)	125 (3.4)
Native Hawaiian or Other Pacific Islander	2 (<0.1)	0	2 (<0.1)
White	2085 (83.9)	1041 (84.0)	3126 (83.9)
Other	27 (1.1)	9 (0.9)	36 (1.0)
Multiracial	118 (4.7)	50 (4.0)	168 (4.5)
Not reported	11 (0.4)	11 (0.9)	22 (0.6)
Unknown	6 (0.2)	1 (<0.1)	7 (0.2)
Ethnicity			
Hispanic or Latino	280 (11.3)	152 (12.3)	432 (11.6)
Not Hispanic or Latino	2188 (88.0)	1076 (86.8)	3264 (87.6)
Not reported	17 (0.7)	10 (0.8)	27 (0.7)
Unknown	1 (<0.1)	2 (0.2)	3 (<0.1)
Race and Ethnicity Group[a]			
White non-Hispanic	1857 (74.7)	912 (73.5)	2769 (74.3)
Communities of Color	625 (25.1)	325 (26.2)	950 (25.5)
Missing	4 (0.2)	3 (0.2)	7 (0.2)
Body Mass Index			
<30 kg/m^2	2316 (93.2)	1146 (92.4)	3462 (92.9)
≥30 kg/m^2	170 (6.8)	94 (7.6)	264 (7.1)

Characteristic	mRNA-1273 (N=2486) n (%)	Placebo (N=1240) n (%)	Total (N=3726) n (%)
Positive baseline SARS-CoV-2 status[b]	147 (5.9)	69 (5.6)	216 (5.8)
Negative baseline SARS-CoV-2 status[c]	2167 (87.2)	1075 (86.7)	3242 (87.0)
Missing baseline SARS-CoV-2 status	172 (6.9)	96 (7.7)	268 (7.2)

Abbreviations: COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

Note: Percentages are based on the number of safety participants (N). The Safety Set consists of all randomized participants who received any study injection.

[a] White non-Hispanic is defined as White and non-Hispanic, and Communities of Color includes all the others whose race or ethnicity is not unknown, unreported, or missing.

[b] Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1.

[c] Negative is defined as a negative RT-PCR test and negative Elecsys result at Day 1.

Source: Study P203, Table 1.3.

The CHMP considered that the demographic and baseline characteristics of the safety set are balanced between the mRNA-1273 group and the placebo group in the older and the younger age cohort. The majority of subjects was enrolled in the younger age cohort ≥12 to 16 years of age (74.3% of subjects). 83.9% of subjects were white. 48.6% of subjects were female and 51.4% were male. The majority of subjects was seronegative for SARS-CoV-2 at baseline (87.0%). SARS-CoV-2 status at baseline has been

determined by a combination of the results of the RT-PCR (nasopharyngeal or nasal swab) and Elecsys binding antibody test specific to SARS-CoV-2 nucleocapsid evaluation.

Safety analysis set

The following two safety sets apply in this trial:

1. Solicited Safety Set:

   The Solicited Safety Set consists of FAS participants who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs. FAS includes all randomised participants who received at least 1 injection of IP.

2. Safety Set:

   The safety Set consists of all randomised participants who receive at least 1 dose of IP (i.e. the FAS). The Safety Set will be used for all analyses of safety except for the solicited ARs.

Adverse events

The overall sample size of the Safety Set included 3,726 subjects, 2,486 who received at least one dose of mRNA-1273 vaccine, and 1,240 who received at least one dose of placebo. The majority of subjects belong to the age cohort ≥12 and <16 years of age (1,838 subjects in the mRNA-1273 vaccine group and 929 in the placebo group). 648 and 311 subjects are included in the age cohort ≥16 to <18 years.

The solicited safety set included almost the same sample size like the safety set, i.e. overall 2,485 subjects in the mRNA-1273 vaccine group (1,838 in the age cohort ≥12 to <16 years of age and 647 ≥16 to <18 years of age), and 1,240 in the placebo group (929 subjects in the younger and 311 in the older age cohort).

Solicited adverse reactions

Solicited local and systemic adverse reactions (ARs) were evaluated through 7 days after each dose (ie, the day of injection and six subsequent days). Solicited ARs were recorded daily using an eDiary, which was unchanged from the eDiary used in the study P301 submission for adults aged ≥ 18 years. The solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness. Solicited systemic ARs included fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting.

Severity grading of reactogenicity occurred automatically based on participant entry into the eDiary according to grading scales modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Solicited local ARs

The incidence of local ARs was higher in the mRNA-1273 group compared with the placebo group after any and after each dose. Any solicited local AR after any dose was recorded for 97.8% of subjects in the mRNA-1273 vaccine group (2,431/2,485) and for 48.5% of subjects (602/1,240) in the placebo group. The most frequently reported local solicited AR in the mRNA-1273 and the placebo group after any dose was injection site pain reported by 97.2% of subjects in the mRNA-1273 vaccine group and by 45.9% of subjects in the placebo group. This was followed by axillary swelling or tenderness (34.6% versus 10.7%), swelling (27.7% versus 1.9%), and erythema/redness (25.8% versus 1.5%). The events of erythema and swelling tended to be more often reported after dose 2, whereas the incidence of pain and axillary swelling or tenderness were comparable after dose 1 and dose 2. The incidence for each solicited local AR after each dose by severity is presented in Table 21, and after any dose in Table 22. The

majority of solicited local ARs was mild to moderate. However, any grade 3 solicited local AR after any dose was recorded for 13.8% of subjects in the mRNA-1273 vaccine group and for 0.3% in the placebo group. The severity slightly increased from dose 1 to dose 2. 6.8% of subjects reported any grade 3 local solicited AR post dose 1 versus 8.9% post dose 2. No grade 4 solicited local AR was recorded. Grade 3 local solicited ARs were mostly recorded for pain (9.1% of subjects in the mRNA-1273 vaccine group after any dose), followed by erythema (3.5%), swelling (3.2%), and axillary swelling or tenderness (0.6%). The majority of solicited local ARs in the mRNA-1273 vaccine group occurred within the first 1 to 2 days after any dose (97.4% of subjects). 1.3% of subjects in the mRNA-1273 vaccine group reported solicited local ARs with onset after day 7. Solicited local ARs usually persisted for a median of 3 days. 6.4% of subjects in the mRNA-1273 vaccine group reported solicited local ARs that persisted beyond day 7 after dose 1 and 1.6% after dose 2. The proportion of subjects in the placebo group was 1.2% and 0.7% after dose 1 and dose 2, respectively.

Table 21: Frequency of Solicited Local Adverse Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants Aged ≥ 12 to < 18 Years (Solicited Safety Set)

	Dose 1		Dose 2	
Event	**mRNA-1273 N = 2482 n (%)**	**Placebo N = 1238 n (%)**	**mRNA-1273 N = 2478 n (%)**	**Placebo N = 1220 n (%)**
Any local adverse reaction	N1 = 2482	N1 = 1238	N1 = 2,478	N1 = 1,220
Any	2,339 (94.2)	455 (36.8)	2,314 (93.4)	398 (32.6)
Grade 3	170 (6.8)	1 (<0.1)	220 (8.9)	3 (0.2)
Grade 4	0	0	0	0
Pain	N1 = 2482	N1 = 1238	N1 = 2,478	N1 = 1,220
Any	2,310 (93.1)	431 (34.8)	2,290 (92.4)	370 (30.3)
Grade 3[a]	133 (5.4)	1 (<0.1)	126 (5.1)	3 (0.2)
Grade 4[a]	0	0	0	0
Erythema (redness)	N1 = 2,482	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	334 (13.5)	8 (0.6)	484 (19.5)	11 (0.9)
Grade 3[b]	21 (0.8)	0	72 (2.9)	0
Grade 4[b]	0	0	0	0

	Dose 1		Dose 2	
Event	**mRNA-1273 N = 2482 n (%)**	**Placebo N = 1238 n (%)**	**mRNA-1273 N = 2478 n (%)**	**Placebo N = 1220 n (%)**
Swelling (hardness)	N1 = 2,482	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	403 (16.2)	12 (1.0)	509 (20.5)	12 (1.0)
Grade 3[b]	27 (1.1)	0	56 (2.3)	0
Grade 4[b]	0	0	0	0
Axillary swelling or tenderness	N1 = 2,481	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	578 (23.3)	101 (8.2)	519 (21.0)	61 (5.0)
Grade 3[c]	10 (0.4)	0	7 (0.3)	0
Grade 4[c]	0	0	0	0

Abbreviation: AR = adverse reaction.

Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days.

[a] Pain Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

[b] Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis.

[c] Axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

Source: Study P203, Table 3.1.1.1; Table 3.1.1.2.

Table 22: Summary of Subjects with Solicited Local Adverse Reactions Within 7 Days After Any Injection in Participants Aged ≥ 12 to < 18 Years by Grade (Solicited Safety Set)

Event Grade	**mRNA-1273 (N = 2,485) n (%)**	**Placebo (N = 1,240) n (%)**
Any local AR	N1 = 2,485	N1 = 1,240
Any	2431 (97.8)	602 (48.5)
Grade 3	344 (13.8)	4 (0.3)
Grade 4	0	0
Pain	N1 = 2,485	N1 = 1,240
Any	2415 (97.2)	569 (45.9)
Grade 3[a]	227 (9.1)	4 (0.3)
Grade 4[a]	0	0
Erythema (redness)	N1 = 2,485	N1 = 1,240
Any	641 (25.8)	19 (1.5)
Grade 3[b]	86 (3.5)	0
Grade 4[b]	0	0
Swelling (hardness) - N1	N1 = 2,485	N1 = 1,240
Any	688 (27.7)	23 (1.9)
Grade 3[b]	80 (3.2)	0

Event Grade	mRNA-1273 (N = 2,485) n (%)	Placebo (N = 1,240) n (%)
Grade 4[b]	0	0
Axillary swelling or tenderness	N1 = 2,484	N1 = 1,240
Any	859 (34.6)	133 (10.7)
Grade 3[c]	16 (0.6)	0
Grade 4[c]	0	0

Abbreviations: AR = adverse reaction; mRNA = messenger ribonucleic acid.

Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received any study injection and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment

[a] Pain Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

[b] Erythema (redness) and swelling (hardness) Grade 3: >100 mm/>10 cm; Grade 4: necrosis/exfoliative dermatitis.

[c] Axillary swelling or tenderness Grade 3: any use of prescription pain reliever/prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

Source: Study P203 Table 3.1.1.3

Solicited systemic ARs

The incidence of systemic ARs was higher in the mRNA-1273 group compared with the placebo group after any and after each dose. Any solicited systemic AR after any dose was recorded for 91.9% of subjects in the mRNA-1273 vaccine group (2,284/2,485) and for 66.9% of subjects (830/1,240) in the placebo group.

The most frequently reported systemic solicited AR in the mRNA-1273 group after any dose was headache reported by 78.4% of subjects in the mRNA-1273 vaccine group and by 50.3% of subjects in the placebo group. This was followed by fatigue (75.2% versus 47.5%), myalgia (54.3% versus 23.5%), chills (49.1% versus 16.2%), arthralgia (34.6 versus 16.9%), and nausea (29.3% versus 15.2%). Fever of any grade was reported by 13.7% versus 1.9% of subjects. The incidence of solicited systemic ARs was notably higher after dose 2 compared with dose 1. Any solicited systemic AR was reported by 68.5% of subjects in the mRNA-1273 vaccine group after dose 1 and by 86.1% after dose 2. The incidence for each solicited systemic AR after each dose by severity is presented in Table 6, and after any dose in Table 7. Though the majority of systemic solicited ARs was mild to moderate it should be noted, that any grade 3 solicited systemic AR after any dose was recorded for 16.5% of subjects in the mRNA-1273 vaccine group (versus 4.6% in the placebo group). Severity of systemic AEs increased from dose 1 to dose 2. Grade 3 AEs were reported by 4.4% versus 13.7% of subjects after each dose. Grade 4 solicited systemic ARs were recorded for 3 subjects in the mRNA-1273 group (fever, headache, nausea/vomiting). Grade 3 systemic solicited ARs were mostly recorded for fatigue (8.5% of subjects in the mRNA-1273 vaccine group after any dose), followed by headache (6.4%), myalgia (5.8%), arthralgia (2.7%), fever (2.2%), chills (0.5%), and nausea (0.2%). The majority of solicited systemic ARs in the mRNA-1273 vaccine group occurred within the first 1 to 2 days after any dose (89.1% of subjects). 0.7% of subjects in the mRNA-1273 vaccine group reported solicited systemic ARs with onset after day 7. Solicited systemic ARs usually persisted for a median of 2 days. 4.7% of subjects in the mRNA-1273 vaccine group reported solicited systemic ARs that persisted beyond day 7 after dose 1 and 3.1% after dose 2. The proportion of subjects in the placebo group was 5.2% and 2.6% after dose 1 and dose 2, respectively. Because of the higher systemic reactogenicity the use of antipyretic or pain medication was notably higher in the mRNA-1273 vaccine group compared with the placebo group. In the mRNA-1273 vaccine group, 30.1% of subjects used such medication after dose 1 and 50.1% after dose 2. The proportion was 9.5% and 8.9% in the placebo group, respectively.

