01 March 2022
EMA/137337/2022 – Rev.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of marketing authorisation

Invented name: Spikevax

International non-proprietary name: elasomeran

Procedure No. EMEA/H/C/005791/II/0041

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 and personal data anonymised.

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List of abbreviations

Ab	Antibody
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
AR	Assessment report
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
bAb	Binding antibody(ies)
BMI	Body mass index
CDC	US Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
cMA	Conditional Marketing Authorisation
COPD	Chronic obstructive pulmonary disease
CoV	Coronavirus(es)
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
CTP	Clinical trial protocol
CVID	Common Variable Immunodeficiency
DSMB	Data safety monitoring board
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
eCRF	Electronic Case Report Forms
eDiary	Electronic diary
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUA	US FDA Emergency Use Authorisation
EURD	European reference date
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GLSM	Geometric least squares mean
GM	Geometric mean
GMFR	Geometric mean fold-rise
GMR	Geometric mean ratio
GMT	Geometric mean titer(s)
HIV	Human immunodeficiency virus
IA	Interim analysis
ICU	Intensive care unit
ID50	50% inhibitory dose
IgG	Immunoglobulin G
IM	Intramuscular(ly)
INN	International non-proprietary name
IP	Investigational product

ISRR	Immunisation stress-related response
LNP	Lipid nanoparticle
LoD	Limit of detection
LLoQ	Lower limit of quantification
LS	Least squares
MAAE	Medically attended adverse event
MAH	Marketing authorisation holder
MERS-CoV	Middle East respiratory syndrome coronavirus
MIS-C	Multisystem inflammatory syndrome in children
mITT	Modified Intent-to-treat
mITT1	Modified Intent-to-treat 1
mRNA	messenger RNA
MSD	MesoScale Discovery
NAAT	Nucleic Acid Amplification Test
nAb	Neutralising antibody(ies)
PDCO	Paediatric Committee
PEG	Polyethylene glycol
PI	Product information
PIM-S	Paediatric inflammatory multisystem syndrome
PIP	Paediatric Investigation Plan
PL	Package Leaflet
PP	Per protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PsVNA	Pseudotyped lentivirus reporter single-round-of-infection neutralisation assay
PsVNT	Pseudotyped lentivirus reporter test
PT	Preferred term
QRD	Quality Review of Documents
RMP	Risk management plan
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike (protein)
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOB	CHMP specific obligation, EMA Post-Authorisation Measure (PAM)
SOC	System organ class
SRR	Seroresponse rate
ssRNA	Single-stranded RNA
TEAE	Treatment-emergent adverse event
ULOQ	Upper limit of quantification
VAED	Vaccine-induced enhancement of disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine efficacy / effectiveness
WHO	World Health Organisation

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 9 November 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 children 6-11 years of age for Spikevax, based on data from study mRNA-1273-P204, an ongoing Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children; 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 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 did not seek Scientific Advice at the CHMP.

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	9 Nov 2021
Start of procedure	10 Nov 2021
CHMP Rapporteur Assessment Report	6 Dec 2021
CHMP members comments	9 Dec 2021
Updated CHMP Rapporteur Assessment Report	15 Dec 2021
Request for supplementary information	16 Dec 2021
MAH's responses submitted to the CHMP	18 Jan 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated	9 Feb 2022
PRAC RMP advice and assessment overview adopted by PRAC	10 Feb 2022
Joint Rapporteur's updated assessment report on the MAH's responses circulated	17 Feb 2022
CHMP opinion	24 Feb 2022
A revised opinion was adopted by the CHMP in order to reflect submission of the final Clinical Study Report for study mRNA-1273-P204 as a Specific Obligation	1 Mar 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

End of December 2019, the World Health Organization (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 30th January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11th 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 the therapeutic indication

The proposed indication and dosing administration for Spikevax are:

- **Proposed indication:** Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 to 11 years of age
- **Dosing administration:** Spikevax is administered as a course of 2 (two) 50 microgram doses. It is recommended to administer the second dose 28 days after the first dose (see sections 4.4 and 5.1).

Epidemiology and risk factors, screening tools/prevention

The majority of infections result in asymptomatic or mild disease with full recovery but 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 use in children 6-11 years old. Although COVID-19 in children is mostly a mild disease severe cases occur rarely. The paediatric inflammatory multisystem syndrome in children (PIMS or MIS-C) is a rare but serious condition associated with COVID-19 and it can result in admission to paediatric intensive care in up to 70% of cases. It seems to occur more often in boys than in girls and more often in young children than older children or adolescents.

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.

Although incidence of severe COVID-19, hospitalization and mortality is lower in children than adults, clinical disease of all severities occurs in children, especially in those with comorbidities and risk factors.

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 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. Neutralizing 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 currently indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older.

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

No scientific advice on the clinical development in children or the paediatric investigation plan was given.

2.1.4. General comments on compliance with 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.

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

- Tabular overview of clinical studies

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-P204 (US, Canada) Ongoing	Healthy children, 3 age groups: ≥6 to <12 years, ≥2 years to < 6 years, and ≥6 months to < 2 years N = 4,000 planned per age group mRNA-1273 n = ~3000 placebo n = ~1000	Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo controlled expansion study	25 µg, 50 µg or 100 µg mRNA-1273 or placebo (3:1) 2 IM doses, 28 days apart	Interim CSR Safety: Day 57 (1-month post-dose 2) for full cohort (3:1) Efficacy/Immunogenicity: *Primary endpoint*: Day 57 serum antibody (Ab) response in a subset of participants of part 1 of the study and NI analyses *Secondary endpoint:* Interim efficacy analyses

2.4. Clinical efficacy

2.4.1. Main study

Study mRNA-1273-P204 (hereafter Study P204) is an ongoing Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of Spikevax (referred to as mRNA-1273) in healthy children 6 months to less than 12 years of age. The study population includes 3 age groups (≥6 years to <12 years, ≥2 years to <6 years, and ≥6 months to <2 years).