Table 23: Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Does, by Maximum Severity, Participants ≥ 12 to < 18 Years (Solicited Safety Set)

Event	Dose 1		Dose 2	
	mRNA-1273 N = 2482 n (%)	**Placebo N = 1238 n (%)**	**mRNA-1273 N = 2478 n (%)**	**Placebo N = 1220 n (%)**
Any systemic AR	N1 = 2,482	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	1,701 (68.5)	687 (55.5)	2,134 (86.1)	561 (46.0)
Grade 3	108 (4.4)	36 (2.9)	340 (13.7)	25 (2.0)
Grade 4	0	0	3 (0.1)	1 (<0.1)
Fever[a]	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,219
≥38.0°C	63 (2.5)	12 (1.0)	302 (12.2)	12 (1.0)
38.0°C to 38.4°C	36 (1.5)	9 (0.7)	162 (6.5)	6 (0.5)
38.5°C to 38.9°C	18 (0.7)	2 (0.2)	93 (3.8)	4 (0.3)
39°C to 40.0°C	9 (0.4)	1 (<0.1)	46 (1.9)	1 (<0.1)
>40.0°C	0	0	1 (<0.1)	1 (<0.1)
Headache	N1 = 2,480	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	1,106 (44.6)	477 (38.5)	1,739 (70.2)	370 (30.3)
Grade 3[b]	56 (2.3)	17 (1.4)	112 (4.5)	14 (1.1)
Grade 4[b]	0	0	1 (<0.1)	0
Fatigue	N1 = 2,481	N1 = 1,238	N1 = 2,478	N1 = 1,220
Any	1,188 (47.9)	453 (36.6)	1,679 (67.8)	353 (28.9)
Grade 3[c]	33 (1.3)	18 (1.5)	188 (7.6)	10 (0.8)
Grade 4[c]	0	0	0	0

Event	Dose 1		Dose 2	
	mRNA-1273 N = 2482 n (%)	Placebo N = 1238 n (%)	mRNA-1273 N = 2478 n (%)	Placebo N = 1220 n (%)
Myalgia	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	668 (26.9)	205 (16.6)	1154 (46.6)	153 (12.5)
Grade 3[c]	24 (1.0)	10 (0.8)	129 (5.2)	3 (0.2)
Grade 4[c]	0	0	0	0
Arthralgia	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	371 (15.0)	143 (11.6)	716 (28.9)	113 (9.3)
Grade 3[c]	15 (0.6)	5 (0.4)	57 (2.3)	2 (0.2)
Grade 4[c]	0	0	0	0
Nausea/vomiting	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	281 (11.3)	110 (8.9)	591 (23.9)	106 (8.7)
Grade 3[d]	2 (<0.1)	0	2 (<0.1)	0
Grade 4[d]	0	0	1 (<0.1)	0
Chills	N1 = 2,480	N1 = 1,238	N1 = 2,477	N1 = 1,220
Any	456 (18.4)	138 (11.1)	1,066 (43.0)	97 (8.0)
Grade 3[e]	4 (0.2)	1 (<0.1)	11 (0.4)	0
Grade 4[e]	0	0	0	0
Use of antipyretic or pain medication	N = 2482	N = 1,238	N = 2,478	N = 1,220
Any	748 (30.1)	118 (9.5)	1,242 (50.1)	108 (8.9)

Abbreviation: AR = adverse reaction.

Note: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received at least 1 dose of IP and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment). The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who received the first (second) study injection and contributed any solicited AR data from the time of the first (second) study injection through the following 6 days. Medications were collected on the eDiary.

[a] Fever is defined as: Grade 1 = 38 to 38.4°C; Grade 2 = 38.5 to 38.9°C; Grade 3 = 39 to 40°C; Grade 4 = greater than 40°C.

[b] Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[c] Fatigue, myalgia, arthralgia: Grade 3 significant, prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[d] Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; Grade 4 requires emergency room visit or hospitalization for hypotensive shock.

[e] Chills: Grade 3 prevents daily activity and requires medical intervention; Grade 4 requires emergency room visit or hospitalization.

Source: Study P203, Table 3.1.1.1; Table 3.1.1.2; Table 1.7.1; Table 1.7.2.

Table 24: Summary of Subjects with Solicited Systemic Adverse Reactions Within 7 Days After Any Injection in Participants Aged ≥ 12 to < 18 Years by Grade (Solicited Safety Set)

Event **Grade**	**mRNA-1273** **(N = 2,485)** **n (%)**	**Placebo** **(N = 1,240)** **n (%)**
Any systemic AR	N1 = 2,485	N1 = 1,240
Any	2284 (91.9)	830 (66.9)
Grade 3	411 (16.5)	57 (4.6)
Grade 4	3 (0.1)	1 (<0.1)
Fever	N1 = 2,484	N1 = 1,240
Any	340 (13.7)	24 (1.9)
Grade 3[a]	54 (2.2)	2 (0.2)
Grade 4[a]	1 (<0.1)	1 (<0.1)
Headache	N1 = 2,485	N1 = 1,240
Any	1947 (78.4)	624 (50.3)
Grade 3[b]	160 (6.4)	29 (2.3)
Grade 4[b]	1 (<0.1)	0
Fatigue	N1 = 2,485	N1 = 1,240
Any	1868 (75.2)	589 (47.5)
Grade 3[c]	210 (8.5)	26 (2.1)
Grade 4[c]	0	0
Myalgia	N1 = 2,484	N1 = 1,240
Any	1349 (54.3)	291 (23.5)

Event Grade	mRNA-1273 (N = 2,485) n (%)	Placebo (N = 1,240) n (%)
Grade 3[c]	143 (5.8)	12 (1.0)
Grade 4[c]	0	0
Arthralgia	N1 = 2,484	N1 = 1,240
Any	859 (34.6)	209 (16.9)
Grade 3[c]	66 (2.7)	7 (0.6)
Grade 4[c]	0	0
Nausea/vomiting	N1 = 2,484	N1 = 1,240
Any	728 (29.3)	188 (15.2)
Grade 3[d]	4 (0.2)	0
Grade 4[d]	1 (<0.1)	0
Chills	N1 = 2,484	N1 = 1,240
Any	1219 (49.1)	201 (16.2)
Grade 3[e]	13 (0.5)	1 (<0.1)
Grade 4[e]	0	0

Abbreviations: AR = adverse reaction; mRNA = messenger ribonucleic acid.

Note: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who were randomized and received at least 1 dose of IP and contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment).

[a] Fever is defined as: Grade 1 = 38°C to 38.4°C; Grade 2 = 38.5°C to 38.9°C; Grade 3 = 39°C to 40°C; Grade 4 = > 40°C.

[b] Headache: Grade 3 significant, any use of prescription pain reliever or prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[c] Fatigue, myalgia, arthralgia: Grade 3 significant, prevents daily activity; Grade 4 requires emergency room visit or hospitalization.

[d] Nausea/vomiting: Grade 3 prevents daily activity, requires outpatient intravenous hydration; Grade 4 requires emergency room visit or hospitalization for hypotensive shock.

[e] Chills: Grade 3 prevents daily activity and requires medical intervention; Grade 4 requires emergency room visit or hospitalization.

Source: Study P203 Table 3.1.1.3

The CHMP noted that, as can be expected, the incidence of solicited local and systemic ARs was higher in the mRNA-1273 group compared with the placebo group. Although the majority of solicited ARs (local and systemic) was mild to moderate, it should be noted that after any dose in the mRNA-1273 vaccine group 13.8% of subjects reported grade 3 solicited local and 16,5% solicited systemic ARs. For solicited local reactions no clear trend could be observed regarding differences in severity post dose 1 and post dose 2. The incidence of solicited systemic ARs however was notably higher post dose 2 compared to post dose 1, i.e. depending on the kind of event approximately 2- to 3-fold higher after dose 2 than after dose 1. Because of the higher systemic reactogenicity, the use of antipyretic or pain medication was notably higher in the mRNA-1273 vaccine group compared with the placebo group. In the mRNA-1273 vaccine group, 30.1% of subjects used such medication after dose 1 and 50.1% after dose 2. The proportion was 9.5% and 8.9% in the placebo group, respectively.

Solicited ARs by age group

The solicited safety set included 1,838 subjects ≥12-<16 years of age who had received at least one dose of mRNA-1273, and 648 subjects ≥ 16 to < 18 years of age who had received at least one dose of mRNA.-1273. In the mRNA-1275 vaccine group, any solicited AR after any dose was recorded by 99.1% of participants ≥12 to <16 years of age and by 99.5% of participants ≥16 to <18 years of age. Any solicited local AR in the mRNA-1273 vaccine group was recorded by 97.9% versus 97.5% of subjects in

the 2 age cohorts, and any solicited systemic AR by 91.6% versus 92.7% respectively. The most often recorded solicited local AR in both age cohorts was pain recorded by 97.4% of subjects ≥12-<16 years of age and by 96.6% of subjects ≥16 to <18 years of age, followed by axillary swelling or tenderness (33.9% and 36.5%), and swelling/hardness (28.9% and 24.3%). Erythema was recorded by 26.7% and 23.3% of participants in the 2 age cohorts, respectively. Any solicited systemic AR after any dose was recorded by 91.6% of subjects ≥12 to <16 years of age and by 92.7% of subjects ≥16 to <18 years of age in the mRNA-1273 vaccine group. The most frequent solicited systemic AR in both age groups was headache (77.6% and 80.4%), followed by fatigue (74.8% and 76.4%), myalgia (52.8% and 58.6%), and arthralgia (32.9% and 39.3%). Any solicited AR grade 3 or more was recorded by 25.6% of subjects in the younger compared to 24.4% of subjects in the older age group. Any local solicited AR grade 3 or more was recorded by 14.6% versus 11.7%, and any systemic solicited AR grade 3 or more by 16.6% versus 16.8% of subjects in the 2 age cohorts.

The CHMP noted that the number of subjects included into the ≥12 to <16 years of age cohort was approximately 3 times higher than the number of subjects in the older age cohort ≥16 to <18 years (1,838 versus 647 subjects in the mRNA-1273 vaccine group). Local and systemic reactogenicity was generally comparable in the 2 age cohorts with regard to frequency and severity.

Data on the solicited systemic and local ARs by dose in the age cohort 18 to 25 years of age from study P301 suggested a higher local reactogenicity for all solicited local ARs except for pain in the age cohort 12 to <18 years compared with the age cohort 18 to 25 years of age. The incidence of solicited systemic ARs tended to be comparable or slightly higher in the age cohort 18 to 25 years of age. Comparing the incidence of severe (grade 3) systemic ARs shows a clear difference between adolescents (4.4% dose 1, 13.7% dose 2) and young adults (5.2% dose 1, 21.6% dose 2), especially after dose 2. It should be taken into account, that the sample size in the age cohort 12 to <18 years was 3-fold higher than in the age cohort 18 to 25 years of age and the control group is a historical one. Solicited local and systemic ARs for the age group 18 to 25 years of age are presented in Table 25 and Table 26.

Table 25: Frequency of Solicited Local Adverse Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants 18 to 25 Years (Solicited Safety Set)

Event	mRNA-1273 N=878 Dose 1 n (%)	Placebo N=900 Dose 1 n (%)	mRNA-1273 N=819 Dose 2 n (%)	Placebo N=839 Dose 2 n (%)
Any local adverse reaction	N1=878	N1=900	N1=819	N1=839
Any	793 (90.3)	242 (26.9)	739 (90.2)	208 (24.8)
Grade 3	52 (5.9)	2 (0.2)	63 (7.7)	0
Grade 4	0	0	0	0
Pain	N1=878	N1=900	N1=819	N1=839
Any	785 (89.4)	213 (23.7)	732 (89.4)	187 (22.3)
Grade 3[a]	47 (5.4)	2 (0.2)	53 (6.5)	0
Grade 4[a]	0	0	0	0
Erythema (redness)	N1=878	N1=900	N1=819	N1=839
Any	33 (3.8)	6 (0.7)	60 (7.3)	3 (0.4)
Grade 3[b]	2 (0.2)	0	7 (0.9)	0
Grade 4[b]	0	0	0	0
Swelling (hardness)	N1=878	N1=900	N1=819	N1=839
Any	71 (8.1)	5 (0.6)	83 (10.1)	3 (0.4)
Grade 3[b]	5 (0.6)	0	8 (1.0)	0
Grade 4[b]	0	0	0	0
Axillary swelling or tenderness	N1=878	N1=900	N1=819	N1=839
Any	160 (18.2)	71 (7.9)	153 (18.7)	48 (5.7)
Grade 3[c]	2 (0.2)	0	3 (0.4)	0
Grade 4[c]	0	0	0	0

Abbreviations: AR=adverse reaction; IP=investigational product.

Notes: N1=number of exposed participants who submitted any data for the event. Any=Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of randomized participants who received at least 1 dose of IP and contributed any solicited AR data, ie, had at least 1 post-baseline solicited safety (eDiary) assessment. The First (Second) Injectio Solicited Safety Set consists of all participants in the Solicited Safety Set who have received the first (second) study injection and have contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days.

[a] Pain Grade 3: any use of prescription pain reliever or prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

[b] Erythema (redness) and swelling (hardness) Grade 3: >100mm/>10cm; Grade 4: necrosis or exfoliative dermatitis (erythema).

[c] Axillary swelling or tenderness Grade 3: any use of prescription (narcotic) pain reliever or prevents daily activity; Grade 4: emergency room visit or hospitalization.

Table 26: Frequency of Solicited Systemic Adverse Reactions Within 7 Days After Each Dose, by Maximum Severity, Participants 18 to 25 Years (Solicited Safety Set)

Event	mRNA-1273 N=878 Dose 1 n (%)	Placebo N=900 Dose 1 n (%)	mRNA-1273 N=819 Dose 2 n (%)	Placebo N=839 Dose 2 n (%)
Any systemic adverse reaction	N1=878	N1=900	N1=819	N1=839
Any	578 (65.8)	486 (54.0)	702 (85.7)	343 (40.9)
Grade 3	46 (5.2)	26 (2.9)	177 (21.6)	23 (2.7)
Grade 4	0	0	0	0
Fever[a]	N1=878	N1=899	N1=819	N1=839
≥38.0°C	15 (1.7)	5 (0.6)	149 (18.2)	1 (0.1)
38.0°C to 38.4°C	12 (1.4)	5 (0.6)	82 (10.0)	1 (0.1)
38.5°C to 38.9°C	3 (0.3)	0	57 (7.0)	0
39°C to 40.0°C	0	0	10 (1.2)	0
>40.0°C	0	0	0	0
Headache	N1=878	N1=900	N1=819	N1=839
Any	376 (42.8)	314 (34.9)	574 (70.1)	222 (26.5)
Grade 3[b]	28 (3.2)	14 (1.6)	52 (6.3)	11 (1.3)
Grade 4[b]	0	0	0	0
Fatigue	N1=878	N1=900	N1=819	N1=839
Any	403 (45.9)	330 (36.7)	567 (69.2)	242 (28.8)
Grade 3[c]	13 (1.5)	12 (1.3)	96 (11.7)	11 (1.3)
Grade 4[c]	0	0	0	0
Myalgia	N1=878	N1=900	N1=819	N1=839
Any	249 (28.4)	134 (14.9)	490 (59.8)	112 (13.3)
Grade 3[c]	12 (1.4)	4 (0.4)	92 (11.2)	4 (0.5)
Grade 4[c]	0	0	0	0
Arthralgia	N1=878	N1=900	N1=819	N1=839
Any	154 (17.5)	98 (10.9)	340 (41.5)	67 (8.0)
Grade 3[c]	5 (0.6)	0	47 (5.7)	4 (0.5)
Grade 4[c]	0	0	0	0
Nausea/vomiting	N1=878	N1=900	N1=819	N1=839
Any	113 (12.9)	98 (10.9)	231 (28.2)	80 (9.5)

Event	mRNA-1273 N=878 Dose 1 n (%)	Placebo N=900 Dose 1 n (%)	mRNA-1273 N=819 Dose 2 n (%)	Placebo N=839 Dose 2 n (%)
Grade 3[d]	0	1 (0.1)	0	2 (0.2)
Grade 4[d]	0	0	0	0
Chills	N1=878	N1=900	N1=819	N1=839
Any	126 (14.4)	75 (8.3)	431 (52.6)	66 (7.9)
Grade 3[e]	0	0	11 (1.3)	1 (0.1)
Grade 4[e]	0	0	0	0
Use of antipyretic or pain medication	224 (25.5)	107 (11.9)	467 (57.0)	78 (9.3)

Abbreviations: AR=adverse reaction; IP=investigational product.

Notes: N1=number of exposed participants who submitted any data for the event. Any=Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of randomized participants who received at least 1 dose of IP and contributed any solicited AR data, ie, had at least 1 post-baseline solicited safety (eDiary) assessment. The First (Second) Injection Solicited Safety Set consists of all participants in the Solicited Safety Set who have received the first (second) study injection and have contributed any solicited AR data (eDiary) from the time of first (second) study injection through the following 6 days.

[a] Fever is defined as: Grade 1=38 to 38.4°C; Grade 2=38.5 to 38.9°C; Grade 3=39 to 40°C; Grade 4=greater than 40°C.

[b] Headache: Grade 3: significant, any use of prescription pain reliever or prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

[c] Fatigue, myalgia, arthralgia: Grade 3: significant, prevents daily activity; Grade 4: requires emergency room visit or hospitalization.

[d] Nausea/vomiting: Grade 3: prevents daily activity, requires outpatient intravenous hydration; Grade 4: requires emergency room visit or hospitalization for hypotensive shock.

[e] Chills: Grade 3: prevents daily activity and requires medical intervention; Grade 4: requires emergency room visit or hospitalization.

Solicited ARs by SARS-CoV-2 serostatus

The solicited safety set of the mRNA-1273 vaccine group includes 2,167 subjects seronegative for SARS-CoV-2 at baseline and 147 subjects seropositive. The respective numbers for the placebo group are 1075 and 69 subjects.

In the mRNA-1275 vaccine group, any solicited AR after any dose was recorded by 99.4% of participants seronegative at baseline, and by 98.6% of participants seropositive at baseline. Any solicited local AR in the mRNA-1273 vaccine group was recorded by 98.1% versus 94.6% of subjects, respectively. Any solicited systemic AR was reported by 91.7% versus 93.9% of seronegative and seropositive subjects. The most often recorded solicited local AR in seronegative and seropositive subjects of the mRNA-1273 vaccine group was pain recorded by 97.5% versus 92.5% of subjects, followed by axillary swelling or tenderness (34.3% and 44.2%), and swelling/hardness (28.3% and 22.4%). Erythema was recorded by 26.5% and 21.1% of participants, respectively. Any solicited systemic AR after any dose was recorded by 91.7% of seronegative subjects and by 93.9% of seropositive subjects in the mRNA-1273 vaccine group. The most frequent solicited systemic AR in both age groups was headache (78.3% and 80.3%), followed by fatigue (74.9% and 80.3%), myalgia (54.0% and 59.2%), chills (48.7% and 61.2%) and arthralgia (34.6% and 38.1%). Any fever was recorded by 13.0% of seronegative and 25.9% of seropositive subjects. Any solicited AR grade 3 or more was recorded by 25.4% of seronegative subjects compared to 24.5% of seropositive subjects. Any local solicited AR grade 3 or more was recorded for 13.8% versus 15.0%, and any systemic solicited AR grade 3 or more by 16.5% versus 20.4% of seronegative and seropositive subjects.

After dose one any solicited AR was recorded by 96.1% of seronegative and 93.9% of seropositive subjects, any solicited local AR was recorded by 94.6% versus 89.1%, and any solicited systemic AR by

67.6 versus 87.1%, respectively. After dose 2 any solicited AR was recorded for 97.5% of seronegative and 91.1% of seropositive subjects, and any solicited local AR by 93.8 and 85.6% of subjects, respectively. Any solicited systemic AR was recorded for 86.3% of seronegative and 83.6% of seropositive subjects.

The CHMP considered that there is an imbalance with regard to the sample size of seronegative and seropositive subjects in the mRNA-1273 and the placebo group. The huge majority of subjects in the solicited safety set of the mRNA-1273 vaccine group was seronegative (2167 subjects). Only 147 subjects were seropositive. This needs to be taken into account when comparing reactogenicity data in that subgroup. Results should be interpreted with caution. The incidence of solicited local and systemic ARs after any dose was nonetheless, except for fever (13.0% versus 25.9% of seronegative and seropositive subjects), in general comparable in the two groups. No notable difference with regard to severity of ARs could be observed. The CHMP considered that the data do not indicate any notable increased reactogenicity for seropositive individuals.

Solicited ARs by gender

The solicited safety set included slightly more males than females (1283 versus 1203 subjects in the mRNA-1273 vaccine group). In the mRNA-1275 vaccine group, any solicited AR after any dose was recorded for 99.1% of male participants, and for 99.4% of female participants. Any solicited local AR in the mRNA-1273 vaccine group was recorded by 97.1% versus 98.6% of subjects, respectively. The most often recorded solicited local AR in male and female subjects was pain recorded by 96.2% versus 98.3% of subjects, followed by axillary swelling or tenderness (35.7% and 33.4%), and swelling/hardness (24.8% and 30.8%). Erythema was recorded by 24.4% and 27.3% of participants, respectively. Any solicited systemic AR after any dose was recorded by 90.2% of male subjects and by 93.8% of female subjects in the mRNA-1273 vaccine group. The most frequent solicited systemic AR in both age groups was headache (75.1% and 81.8%), followed by fatigue (72.6% and 77.9%), myalgia (52.3% and 56.4%), and chills (47.6% and 50.6%). Any fever was recorded by 15.1% of male and 12.1% of female subjects. Any solicited AR grade 3 or more was recorded by 22.7% of male subjects compared to 28.1% of female subjects. Any local solicited AR grade 3 or more was recorded by 11.5% versus 16.3%, and any systemic solicited AR grade 3 or more by 15.3% versus 18.1% of male and female subjects.

The CHMP considered that the solicited safety set was rather balanced with regard to gender with only slightly more males than females being enrolled (1283 versus 1203 subjects each). In contrast to the placebo group were notable differences between males and females with regard to the incidence of any solicited AR could be observed, only a slight increase in reports of any solicited ARs post dose 1 in females compared to males (97.4% versus 94.5%) could be seen; the incidence post dose 2 was comparable (97.9 in females versus 96.2% in males). The incidence of any solicited AR after any dose was 99.4% in females versus 99.1% in males. Local reactogenicity was comparable between males and females with regard to frequency and severity. Systemic ARs tended to be numerically slightly higher in female compared with male subjects but were overall within the same range. The same was observed for grade 3 and more systemic ARs that tended to be slightly higher in females, but overall within the same range compared to males. In general, no clinical meaningful difference is observed with regard to reactogenicity of mRNA-1273 between females and males.

Unsolicited adverse events

Unsolicited AEs are in the submitted clinical overview and tables also referred to as treatment-emergent adverse events (TEAEs) were recorded through 28 days after each Injection. Adverse events leading to discontinuation from vaccination and/or study participation, medically attended adverse events (MAAEs), SAEs, AESIs (in this study an AESI is the event of Multisystem Inflammatory Syndrome in Children, MIS-C), and pregnancies are being collected from Day 1 through the entire study period or until last day of study participation.

Summary of unsolicited AEs irrespective of causality

The incidence of unsolicited TEAEs was higher in the mRNA-1273 vaccine group compared with the placebo group. Unsolicited TEAEs irrespective of causality up to 28 days after any dose were reported by 20.5% of subjects in the mRNA-1273 group (510/2,486 subjects) compared to 15.9% of participants in the placebo group (197/1,240 subjects).

An overview of unsolicited AEs with a frequency of more than 1% up to 28 days after any dose for all ages irrespective of causality is given in Table 27.

Table 27: Incidence of Unsolicited TEAEs With Occurrence in ≥ 1% of Participants in Any Treatment Group up to 28 Days After Any Dose Classified by MedDRA Primary System Organ Class and Preferred Term, All Participants Aged ≥ 12 to < 18 Years (Safety Set)

Primary System Organ Class Preferred Term	mRNA-1273 (N = 2,486) Any n (%)	mRNA-1273 (N = 2,486) Severe n (%)	Placebo (N = 1,240) Any n (%)	Placebo (N = 1,240) Severe n (%)
Infections and infestations				
Adverse events in any PT[a]	76 (3.1)	1 (<0.1)	51 (4.1)	0
COVID-19	5 (0.2)	0	13 (1.0)	
Nervous system disorders				
Adverse events in any PT[a]	68 (2.7)	0	31 (2.5)	0
Headache	60 (2.4)		28 (2.3)	
Respiratory, thoracic, and mediastinal disorders				
Adverse events in any PT[a]	34 (1.4)	0	12 (1.0)	0
Gastrointestinal disorders				
Adverse events in any PT[a]	28 (1.1)	1 (<0.1)	20 (1.6)	0
Skin and subcutaneous tissue disorders				
Adverse events in any PT[a]	28 (1.1)	0	7 (0.6)	0
Musculoskeletal and connective tissue disorders				
Adverse events in any PT[a]	58 (2.3)		32 (2.6)	
Myalgia	29 (1.2)	0	14 (1.1)	0
General disorders and administration site conditions				
Adverse events in any PT[a]	250 (10.1)	0	50 (4.0)	0
Injection site lymphadenopathy	108 (4.3)		5 (0.4)	
Injection site erythema	48 (1.9)		3 (0.2)	
Fatigue	46 (1.9)		23 (1.9)	
Injection site induration	28 (1.1)		3 (0.2)	
Injection site pain	28 (1.1)		8 (0.6)	
Injury, poisoning, and procedural complications				
Adverse events in any PT[a]	55 (2.2)	1 (<0.1)	31 (2.5)	0

Abbreviations: COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Note: Percentages are based on the number of safety participants. The Safety Set consists of all randomized participants who received any study injection. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.

[a] Participant experienced at least 1 TEAE within the SOC regardless of the MedDRA PT.

Source: Study P203 Table 3.2.2.1 and Table 3.2.8.

The most commonly recorded unsolicited TEAEs with a frequency of more than 1% occurred in the SOC General disorders and administration site conditions, reported by 10.1% of subjects in the mRNA-1273 vaccine group and by 4.0% of subjects in the placebo group. This included events of injection site lymphadenopathy (4.3% versus 0.4%), injection site erythema (1.9% versus 0.2%), fatigue (1.9% each), injection site induration (1.1% versus 0.2%), and injection site pain (1.1 versus 0.6%). All of the reports of injection site lymphadenopathy were identified as axillary (underarm) swelling or tenderness

ipsilateral to the side of the injection. The incidence of lymphadenopathy within 28 days after any dose was 0.7% in the mRNA-1273 vaccine group (18 subjects) and < 0.1% in the placebo group (1 subject). Within the SOC Skin and subcutaneous tissue disorders 1.1% of subjects in the mRNA-1273 vaccine group and 0.6% in the placebo group reported any unsolicited AE. This imbalance is mostly attributable to the events of urticaria (6 subjects/0.2% versus 1 subject/<0.1%), pityriasis rosea (3 subjects/0.1% versus 0 subjects), and rash. Rash included any rash (3 subjects/0,1% versus 1 subject/<0.1%), rash pruritic (1 subject/0.1% versus 0 subjects) and rash vascular (1 subject/<0.1 versus 0 subjects).

Other numerical imbalances were observed in the SOC of:

- Immune system disorders
    - Type IV hypersensitivity reaction: 3 subjects (0.1%) in the mRNA-1273 vaccine group and no subjects in the placebo group.
- Psychiatric disorders (ADHD, anxiety)
    - attention deficit hyperactivity disorder: 6 subjects in the mRNA-1273 vaccine group (0.2%) versus no subject in the placebo group
    - anxiety and anxiety disorder together: 8 subjects in the mRNA-1273 vaccine group and 2 subjects in the placebo group.
- Endocrine disorders
    - Hypothyroidism: 2 subjects in the mRNA-1273 vaccine group (<0.1%) and no subject in the placebo group.
- Nervous system disorders:
    - dizziness 4 subjects in the mRNA-1273 vaccine group and no subject in the placebo group.
- Eye disorders: 5 subjects in the mRNA-1273 vaccine group versus one subject in the placebo group. The individual events in the mRNA-1273 vaccine group included (eye pain, eye swelling, eyelid oedema, periorbital inflammation, and transient blindness).

Single events of interest are metabolic glucose tolerance impairment (diagnosed as prediabetic), insulin resistance, cardiac disorder of palpitation.

Severe unsolicited AEs were reported by 0.2% of subjects (4/2,486) in the mRNA-1273 vaccine group and by <0.1% (1 subject) in the placebo group. The severe unsolicited AEs in the mRNA-1273 vaccine group were one event each of appendicitis, diarrhoea, vomiting, drug-induced liver injury, testicular torsion, and concussion in a total of 4 participants.

Any COVID-19 was reported in 0.2% of subjects in the mRNA-1273 vaccine group (5 subjects) versus 1.0% in the placebo group (13 subjects).

The CHMP noted that the incidence of unsolicited adverse events irrespective of causality was higher in the mRNA-1273 vaccine group compared with the placebo group. None of the severe unsolicited AEs that occurred in the mRNA-1273 vaccine group were considered being vaccine related. The grade 3 events of vomiting and diarrhoea occurred in one subject together with the event of appendicitis, which is listed as an AESI in the EMA monthly summary safety report (MSSR). The case of drug-induced liver injury is discussed in the SAE section of this report.

<u>Psychiatric disorders:</u>

A numerical disbalance is observed for the event of attention deficit hyperactivity disorder within 28 days after vaccination (6 subjects [0.2%] in the mRNA-1273 versus no subject in the placebo group). It should be noted that 2 cases of ADHD in the placebo group occurred after day 28 (day 29 [grade 2, ongoing] and day 59 [grade 2, ongoing], both post dose 2). Considering that ADHD is no acute event that leads to an immediate diagnosis, it seems legitimate to include these events from the placebo group for considerations regarding relatedness and relevance of this AE. The difference for other psychiatric disorders was less pronounced. Anxiety/anxiety disorder e.g. was recorded for 8 subjects in the mRNA-1273 vaccine group and for 2 subjects in the placebo group (0.3% versus 0.2%). The overall incidence of events in the SOC of psychiatric disorder was 0.7% versus 0.5%. The MAH submitted narratives for all subjects receiving placebo or mRNA-1273 with at least one AE within the SOC of psychiatric disorders with onset within 28 days following any injection. Some of the events in the placebo and the vaccine group were already known from the subjects medical history and need to be classified as worsening of event (e.g. one event of tic, one of depression, one of anxiety, and one of ADHD in the vaccine group). All others are new onset events, the majority not resolved at the time of data snapshot. None of the events of psychiatric disorders in the vaccine group except of tic (actually worsening of pre-existing motor tic) was assessed as vaccine related by the investigator. The field of psychiatric disorders is complex and major changes in the neural system happen during childhood and adolescence. According to CDC in the US 9.4% of children aged 2-17 years have received an ADHD diagnosis, 7.4% of children aged 3-17 years have a diagnosed behaviour problem, 7.1% of children aged 3-17 years have diagnosed anxiety, and 3.2% of children aged 3-17 years have diagnosed depression. The incidence of psychiatric disorders in this trial is below that number in both groups and there is no notable difference between the placebo and the vaccine group with overall 18 events (0.7%) versus 6 events (0.5%). A final conclusion on vaccine relatedness based on this small sample size would be premature and unreliable.

Endocrine disorders:

Two cases of hypothyroidism were reported in the vaccine group. One grade 1 event was reported on day 3 after dose 2. Another grade 2 event occurred on day 23 after dose 2. The first case was resolving and ongoing, the second case ongoing at the time of data snapshot. Both cases were assessed as not related to the mRNA-1273 vaccine. For both cases no clinical information has been submitted. It is unclear whether the cases of hypothyroidism are caused by autoimmune thyroiditis, the most common cause of acquired hypothyroidism in children and adolescents. From the 2 cases of hypothyroidism in the vaccine group a final conclusion on causality is not possible.

Metabolism disorders:

Two cases of glucose metabolism disorders occurred in the mRNA-1273 vaccine group and one in the placebo group. The first case of prediabetic diagnosed in the vaccine group was recorded for an obese study participant (BMI of 39.6 kg/m2 [BMI Z-score 2.42]. The event started on day 22 after dose 2. An event of insulin resistance was recorded for an overweight study participant (BMI of 27.9kg/m2 (BMI Z-score 1.40). The event started on day 6 after dose 2. The event of diabetes mellitus in the placebo group happened to an obese study participant with a BMI of 53.9 kg/m2 (Z-score 3.10) with onset on Day 10 after the first dose of placebo.

With regard to the cases of glucose metabolism disorders vaccine relatedness cannot be concluded on. All 3 subjects were obese or overweight, which is an additional risk factor for glucose metabolism disorders. One subject is Hispanic, a population at higher risk for prediabetes. The prevalence of prediabetes among adolescents is high in the US with nearly 1 in 5 adolescents (Andes LJ, Cheng YJ, Rolka DB et al. Prevalence of Prediabetes Among Adolescents and Young Adults in the United States, 2005-2016. JAMA Pediatr. 2020;174(2):e194498.

Eye disorders:

A minor numerical imbalance was observed for eye disorders (<0.1% in the placebo versus 0.2%) in the vaccine group. Of interest was the event of transient blindness, which was assessed as vaccine related by the investigator and a case of eyelid swelling after both doses of mRNA-1273. The MAH submitted narratives for 6 cases of eye disorders in the vaccine group and 2 in the placebo group.

A case of transient blindness was reported. The subject woke up in the middle of the night, turned on the bedroom light, and was unable to see anything before regaining vision after approximately 1 minute. The CHMP supports the MAH's assessment that this event is unlikely to represent a primary eye disorder or thromboembolic event and most likely related to adaptation to light.

The event of eyelid swelling on day 10 and day 3 post dose 1 and post dose 2 was recorded for a study participant with an ongoing medical history of red dye allergy, asthma, and seasonal allergies. Both events of eye lid swelling happened after nut/ and or almond exposure.

The other 4 events of eye disorder in the mRNA-1273 vaccine group included conjunctival haemorrhage, eye swelling diagnosed as trochleitis, eye pain, and eye swelling.

The events of type IV hypersensitivity reactions, and dizziness, are discussed in the section below "AEs considered being vaccine related". The event of palpitation is discussed in the section myocarditis/pericarditis.

Summary of unsolicited AEs considered being vaccine related

Unsolicited TEAEs considered being vaccine related were recorded by 12.6% of subjects in the mRNA-1273 vaccine group (312/2,486) and by 5.8% of subjects (72/1,240) in the placebo group. Most frequently TEAEs considered being vaccine related were reported in the SOC of General disorders and administration site conditions (9.6% of subjects [238/2,486] in the mRNA-1273 vaccine group and 3.5% in the placebo group [43/1,240]), followed by the SOC of Nervous system disorders (2.4% [59/2,486) versus 1.8% [22/1,240]).

TEAEs considered being vaccine related and reported by ≥ 2% of participants in the mRNA-1273 vaccine group through 28 days after any dose were injection site lymphadenopathy reported by 4.3% (108/2,486) of subjects and headache reported by 2.2% (55/2,486) of subjects. Lymphadenopathy (not restricted to injection site) considered being vaccine related was reported by 0.6% of subjects (16/2,486).

The following vaccine related unsolicited AEs in the mRNA-vaccine group occurred in a lower frequency than 2% but with an imbalance compared to the placebo group. Some of these events (injection site urticaria, hypersensitivity, lymphadenopathy) are already listed as AE for adult subjects:

- Lymphadenopathy: 0.6% of subjects in the mRNA-1273 vaccine group and no subject in the placebo group
- Type IV hypersensitivity reaction: 3 subjects in the mRNA-1273 vaccine group and no subject in the placebo group
- Dizziness: 3 subjects in the mRNA-1273 vaccine group and no subject in the placebo group
- Oropharyngeal pain: 5 subjects in the mRNA-1273 vaccine group and no subject in the placebo group
- Urticaria: 4 subjects in the mRNA-1273 vaccine group and 1 subject in the placebo group
- Injection site hypersensitivity: 8 subjects in the mRNA-1273 vaccine group (0.3%) and no subject in the placebo group

- Injection site urticaria: 4 subjects in the mRNA-1273 vaccine group (0.2%) and no subject in the placebo group.

The CHMP considered that most of unsolicited AEs considered being vaccine related are attributable to events of local injection site reactions in the SOC of general disorders and administration site conditions. Not all of the unsolicited AEs that were recorded in this trial and that were considered being vaccine related are covered in the SmPC for the paediatric population yet.

With regard to the adverse reaction table in section 4.8 of the SmPC, the CHMP decided that a single table for all ages is appropriate, i.e. all AEs from the paediatric population not listed yet in the "adult" table should be included in the existing table, with correct frequency.

Type IV hypersensitivity reactions:

The three unsolicited AEs of type IV hypersensitivity reactions in the 3 subjects were all events of delayed cutaneous hypersensitivity reactions with onset on Day 8 to 11 after the first dose of mRNA-1273. One subject did not provide an additional description about the event. A second subject noted a non-urticarial rash on the left upper arm (ipsilateral to where the injection was given) and the third reported a pruritic, papular non-urticarial rash on the lower legs. None of the three subjects reported notable solicited local adverse reactions in the eDiary after the first dose of mRNA-1273 other than Grade 1 injection site pain. Because of the timing being consistent with reports of delayed cutaneous hypersensitivity reactions, the events of type IV hypersensitivity reactions are considered most probably vaccine associated. A separate variation is already under discussion to update the product information regarding delayed injection site reactions. It is therefore decided to include delayed injection site reactions as an AR in the SmPC.

Dizziness:

3 cases of dizziness are considered being vaccine related by the investigator. The onset was on day 2, 1, and 10. The onset time of one of the 3 events, i.e. 10 days after vaccination, is long for vaccine related dizziness. A biological plausibility for dizziness being vaccine related is given. A causal relationship between vaccination with mRNA-1273 and the adverse event of dizziness is at least a reasonable possibility. The event of dizziness is therefore included in section 4.8 of the SmPC.

Urticaria/Hypersensitivity:

Four subjects (0.2%) in the mRNA-1273 group and 1 subject (<0.1%) in the placebo group had at least one unsolicited treatment-related TEAE of urticaria up to 28 days after any injection. The 4 events in the mRNA-1273 vaccine group occurred on day 1,4,11, and 21 after vaccination and were either generalised (one case) or restricted to parts of the body (feet and elbows, groin, left deltoid, back and right leg). All 4 events were assessed as being vaccine related by the investigator. The assessment is supported. The events are suggestive of a hypersensitivity response. The event of hypersensitivity is covered in the SmPC, but only for adult subjects. During licensure of mRNA-1273 it was agreed to summarise all events indicative of hypersensitivity under the PT "hypersensitivity" and not to list them separately (leading to the frequency calculation "unknown"). The events of hypersensitivity and injection site urticaria are already covered in the SmPC.

Hot flush:

One case of hot flush was reported 6 hours after dose 1. The event resolved at midnight and did not reoccur after dose 2. The case was assessed as being vaccine related by the investigator. Hot flush is a commonly described reaction after a vaccination procedure. A procedure related stress response cannot be excluded.

Discoloration at injection site:

One subject experienced injection site discoloration on day 11 after dose 1, resolving on day 15. Other local injection site reactions after dose 1 included grade 1 pain and grade 1 redness. The event was actually not assessed as vaccine related by the investigator. However, such local AR cannot totally be excluded.

For the two events of hot flush and injection site discoloration a causal relationship cannot be excluded. Both are singular events, were mild and resolved. It is considered acceptable to not include them in the SmPC for the time being.

Hypoaesthesia:

There was one event of treatment-related hypoaesthesia (bilateral arm numbness, grade 2, onset on day 5 after first vaccination, still ongoing). Considering that there was also an imbalance for treatment-related events of hypoaesthesia in the adult study (vaccine: 4 events, placebo: no event), this AE is therefore added in section 4.8 of the SmPC.

Chilblains:

There was one event of treatment-related chilblains in the vaccine group. Of note, the event of chilblains has been associated with (often otherwise asymptomatic) COVID-19 infection and was also referred to as "COVID toe" (https://doi.org/10.1053/j.seminoncol.2020.05.012, DOI: 10.1111/jdv.16753). According to narratives for this event (verbatim worsening pernio, right foot), the subject had a history of acrocyanosis (since April 2020), chronic chilblains (since March 2020), coagulation disorders (FV and FVII deficiency, since June 2020) and chronic toe infections prior to receipt of mRNA-1273. Therefore, it is agreed with the MAH that a causal association with vaccination is improbable for the time being.

Lymphadenopathy:

The AE of lymphadenopathy is listed as an adverse reaction with the frequency of very common. This event was solicited as axillary swelling ipsilateral to the vaccination arm. The provided AE listings indicate that in some cases other lymph nodes (e. g. 4x cervical, 6x supraclavicular) were also involved. Similar observations were made in the adult study. Therefore, the footnote of Table 1 of section 4.8 of the SmPC is amended to inform about these findings.

Anaphylaxis

No cases of anaphylactic reaction considered being vaccine related were reported in the mRNA-1273 vaccine group.

Hypersensitivity

Taking the narrow and broad hypersensitivity SQM together 1.9% (46) of subjects in the mRNA-1273 vaccine group and 0.8% (10) of subjects in the placebo group reported any event indicating hypersensitivity. Taking the narrow scope, the proportion was 1.6% (39) and 0.5% (6) of subjects.

The most frequently reported events considered being vaccine related (narrow and broad hypersensitivity SMQ) in the mRNA-1273 group were injection site hypersensitivity (8 subjects, 0.3%), injection site urticaria (0.2%, 4 subjects), rash (0.2%, 4 subjects) and urticaria (0.2%, 6 subjects). 3 subjects (0.1%) reported a type IV hypersensitivity reaction. This included a non-urticarial rash at the upper arm, and a pruritic rash of lower legs. One type IV hypersensitivity reaction was not further specified. Injection site rash was reported by 2 subjects (<0.1%). Individual reports of vaccine related events indicating hypersensitivity included worsening of photosensitivity, sneezing, wheezing, pruritus, and vesicular, pruritic and urticarial rash. Hypersensitivity reactions also include cases of delayed cutaneous hypersensitivity reactions. One case of anaphylactic reaction not assessed as vaccine related was reported (anaphylactic reaction to tree nut).

A separate variation is already under discussion to update the product information regarding delayed injection site reactions. Considering that an imbalance in delayed / type IV hypersensitivity reactions was noted in the clinical trials, it is therefore decided to include delayed injection site reactions as an AR in the SmPC.

Serious adverse event/deaths/other significant events

SAEs

Within 28 days after each vaccination any SAE was reported by 2 subjects in the mRNA-1273 vaccine group any by 1 subject in the placebo group (<0.1%). The 2 SAEs in the mRNA-1273 vaccine group included one event of drug-induced liver injury in one participant and one event each of appendicitis, diarrhoea, vomiting, and post-procedural fever in a second participant.

The event of drug-induced liver injury occurred in a study participant who received the first dose of 100 µg mRNA1273 in the left arm. 7 days later the participant was found to have a Bartholin gland cyst that was treated for 7 days with sulfamethoxazole/trimethoprim. On day 13, the study participant experienced fever, fatigue, and generalised body aches. Per report, a COVID-19 test was negative. On day 16, the study participant went to the emergency room with intermittent fevers, nausea, vomiting, and decreased oral intake. The rash was largely resolved at this time. The study participant was admitted to hospital for treatment of nausea and vomiting. Laboratory results and ultrasound indicated liver involvement. The study participant reported malaise and headaches for 1.5 weeks, fevers for 4 days, and nausea/vomiting for 1 day, moreover progressively dark coloured urine, no jaundice and clay coloured stool. Hepatitis panel including hepatitis A IgM, hepatitis B core IgM, hepatitis B surface Ag and hepatitis C Ab were non-reactive. Cytomegalovirus test, Epstein Barr Virus Quantitative PCR test and Herpes Simplex Qualitative PCR were negative. The participant was diagnosed with hepatitis, most likely drug-induced liver injury secondary to sulfamethoxazole/trimethoprim. Treatment for the drug-induced liver injury included ondansetron, IV electrolyte solution and sodium chloride 0.9% IV solution. The event of drug-induced liver injury was considered to be resolved on day 30. The investigator assessed the event of drug-induced liver injury to be not related to the IP. The second dose on Day 29 was not administered per Sponsor recommendation and physician decision to discontinue the participant from IP. The participant was discontinued from the study and IP on day 42.

The case of appendicitis together with diarrhoea, vomiting, and post-procedural fever occurred in a study participant who received the first two doses of 100 µg mRNA-1273 30 days apart. Three days after the first dose, the participant experienced a grade 3 severe SAE of appendicitis and underwent a laparoscopic appendectomy. The participant was discharged from the hospital on day 5. The event of appendicitis was considered to be resolved on day 4. The investigator assessed the event of appendicitis not to be related to the IP.

At the time of data snapshot SAEs were reported by 0.2% of subjects each in the MRNA-1273 vaccine group (6 subjects) and the placebo group (2 subjects). SAEs in the mRNA-1273 vaccine group beside the 2 events of drug-induced liver injury and appendicitis together with diarrhoea, vomiting, and post-procedural fever were pectus excavatum, suicidal ideation (2 subjects, none in the placebo group), and depression suicidal (1 subject, none in the placebo group). In the placebo group one suicide attempt and one case of obstructive nephropathy were recorded as SAE by one subject each.

None of the SAEs reported at the time of data snapshot were considered being vaccine related.

SAEs considered being vaccine related

No SAEs being considered vaccine related were reported at the time of data snapshot.

Deaths

At the time of the data snapshot (08 May 2021), no SAEs with fatal outcome or deaths were reported.

AESI

Multisystem Inflammatory Syndrome in Children (MIS-C) was defined as AESI in this trial. No cases were reported at the time of data snapshot.

Myocarditis

No cases of myocarditis have been reported at the time of data snapshot.

Three subjects in the mRNA-1273 vaccine group reported symptoms that could be consistent with myocarditis or pericarditis.

1.) The first case is a study participant who, on the day after the second dose of mRNA 1273 at 07:00, experienced a Grade 2 non-serious MAAE of Palpitations (verbatim: intermittent tachy-palpitations). The participant also experienced the Grade 2 non-serious MAAEs of wheezing with onset on the same day at 09:00 and the Grade 2 non-serious MAAE of Non-cardiac chest pain with onset on the very same day. Other relevant unsolicited adverse events reported near the time of event onset included a Grade 1 non-serious TEAE of Viral infection with onset 16 days before the second dose and resolution 2 days before the second dose. The event of palpitations was considered resolved on day 2, the event of non-cardiac chest pain and the event of wheezing were considered resolved on day 3. The CHMP considered that the symptoms are in general consistent with myocarditis or pericarditis. However, the AE of palpitations resolved within 1 day and the AEs of wheezing and non-cardiac chest pain resolved within 3 days, which makes this diagnose rather unlikely. An inclusion of the singular events of wheezing, palpitation, and non-cardiac chest pain as AEs into the SmPC is currently not supported.

2.) A study participant without any medication and medical history, reported an event of Grade 2 non serious MAAE of painful respiration (chest pain with painful respirations) and a Grade 2 non-serious MAAE of dyspnoea, one day after dose 2. Additional solicited ARs post dose 2 included grade 1 and grade 2 headache on day 1 and 2, grade 2 and grade 3 3 fatigue on day 1 and 2, grade 2 myalgia on day 1 and 2, grade 1 arthralgia on day 1, and grade 1 and grade 2 chills on day 1, 2, and 4. The two events of painful respiration, and dyspnoea resolved the same day. Both events were assessed as being vaccine related by the investigator. The CHMP considered that relatedness of chest pain, painful breathing and dyspnoea to study vaccination cannot be excluded. The events resolved within one day and are therefore not likely indicative of myocarditis or pericarditis. The two events were accompanied by other grade 1 to grade 3 solicited ARs, which might have induced or stimulated the breathing problems. It can be acceptable to not include these singular events in the SmPC for the time being.

3.) A study participant reported pain to the left side of the chest with deep inspiration and position changes 4 days after dose 2 of mRNA-1273. The event was diagnosed and classified as Grade 2 non-serious MAAE of costochondritis. The subject went to the ER and had a chest x-ray and an electrocardiogram 5 days after dose 2. Both examinations without findings. Solicited systemic adverse reactions reported after dose 2 included Grade 1 fatigue and Grade 1 arthralgia on Day 3. Solicited local adverse reactions after dose 2 included Grade 1 to Grade 2 injection site pain on Day 1 to Day 3 and Grade 2 to Grade 3 injection site swelling on Day 1 to Day 2. The event was ongoing at the time of data snapshot. The event of costochondritis was assessed as not being vaccine related by the investigator. The CHMP noted that the symptoms leading to the diagnosis of osteochondritis are rather unspecific. The event was ongoing at the time of data snapshot. Without follow up information and based on the limited clinical information a final conclusion is

not possible. Myocarditis/pericarditis appears unlikely as the ECG and x-ray did not reveal any findings.

Overall comment on myocarditis/pericarditis:

The issue of myocarditis after vaccination with COVID-19 mRNA vaccines was first flagged by Israel health officials, when during the COVID-19 vaccine campaign in Israel a more than expected number of myocarditis cases occurred. The cases were mostly reported in young men who had received their second dose of vaccine a few days earlier. Following PRAC evaluation of the safety signal of myocarditis/pericarditis these two events have been included into the SmPC section 4.8. in the SOC: "Cardiac disorders" with frequency "unknown. For 3 presented cases with symptoms indicative of myocarditis clinical medical information is limited. A diagnosis of myocarditis/pericarditis based on the information provided in the narratives however is considered unlikely. For the singular events of palpitation, non-cardiac chest pain, wheezing, painful breathing, painful respiration, and dyspnoea it is difficult to establish a causal association. The events were accompanied by solicited ARs and might be indicative of the general reactogenicity of the mRNA-1273 vaccine. It is deemed acceptable to not include them into the SmPC so far.

Laboratory findings

Laboratory safety analyses were not carried out.

Safety in special populations

The population of the trial included healthy adolescents 12 to 18 years of age. Individuals with a HIV infection or individuals under immunosuppressants or immune-modifying medication for more than 14 days in total within 6 months prior to the day of enrolment were not allowed to participate.

Safety related to drug-drug interactions and other interactions

No interaction study has been performed.

Discontinuation due to adverse events

Until data lock point, three subjects discontinued due to AEs, all of them were from the mRNA-1273 vaccine group. None of the AEs leading to discontinuation is considered being vaccine related. No subject in the placebo group discontinued due to an AE.

One participant in the mRNA-1273 group discontinued from study vaccine due to a grade 1 MAAE of COVID-19 that began on Day 10 day after dose 1 of mRNA-1273.

One study participant in the mRNA-1273 group discontinued the study 4 days after dose 2 due to a MAAE of grade 2 right eye swelling. In addition a study participant did not receive dose 2 of mRNA-1273 and was discontinued from the study vaccine per physician decision and discussion with the Sponsor, following a grade 3 serious MAAE of drug-induced liver injury. Details about the case of liver injury are discussed in the serious adverse event section.

Post-marketing experience

The MAH has not submitted a summary of safety data after approval. mRNA-1273 received a Conditional Marketing Authorisation in the EU on 6th of January 2021 under the invented name COVID-19 Vaccine Moderna for individuals of 18 years of age and older. The vaccine has moreover been authorised for emergency use in 15 other countries or regions (including WHO authorisation). Since the approval, the vaccine has been used extensively. Safety data updates are summarised in the EMA Monthly Summary Safety Reports (MSSRs). As of 31 May 2021, a total of 155,522,108 doses of the vaccine had been administered (5th EMA MSSR).

2.5.1. Discussion on clinical safety

Safety data base:

In this trial, subjects were randomised in a 2:1 randomisation ratio to receive either mRNA-1273 or placebo. Therefore, the two groups were not balanced with regard to the sample size, which is deemed acceptable. The overall sample size of the Safety Set included 3,726 subjects. 2,486 subjects received at least one dose of mRNA-1273 vaccine, and 1,240 received at least one dose of placebo. The majority of subjects belonged to the younger age cohort 12 to 16 years of age. The number of subjects included into the ≥12 to <16 years of age cohort was approximately 3-fold higher than the number of subjects in the older age cohort ≥16 to <18 years. In the mRNA-1273 vaccine group 1,838 subjects belonged to the age range of ≥12 and <16 years of age and 648 subjects to the age range ≥16 and <18 years. In the placebo group, the sample size in the two age cohorts was 929 and 311 subjects, respectively.

The solicited safety set includes almost the same sample size like the safety set, i.e. overall 2,485 subjects in the mRNA-1273 vaccine group (1,838 in the age cohort ≥12 to <16 years of age and 647 ≥16 to <18 years of age), and 1,240 in the placebo group (929 subjects in the younger and 311 in the older age cohort).

The safety data base is deemed acceptable.

Exposure to vaccine:

Data cut-off date is 08 May 2021. As of 08 May 2021 (data snapshot date), 2,486 of 2,489 randomised participants (99.9%) in the mRNA-1273 group and 1,240 of 1,243 randomised (99.8%) in the placebo group received dose 1, and 2,480 (99.6%) in the mRNA-1273 group and 1,222 (98.3%) in the placebo group received dose 2, respectively.

The median follow-up duration post dose 2 was 53 days for vaccine recipients and 51 days for placebo recipients at the data snapshot on 08 May 2021. Follow up period in the Safety Set of the mRNA-1273 vaccine group was comparable between the 2 age cohorts ≥12 and <16 years and ≥16 and <18 years. In the Safety Set of the mRNA-1273 group, 43.6% of subjects ≥12 to <16 years of age and 44.1% of subjects ≥16 to <18 years had a follow-up period of more than 56 days after dose 2. 54.9% (1,366) of subjects in the mRNA-1273 group had a follow-up between ≥28 and <56 days after dose 2. All subjects except of 12 in the mRNA vaccine group had a follow-up time of 7 days after dose 2 (99.5%).

Dropout rate was low in the mRNA-1273 vaccine group (overall 2.3% of subjects), but notably higher in the placebo group (overall 15.1%, respectively, because of the increasing availability of authorised mRNA-COVID-19 vaccines. Mainly adolescents between 16 to 18 years of age requested early unblinding. This was confirmed by the sponsor.

No subject in the vaccine group discontinued due to a vaccine related AE.

Demography:

Demographic and baseline characteristics of the safety set are balanced between the mRNA-1273 group and the placebo group in the older and the younger age cohort. The majority of subjects was enrolled in the younger age cohort ≥12 to 16 years of age (74.3% of subjects). 83.9% of subjects were white. 48.6% of subjects were female and 51.4% were male. The majority of subjects was seronegative for SARS-CoV-2 at baseline (87.0%).

Local and systemic reactogenicity:

The incidence of solicited local and systemic ARs was as it can be expected higher in the mRNA-1273 group compared with the placebo group. The mRNA-1273 vaccine is reactogenic. Any solicited local AR after any dose was recorded for 97.8% of subjects in the mRNA-1273 vaccine group (2,431/2,485) and for 48.5% of subjects (602/1,240) in the placebo group. The most frequently reported local solicited AR in the mRNA-1273 and the placebo group after any dose was injection site pain reported by 97.2% of subjects in the mRNA-1273 vaccine group and by 45.9% of subjects in the placebo group. This was followed by axillary swelling or tenderness (34.6% versus 10.7%), swelling (27.7% versus 1.9%), and erythema/redness (25.8% versus 1.5%).

The incidence of any solicited systemic AR after any dose was 91.9% in the mRNA-1273 vaccine group (2,284/2,485 subjects), and 66.9% of subjects in the placebo group (830/1,240 subjects). The most frequently reported systemic solicited AR in the mRNA-1273 group after any dose was headache reported by 78.4% of subjects in the mRNA-1273 vaccine group and by 50.3% of subjects in the placebo group. This was followed by fatigue (75.2% versus 47.5%), myalgia (54.3% versus 23.5%), chills (49.1% versus 16.2%), arthralgia (34.6 versus 16.9%), and nausea (29.3% versus 15.2%). Fever of any grade was reported by 13.7% versus 1.9% of subjects.

The majority of solicited local ARs occurred within the first 1 to 2 days after any dose and persisted for a median of 3 days. The majority of systemic ARs had an onset within the first 2 days and a median duration of 2 days.

Though the majority of solicited ARs (local and systemic) was mild to moderate it should be noted, that after any dose in the mRNA-1273 vaccine group 13.8% of subjects reported grade 3 solicited local and 16,5% solicited systemic ARs. The severity of local and systemic reactogenicity increased from dose 1 to dose 2. Any grade 3 local solicited AE was reported by 6.8% versus 8.9% of subjects after any dose. Any grade 3 systemic solicited AE by 4.4% and 13.7%, respectively. The relatively high incidence of grade 3 events after the second injection was mainly caused by fatigue (7.6%), myalgia (5.2%), and headache (4.5%). Grade 3 fever occurred in 1.9% of the vaccinated participants after the second injection. Of note, some of the vaccinees reported more than one of these events at the same time, which is the reason why the sum of the individual incidences does not fit the total incidence of 13.7%. There were three grade 4 events in the mRNA-1273 group (1x fever [>40°C], 1x headache, 1x nausea/vomiting).

Reactogenicity by dose:

For solicited local reactions no clear trend could be observed regarding differences in severity post dose 1 and post dose 2. The incidence of solicited systemic ARs however was notably higher post dose 2 compared to post dose 1, i.e. depending on the kind of event approximately 2 to 3 fold higher after dose 2 than after dose 1.

By age:

Local and systemic reactogenicity was generally comparable in the 2 age cohorts included in the trial with regard to frequency and severity. It must be taken into account that the sample size in the younger age cohort was 3-fold higher than the sample size in the older age cohort.

Data on solicited systemic and local ARs in the age cohort 18 to 25 years of age from study P301 suggested a higher local reactogenicity for all solicited local ARs except for pain in the age cohort 12 to <18 years compared with the age cohort 18 to 25 years of age. The incidence of systemic solicited ARs tended to be comparable or slightly higher in the age cohort 18 to 25 years of age compared with the age cohort 12 to <18 years of age. The incidence of grade 3 systemic ARs is lower for adolescents (4.4% dose 1, 13.7% dose 2), compared to young adults (5.2% dose 1, 21.6% dose 2). In contrast, the incidence of grade 3 local ARs tends to be slightly higher for adolescents (6.8% dose 1, 8.9% dose 2), compared to young adults (5.9% dose 1, 7.7% dose 2). It should be noted, that the sample size in the age cohort 12 to <18 years was 3 fold higher than in the age cohort 18 to 25 years of age.

No dose finding studies were performed for the younger age group below 25 years of age. The paediatric dose is the same as for adults. It cannot be excluded, that a lower dose with lower reactogenicity could induce a non-inferior immune response and protection.

By SARS-CoV-2 serostatus:

The incidence of solicited local and systemic ARs after any dose was, except for fever (13.0% versus 25.9% in seronegative and seropositive subjects in the mRNA-1273 vaccine group) in general comparable in subjects seropositive and seronegative for SARS-CoV-2 at baseline. No notable difference with regard to severity of ARs could be observed. There is an imbalance with regard to the sample size of seronegative and seropositive subjects in the mRNA-1273 and the placebo group. The huge majority of subjects in the solicited safety set of the mRNA-1273 vaccine group was seronegative (2167 subjects). Only 147 subjects were seropositive. This needs to be taken into account when comparing reactogenicity data in the subgroups of seropositive and seronegative subjects.

By sex:

The solicited safety set was rather balanced with regard to sex. Local reactogenicity was comparable between males and females with regard to frequency and severity. Systemic ARs tended to be numerically slightly higher in female compared with male subjects but were overall within the same range. The same was observed for grade 3 and more systemic ARs that tended to be slightly higher in females, but were overall also within the same range compared to males. In general, no clinical meaningful difference is observed with regard to reactogenicity of mRNA-1273 between females and males.

Use of pain medication:

The high reactogenicity of the mRNA-1273 vaccine is reflected in the use of antipyretic and pain medication. The use of antipyretic or pain medication was notably higher in the mRNA-1273 vaccine group compared with the placebo group. In the mRNA-1273 vaccine group, 30.1% of subjects used such medication after dose 1 and 50.1% after dose 2. The proportion was 9.5% and 8.9% in the placebo group, respectively. Also the severity particularly for systemic AEs increased from post dose 1 to post dose 2.

Unsolicited AEs:

The incidence of unsolicited adverse events irrespective of causality was higher in the mRNA-1273 vaccine group compared with the placebo group. Unsolicited TEAEs irrespective of causality up to 28 days after any dose were reported by 20.5% of subjects in the mRNA-1273 group (510/2,486 subjects) compared to 15.9% of participants in the placebo group (197/1,240 subjects). The most commonly recorded unsolicited TEAEs with a frequency of more than 1% occurred in the SOC General disorders and administration site conditions, reported by 10.1% of subjects in the mRNA-1273 vaccine group and by 4.0% of subjects in the placebo group. This included events of injection site lymphadenopathy (4.3% versus 0.4%), injection site erythema (1.9% versus 0.2%), fatigue (1.9% each), injection site induration

(1.1% versus 0.2%), and injection site pain (1.1 versus 0.6%). Severe unsolicited AEs were reported by 0.2% of subjects (4/2,486) in the mRNA-1273 vaccine group and by <0.1% (1 subject) in the placebo group. The severe unsolicited AEs in the mRNA-1273 vaccine group were one event each of appendicitis, diarrhoea, vomiting, drug-induced liver injury, testicular torsion, and concussion in a total of 4 participants. None of the severe unsolicited AEs that occurred in the mRNA-1273 vaccine group were considered being vaccine related.

Metabolic, endocrine and autoimmune disorders:

Two cases of prediabetic diagnose were reported in the vaccine group and one in the placebo group. Both subjects in the vaccine group had additional risk factors (both overweight/obesity, one subject is of Hispanic origin).

Two cases of hypothyroidism were reported in the vaccine group and none in the placebo group. Only very limited clinical information is available. The cases of hypothyroidism were diagnosed on day 3 and day 23 post dose 2 in one male and one female subject. It is unclear whether the cases are caused by autoimmune thyroiditis. From the two cases no conclusion on vaccine relatedness can be drawn.

There was one event of treatment-related chilblains in the vaccine group. Of note, the event of chilblains has been associated with (often otherwise asymptomatic) COVID-19 infection and was also referred to as "COVID toe" (https://doi.org/10.1053/j.seminoncol.2020.05.012, DOI: 10.1111/jdv.16753). According to the narratives for this event (verbatim worsening pernio, right foot), the subject had a history of acrocyanosis (since April 2020), chronic chilblains (since March 2020), coagulation disorders (FV and FVII deficiency, since June 2020) and chronic toe infections prior to receipt of mRNA-1273. Therefore, it is agreed with the MAH that a causal association with vaccination is improbable at the time being.

Psychiatric disorders

There was an imbalance for the SOC of Psychiatric Disorders (vaccine: 0.7%, placebo: 0.5%). However, the only event that was considered treatment-related (and also related to the study procedure itself) by the Investigator was the AE of tic (verbatim Worsening of Motor Tic). The subject had a history of motor tics since 2019. No action was taken with study vaccine due to MAAE of tic and no concomitant treatment was given for the event of tic.

Vaccine related unsolicited AEs:

Unsolicited TEAEs considered being vaccine related were recorded by 12.6% of subjects in the mRNA-1273 vaccine group (312/2,486) and by 5.8% of subjects (72/1,240) in the placebo group. Most frequently TEAEs considered being vaccine related were reported in the SOC of General disorders and administration site conditions (9.6% of subjects [238/2,486] in the mRNA-1273 vaccine group and 3.5% in the placebo group [43/1,240]), followed by the SOC of Nervous system disorders (2.4% [59/2,486) versus 1.8% [22/1,240]). TEAEs considered being vaccine related and reported by ≥ 2% of participants in the mRNA-1273 vaccine group through 28 days after any dose were injection site lymphadenopathy reported by 4.3% (108/2,486) of subjects and headache reported by 2.2% (55/2,486) of subjects. Lymphadenopathy (not restricted to injection site) considered being vaccine related was reported by 0.6% of subjects (16/2,486).

Not all AEs considered being vaccine related are yet listed in section 4.8 of the SmPC for the adolescent population, but some of them already for the adult population. The CHMP decided that a single table for all ages is appropriate, i.e. all AEs from the paediatric population not listed yet in the "adult" table should be included in the existing table, with correct frequency.

The following AEs should be reflected based on data from the paediatric population:

- Type IV hypersensitivity reactions/delayed injection site reaction:

The three unsolicited AEs of type IV hypersensitivity reactions in the 3 subjects were all events of delayed cutaneous hypersensitivity reactions with onset on Day 8 to 11 after the first dose of mRNA-1273. Because of the timing being consistent with reports of delayed cutaneous hypersensitivity reactions, the events of type IV hypersensitivity reactions are considered most probably vaccine associated. A separate variation is already under discussion to update the product information regarding delayed injection site reactions. It is therefore decided to include delayed injection site reactions as an AR in the SmPC.

- Dizziness:

3 cases of dizziness are considered being vaccine related by the investigator. The onset was on day 2, 1, and 10. A biological plausibility for dizziness being vaccine related is given. A causal relationship between vaccination with mRNA-1273 and the adverse event of dizziness is at least a reasonable possibility. The event of dizziness is therefore included into section 4.8 of the SmPC with a frequency uncommon.

- Urticaria/Hypersensitivity:

Four subjects (0.2%) in the mRNA-1273 group and 1 subject (<0.1%) in the placebo group had at least one unsolicited treatment-related TEAE of urticaria up to 28 days after any injection. The 4 events in the mRNA-1273 vaccine group occurred on day 1,4,11, and 21 after vaccination and were either generalised (one case) or restricted to parts of the body (feet and elbows, groin, left deltoid, back and right leg). All 4 events were assessed as being vaccine related by the investigator. The assessment is supported. The events are suggestive of a hypersensitivity response. The event of hypersensitivity is covered in the SmPC, but only for adult subjects. During licensure of mRNA-1273 it was agreed to summarise all events indicative of hypersensitivity under the PT "hypersensitivity" and not to list them separately (leading to the frequency calculation "unknown").

- Hypoaesthesia:

There was one event of treatment-related hypoaesthesia (bilateral arm numbness, grade 2, onset on day 5 after first vaccination, still ongoing). Already in the adult trial an imbalance for treatment-related events of hypoaesthesia was observed (vaccine: 4 events, placebo: no event). This AE is therefore included in section 4.8 of the SmPC with a frequency rare.

- Blood and lymphatic system disorders:

There were 16 treatment-related events of lymphadenopathy in the vaccine group, compared to none in the placebo group. Lymphadenopathy, which was captured as a solicited event (axillary lymphadenopathy on the same side of the injection site) is already included in the SmPC with the frequency of "very common". However, there were also some cases of lymph nodes swellings at other sites (e.g. cervical or supraclavicular) in both the adolescent and adult studies. Therefore, a small amendment of the legend of the table in section 4.8 is implemented.

<u>SAEs:</u>

At the time of data snapshot SAEs were reported by 0.2% of subjects each in the MRNA-1273 vaccine group (6 subjects) and the placebo group (2 subjects). SAEs in the mRNA-1273 vaccine group included drug-induced liver injury, appendicitis together with diarrhoea, vomiting, and post-procedural fever, pectus excavatum, suicidal ideation (2 subjects, none in the placebo group), and depression suicidal (1 subject, none in the placebo group). In the placebo group one suicide attempt and one case of obstructive nephropathy were recorded as SAE by one subject each.

None of the SAEs reported at the time of data snapshot were considered being vaccine related.

<u>AESI:</u>

Multisystem Inflammatory Syndrome in Children (MIS-C) was defined as AESI in this trial. No cases were reported at the time of data snapshot.

Myocarditis/pericarditis:

The issue of myocarditis after vaccination with COVID-19 mRNA vaccines was first flagged by Israel health officials, when during the COVID-19 vaccine campaign in Israel a more than expected number of myocarditis cases occurred. The cases were mostly reported in young men who had received their second dose of vaccine a few days earlier. On 09 July 2021, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded to recommend listing myocarditis and pericarditis as a side effect in the product information of both currently authorised mRNA vaccines, due to the occurrence of very rare cases in the post-marketing phase. The two events have been included into the SmPC section 4.8 in the SOC "Cardiac disorders" with a frequency "unknown". No cases of myocarditis or pericarditis were reported in this trial.

Unsolicited AEs from this trial do not reveal clinical signs of immune thrombocytopenia, an AE under close monitoring in the context of the Periodic Safety Update Reports. Safety lab was not performed in this trial. In the COVID-19 vaccine safety update report for Spikevax from 14th of July 2021, nine cases were considered possibly related to the vaccine. No clear causal relationship could be established in any of these cases.

The sample size of the trial is overall not sufficient to evaluate rare or very rare events like e.g. autoimmune disorders. The trial was restricted to healthy adolescents. No safety data are available for adolescents with underlying chronic medical conditions and immune suppression. In the Safety Set of the mRNA-1273 group, only 43.6% of subjects ≥12 to <16 years of age and 44.1% of subjects ≥16 to <18 years had a follow-up period of more than 56 days after dose 2. Long-term safety data are not available yet. The study period of this trial will be 1 year.

The following AEs should be added in the SmPC:

- Delayed injection site reactions
- Dizziness
- Hypersensitivity
- Hypoaesthesia

A single AE table should be used for all age groups. Hypersensitivity and injection site urticarial are already covered in table 1 in section 4.8 of the SmPC. Dizziness, hypoaesthesia, and delayed injection site reactions must be added with corresponding frequency. For hypersensitivity the frequency is listed as unknown, due to a decision made during licensure (inclusion of all AEs indicative of hypersensitivity, e.g. urticaria, instead of separate listing).

The final clinical study report for study mRNA-1273-P203 will be submitted no later than September 2022 and is subject to a specific obligation laid down in the marketing authorisation, in order to provide long-term safety data in adolescents 12-17 years of age.

2.5.2. Conclusions on clinical safety

This type II variation aims to extend the indication to include adolescents aged 12 to <18 years of age for Spikevax. The database for evaluation of the safety profile of mRNA-1273 in the paediatric population 12 to <18 years of age derives from an ongoing Phase 2/3, randomised, placebo-controlled trial. Route of administration, dose and schedule were the same as for the adults, i.e. 100 µg IM, given as 2 injections, 28 days apart. Safety data are available from 3,726 subjects recruited in the US, of whom 2,486 were exposed to the Spikevax vaccine and 1,240 who received saline placebo. The median follow-up duration

post dose 2 was 53 days for vaccine recipients and 51 days for placebo recipients at the data snapshot on 08 May 2021. Spikevax (mRNA-1273) is reactogenic in the paediatric population and the observed rates of adverse reactions were higher in comparison to adults, which is not unexpected. The low incidence of severe cases of COVID-19 in the healthy paediatric population must be taken into account here. The reactogenicity and safety profile of the vaccine is however not clinically meaningful different from that in the adult subpopulation 18 to 25 years of age. Study P203 confirmed the previous finding that the majority of solicited ARs are mild or moderate in severity and occur within the first 1 to 2 days after IP injection. The individual adverse reactions persisted for a median of 1 to 3 days.

There was an imbalance regarding the number of subjects reporting unsolicited AEs up to 28 days after any vaccination. The difference was mainly caused by injections site reactions (e.g. injection site lymphadenopathy, injection site erythema) persisting beyond day 7 after vaccination. There was no difference regarding the incidence of MAAEs between the vaccine and the placebo group.

Some amendments of section 4.8 of the SmPC are considered necessary, mainly based on imbalances for some particular AEs (dizziness, hypoaesthesia). The study was restricted to healthy paediatric individuals. No conclusion on the safety profile in individuals with comorbidities or under immunosuppression who have a higher risk for severe COVID-19 can be drawn. Only 2 SAEs were reported in the mRNA-1273 vaccine group none of them considered being vaccine related. No cases of myocarditis or pericarditis and no case of Multisystem Inflammatory Syndrome in Children or immune thrombocytopenia were reported. The sample size of note is not sufficient to detect rare or very rare AEs. The observed safety profile is considered favourable within the context of a conditional marketing authorisation. The benefit-risk ratio of mRNA-1273 in this age group is considered positive.

The CHMP considers the following measure (**SOB**) necessary to address the missing safety data

- The final clinical study report for study mRNA-1273-P203 including the full bioanalytical report will be submitted no later than September 2022 and is subject to a specific obligation laid down in the marketing authorisation. This will provide long-term data.

In addition, the following recommendation (**REC**) is made:

- Since no dose finding trial in this population has been conducted it is not possible to conclude whether lower dose could have resulted in a lower reactogenicity with comparable immune response and efficacy. The MAH should further explore lower dose levels in adolescents 12-17 years of age given the high reactogenicity of Spikevax and the usually mild course of infection caused by SARS-CoV-2 in this age group.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH did not submit an updated RMP version with this application. The Spikevax RMP will be updated in line with the conclusions of this assessment in the context of a separate, subsequent procedure.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and Annex II.E are updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COVID-19 is the disease caused by a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2). COVID-19 is primarily recognised as a 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 obesity, pre-existent diabetes, cardiovascular disease, lung disease, immuno-deficiency and pregnancy. COVID-19 can be considered confirmed by the existence of above clinical signs and proof of the presence of the virus e.g. by NAAT.

In adolescents SARS-CoV-2 infections cause mostly asymptomatic or mild disease. Severe COVID-19 cases occur rarely, and predominantly in subjects with comorbidities.

The MAH is seeking an extension of the indication for Spikevax in adolescents from 12 to less than 18 years.

3.1.2. Available therapies and unmet medical need

While care for individuals with COVID-19 has improved with clinical experience gained over time, there remains an urgent and unmet need for a vaccine able to prevent or mitigate COVID-19 during the ongoing pandemic. Especially protection of particularly vulnerable groups and mitigating the effects of the pandemic on a population level are desired. Although one vaccine for prevention of COVID-19 in adolescents is available there is still a need for additional vaccines to meet demand.

3.1.3. Main clinical studies

This submission is based on one clinical trial conducted in adolescents.

Study P203 is an ongoing Phase 2/3, randomised (2:1), observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, immunogenicity and efficacy of Spikevax in healthy adolescents aged ≥ 12 to < 18 years.

Vaccine efficacy is inferred based on demonstrating non-inferiority of the geometric mean value of serum Ab and the seroresponse rate from adolescent participants compared with those obtained from young adults (≥ 18 to ≤ 25 years of age) enrolled in the ongoing adult study (Study P301). Additionally, secondary study endpoints assessed the effect of Spikevax on COVID-19 and asymptomatic infection.

3.2. Favourable effects

Based on in vitro and in vivo studies it has been demonstrated that neutralising antibodies play a crucial role in preventing COVID-19. Spikevax was shown to elicit non-inferior neutralising antibody levels and seroresponse rates in subjects 12-17 years of age without previous SARS-CoV-2 infection compared to young adults 18-25 years. Based on these immunobridging results efficacy can be inferred for adolescents.

In addition, vaccine efficacy (exploratory) against prevention of COVID-19 was also evaluated. The vaccine efficacy results indicate that in SARS-CoV-2 baseline negative adolescents from 12 to <18 years Spikevax is efficacious in preventing laboratory confirmed symptomatic infection although only a low number of cases were observed using the same stringent case definition as in the pivotal study P301 in adults. A VE of 100.0% (95% CI: 28.9%, NE) was estimated. Using the less stringent CDC definition amended to reflect the clinical course in adolescents a VE of 93.3% (95% CI: 47.9%, 99.9%) is estimated starting 14 days post dose 2 with 1 case reported in the vaccine group and 7 cases observed in the placebo group with a mean follow-up of 53 days.

Overall, the vaccine efficacy results in the adolescent population are consistent with the vaccine efficacy reported in older age groups.

3.3. Uncertainties and limitations about favourable effects

No data are available from adolescents with a risk of more severe disease, including those with comorbidities such as diabetes or those under immune suppressive therapy. A study in immunocompromised children is however included in the PIP.

It is also currently unknown how long protection will last in adolescents and adults and if vaccination provides protection against newly emerging variants (**REC**). The impact on transmission is also currently unknown.

In addition, no (immune) correlate of protection has been identified to date.

Finally, the efficacy analyses are hampered by very low case counts.

As the study is ongoing, results were not provided for all endpoints.

3.4. Unfavourable effects

The evaluation of solicited ARs was performed in the Solicited Safety Set that consisted of randomised participants who received at least one injection of the vaccine and contributed any solicited adverse reaction data. The evaluation of unsolicited AEs, SAEs, and AESIs was conducted in the Safety Set including all randomised participants who received at least 1 dose. As of 08 May 2021 (data cut-off date) in the Safety Set population 2,480 participants of the mRNA-1273 group (99.8%) and 1,222 of the placebo group (98.5%) had received 2 vaccinations. In the Solicited Safety Set population the numbers were 2,478 (99.7%) and 1,220 (98.4%) participants, respectively. In the Safety Set 1087 subjects in the mRNA-1273 group and 474 in the placebo group had a follow-up time-period of ≥56 days post dose 2.

Spikevax is reactogenic. Almost all subjects in the mRNA-1273 vaccine group (97.8%) reported any solicited local AR compared to 48.5% of subjects in the placebo group. The most frequently reported local solicited AR in the mRNA-1273 was injection site pain reported by 97.2% of subjects in the mRNA-1273 vaccine group and by 45.9% of subjects in the placebo group. Any grade 3 solicited local AR after any dose was recorded for 13.8% of subjects in the mRNA-1273 vaccine group and for 0.3% in the placebo group. This was followed by axillary swelling or tenderness (34.6% versus 10.7%), swelling (27.7% versus 1.9%), and erythema/redness (25.8% versus 1.5%). Any solicited systemic AR after any dose was recorded for 91.9% of subjects in the mRNA-1273 vaccine group and for 66.9% of subjects in the placebo group. The most frequently reported systemic solicited AR in the mRNA-1273 group after any dose was headache reported by 78.4% of subjects in the mRNA-1273 vaccine group and by 50.3% of subjects in the placebo group. This was followed by fatigue (75.2% versus 47.5%), myalgia (54.3% versus 23.5%), chills (49.1% versus 16.2%), arthralgia (34.6 versus 16.9%), and nausea (29.3% versus 15.2%). Fever of any grade was reported by 13.7% versus 1.9% of subjects. For solicited local reactions no clear trend could be observed regarding differences in severity post dose 1 and post dose 2. The incidence of solicited systemic ARs however was notably higher post dose 2 compared to post dose 1 (depending on the kind of event approximately 2 to 3-fold higher).

Study P203 confirmed the previous finding that the majority of solicited ARs are mild or moderate in severity, occur within the first 1 to 2 days after IP injection and persist for a median of 1 to 3 days, depending on the type of the reaction. It should be noted, that after any dose in the mRNA-1273 vaccine group 13.8% of subjects reported grade 3 solicited local and 16.5% solicited systemic ARs. Because of the higher systemic reactogenicity the use of antipyretic or pain medication was notably higher in the mRNA-1273 vaccine group compared with the placebo group. In the mRNA-1273 vaccine group, 30.1% of subjects used such medication after dose 1 and 50.1% after dose 2. The proportion was 9.5% and 8.9% in the placebo group, respectively. The severity of local and systemic reactogenicity increased from dose 1 to dose 2. Any grade 3 local solicited AE was reported by 6.8% versus 8.9% of subjects after each dose; any grade 3 systemic solicited AE by 4.4% and 13.7%, respectively.

A comparison with reactogenicity data from the age cohort 18 to 25 years from study P301 indicated a higher local reactogenicity for all solicited local ARs except for pain in the age cohort 12 to <18 years compared with the age cohort 18 to 25 years of age. No clinical meaningful difference could be observed for solicited systemic ARs. The incidence tended to be comparable or slightly higher in the age cohort 18 to 25 years of age compared with the age cohort 12 to <18 years of age. Interestingly, a comparison between adolescents and young adults suggests that the incidence of severe (grade 3) systemic ARs is lower for adolescents (4.4% dose 1, 13.7% dose 2), compared to young adults (5.2% dose 1, 21.6% dose 2). Results must be interpreted with caution since the sample size in the age cohort 12 to <18 years was 3-fold higher than in the age cohort 18 to 25 years of age and it is a historical control group.

The incidence of unsolicited TEAEs was higher in the mRNA-1273 vaccine group compared with the placebo group. Unsolicited TEAEs irrespective of causality up to 28 days after any dose were reported by 20.5% of subjects in the mRNA-1273 group compared to 15.9% of participants in the placebo group. The most commonly recorded unsolicited TEAEs with a frequency of more than 1% occurred in the SOC General disorders and administration site conditions, reported by 10.1% of subjects in the mRNA-1273 vaccine group and by 4.0% of subjects in the placebo group. This included events of injection site lymphadenopathy (4.3% versus 0.4%), injection site erythema (1.9% versus 0.2%), fatigue (1.9% each), injection site induration (1.1% versus 0.2%), and injection site pain (1.1 versus 0.6%).

The incidence of MAAEs until the data cut (08 May 2021) was nearly identical between the groups (mRNA-1273: 8.2%, placebo: 8.4%).

Unsolicited TEAEs considered being vaccine related were recorded by 12.6% of subjects in the mRNA-1273 vaccine group and by 5.8% of subjects in the placebo group. Most frequently TEAEs considered

being vaccine related were reported in the SOC of General disorders and administration site conditions (9.6% versus 3.5%), followed by the SOC of Nervous system disorders (2.4% versus 1.8%).

TEAEs considered being vaccine related and reported by ≥ 2% of participants in the mRNA-1273 vaccine group through 28 days after any dose were injection site lymphadenopathy reported by 4.3% of subjects and headache reported by 2.2%. Lymphadenopathy (not restricted to injection site) considered being vaccine related was reported by 0.6% of subjects.

At the time of data snapshot SAEs were reported by 0.2% of subjects each in the MRNA-1273 vaccine group (6 subjects) and the placebo group (2 subjects). SAEs in the mRNA-1273 vaccine group included drug-induced liver injury, appendicitis together with diarrhoea, vomiting, and post-procedural fever, pectus excavatum, suicidal ideation (2 subjects, none in the placebo group), and depression suicidal (1 subject, none in the placebo group). In the placebo group one suicide attempt and one case of obstructive nephropathy were recorded as SAE by one subject each.

None of the SAEs reported at the time of data snapshot were considered being vaccine related.

Multisystem inflammatory syndrome in children (MIS-C) was defined as an AESI in this trial. Up to the
Uncertainties and limitations about unfavourable effects

3.5. Uncertainties and limitations about unfavourable effects

No clinically meaningful difference was observed with regard to incidence and severity of reactogenicity in subjects who were seropositive for SARS-CoV-2 at baseline compared with subjects who were seronegative at baseline. The majority of subjects however was SARS-CoV-2 negative at baseline (87.0%). Long-term safety data are not available yet. In the Safety Set 1087 subjects (43.7%) in the mRNA-1273 group and 474 subjects (38.2%) in the placebo group had a follow-up time-period of ≥56 days post dose 2. The study is ongoing and the study period will be 1 year.

The sample size of trial P203 is not sufficient to evaluate rare or very rare events like e.g. Multisystem Inflammatory Syndrome in Children, autoimmune disorders or rare vaccine related events like myocarditis or pericarditis. Post-marketing reports of the very rare AEs of myocarditis/pericarditis in adults investigated by PRAC suggest that the risk for myocarditis is especially increased in young male adults. The trial was restricted to healthy adolescents. No safety data are available for adolescents with underlying chronic medically conditions and/or immune suppression. Concomitant use of mRNA-1273 and any other vaccine or any other medication was not evaluated.

Since no dose finding trial in this population has been conducted it is not possible to conclude whether lower dose could have resulted in a lower reactogenicity with comparable immune response and efficacy. Further evaluation of lower dose levels in adolescents 12-17 years of age are desirable given the high reactogenicity of Spikevax and the usually mild course of infection caused by SARS-CoV-2 in this age group (**REC**).

3.6. Effects Table

Table 28 - Effects Table for Spikevax indicated for adolescents from 12 to <18 years (data cut-off: 08 May 2021)

Effect	Short Description	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects					

Effect	Short Description		Treatment	Control	Uncertainties/ Strength of evidence	References
Immunogenicity			**12-<18y N=340**	**18-25y N=305**		
	GMR (nAb) (95% CI)	**1.077** (0.991, 1.260)			Non-inferiority demonstrated	
	Difference in nAb Seroresponse rate at day 57 (95% CI)	**0.2** (-1.6, 2.4)			Non-inferiority demonstrated	
Vaccine efficacy	(P301 case definition) starting 14 days after Dose 2, without prior evidence of SARS-COV-2 infection, PP set	VE % Vaccine Efficacy (95% CI) Confidence Interval	mRNA-1273 (100 µg) N=2,163 COVID-19 cases	Placebo N=1073 COVID-19 cases		
		100 % (28.9%, NE)	0/ 2,163	4/1,073	Secondary objective, Short follow-up period of 57 days / Fewer cases in Spikevax group	

Unfavourable Effects							
Local and systemic Reactogenicity Solicited safety set		mRNA-1273 100µg (N=2,485)		Saline placebo Group (N =1,240)			
		Post dose 1	Post dose 2	Post dose 1	Post dose 2		
Any grade 3 solicited systemic AR		4.4%	13.7%	2.9%	2.0%		Notable increase of grade 3 systemic AE post dose 2
Any grade 4 solicited systemic AR		0	0.1 (3 events)	0	0		
Any grade 3 solicited local AR		6.8%	8.9%	<0.1%	0.2%		Slight increase of grade 3 local AEs post dose 2
Any grade 4 solicited local AR		0	0	0	0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important favourable effect of vaccination is the prevention of symptomatic disease that has been demonstrated for Spikevax in the pivotal trials that were submitted for marketing authorisation. A similar degree of benefit of Spikevax in adolescents 12-17 years of age can be inferred by the successful immunobridging approach to young adults, 18-25 years of age. A non-inferior immune response with respect to neutralising antibody levels and seroresponse rates was clearly demonstrated. Clinical data

(exploratory) also show short-term protection against symptomatic COVID-19 in adolescents 12-17 years of age supporting the immunobridging approach.

Results from some of the defined endpoints were not provided as the study is still ongoing. While this is acceptable for the time being as the relevant results supporting the immunobridging were provided, final study results should be submitted as soon as available (**SOB**).

Data from relevant endpoints, e.g. immunogenicity data over time, efficacy against variants, immunogenicity data from breakthrough cases, should be provided on a regular basis and as soon as (interim) results are available (**REC**).

The most common and important unfavourable effects are related to reactogenicity. Local reactogenicity was slightly higher, but systemic reactogenicity comparable to that observed in the adult population 18 to 25 years of age that was evaluated in a previous application. No new safety concerns were observed and local and systemic reactogenicity are transient and reversible. The study size did not allow detection of rare adverse events. However, evidence transfer from adults as regards type and occurrence of rare AE is considered justified making the safety database considerably larger than just this paediatric trial.

A possible link of vaccination with very rare cases of myocarditis and pericarditis has been confirmed and these events were included in the product information. According to investigations by PRAC, young adults are more often affected than older adults, which increases the relevance of these very rare events for adolescents. It should however be noted that SARS-CoV-2 infection itself can cause these events, as for example recently shown in a cohort study with 1597 young competitive athletes at US universities, revealing that 2.3% were diagnosed with clinical (0.5%) or subclinical myocarditis after COVID-19 infection (doi:10.1001/jamacardio.2021.2065).

Study P203 is not large enough to detect new rare events or to estimate the risk of established adverse events such as myocarditis or pericarditis in adolescents. However, the overall safety profile determined in adults was confirmed in the adolescent study and is considered favourable to support a positive benefit/risk.

3.7.2. Balance of benefits and risks

Even though the course of COVID-19 in adolescents is generally milder than in the older population there are individuals that suffer from direct consequences of the infection. The favourable effects of preventing COVID-19 with potential irreversible and long-lasting consequences outweigh the identified risks of vaccination.

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-marketing in the context of the existing conditional marketing authorisation, including the continuation of the pivotal study as long as possible, post-approval effectiveness studies and routine disease surveillance.

3.8. Conclusions

The overall benefit-risk of Spikevax is positive provided that the MAH submits the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P203, including the full bioanalytical report (SOB, due date 30/09/2022).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include use in adolescents from 12 to 17 years of age for Spikevax; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and Annex II.E are updated. The Package Leaflet is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0481/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA/H/C/005791/II/0021