Age Group	**Part 1**			**Part 2**	
	mRNA-1273 25 µg	**mRNA-1273 50 µg**	**mRNA-1273 100 µg**	**Selected Dose Level of mRNA-1273 From Part 1**	**Placebo**
6 to < 12 years		Study Arm 1 (n=375)	Study Arm 2 (n=375)	Study Arm 8 (n=3,000)	Study Arm 9 (n=1,000)
2 to < 6 years	Study Arm 7 (Optional) (n=75)	Study Arm 3 (n=75)	Study Arm 4 (n=75)	Study Arm 10 (n= up to 3,000)	Study Arm 11 (n= up to 1,000)
6 months to < 2 years	Study Arm 5 (n=150)	Study Arm 6 (n=150)		Study Arm 12 (n= up to 3,000)	Study Arm 13 (n= up to 1,000)

With this submission interim data of children ≥6 to <12 years of age randomised in study arms 1, 2 (both from open-label Part 1), 8 and 9 (both from blinded Part 2) were provided.

Vaccine effectiveness is inferred based on demonstrating non-inferiority of the neutralising antibody responses compared with those obtained from young adults (≥18 to <25 years of age) enrolled in the ongoing adult study mRNA-1273-P301 (hereafter Study P301). Immunogenicity data from the comparator group of young adults in study P301 are based on a data snapshot on 8th May 2021.

Methods

Study participants

Participants were enrolled at approximately 75 to 100 study sites in the United States and Canada.

Inclusion criteria:

Participants are eligible to be included in the study only if all the following criteria apply:

1. The participant is male or female, 6 months to < 12 years of age at the time of consent/assent (Screening Visit), who is in good general health, in the opinion of the investigator, based on review of medical history and screening physical examination.
2. If the participant has a chronic disease (e.g., asthma, diabetes mellitus, cystic fibrosis, human immunodeficiency virus [HIV] infection), the disease should be stable, per investigator assessment, so that the participant can be considered eligible for inclusion. Stable diseases are those which have had no change in their status or in the medications required to control them in the 6 months prior to Screening Visit.

   Note: a change in medication for dose optimisation (e.g., insulin dose changes), change within class of medication, or reduction in dose are not considered signs of instability.
3. In the investigator's opinion, the parent(s)/LAR(s) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures, and provide written informed consent and participants are willing to provide assent.
4. The participant is 2 years or older and has a body mass index (BMI) at or above the third percentile according to WHO Child Growth Standards at the Screening Visit
5. Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as premenarche.

Special inclusion criteria for female participants who have reached menarche:

6. Female participants of childbearing potential may be enrolled in the study if the participant fulfils all of the following criteria:
   - Has a negative pregnancy test at Screening. Pregnancy test will be performed if deemed appropriate by the investigator.
   - 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).
   - Is not currently breastfeeding.
   - Adequate female contraception is defined as abstinence or consistent and correct use of a US FDA-approved contraceptive method in accordance with the product label

Exclusion Criteria

Participants will be excluded from the study if any of the following criteria apply:

1. Has a known history of SARS-CoV-2 infection within 2 weeks prior to administration of IP or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of IP.
2. Is acutely ill or febrile 24 hours prior to or at the Screening Visit. 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.
3. Has previously been administered an investigational or approved CoV (e.g., SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.

4. Has undergone treatment with investigational or approved agents for prophylaxis against COVID-19 (e.g., receipt of SARS-CoV-2 monoclonal antibodies) within 6 months prior to enrolment.
5. Has a known hypersensitivity to a component of the vaccine or its excipients. Hypersensitivity includes, but is not limited to, anaphylaxis or immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG] or immediate allergic reaction of any severity to polysorbate).
6. Has a medical or psychiatric condition that, according to the investigator's judgment, may pose additional risk as a result of participation, interfere with safety assessments, or interfere with interpretation of results.
7. Has a history of diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically the following:
   - Congenital or acquired immunodeficiency, excluding HIV infection, as described in Inclusion Criteria 2
   - Chronic hepatitis or suspected active hepatitis
   - A bleeding disorder that is considered a contraindication to IM injection or phlebotomy
   - Dermatologic conditions that could affect local solicited AR assessments
   - Any prior diagnosis of malignancy (excluding non-melanoma skin cancer)
   - Febrile seizures*

     *In Part 2 of the study, a history of a simple, single febrile seizure is allowed for children 6 years and older.
8. Has received the following:
   - Any routine vaccination with inactivated or live vaccine(s) within 14 days prior to first vaccination or plans to receive such a vaccine through 14 days following the last study vaccination.

     Note: This excludes influenza vaccine that may be given, however, not within 14 days prior to or post-Dose 1 or Dose 2. If a participant receives an influenza vaccine, this should be captured within the concomitant medication electronic case report form (eCRF) (Section 5.5.2).
   - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrolment (for corticosteroids, ≥ 1 mg/kg/day or ≥10 mg/day prednisone equivalent, if participant weighs > 10 kg). 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 or subcutaneous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrolment.
9. Has participated in an interventional clinical study within 28 days prior to the Screening Visit or plans to do so while participating in this study.
10. Is an immediate family member, or household contact, of an employee of the study site or Moderna or someone otherwise directly involved with the conduct of the study. As applicable, family members / household contacts of employees of the larger institution or affiliated private practice not part of the study site may be enrolled.

The CHMP considered the inclusion and exclusion criteria to be acceptable.

Treatments

In the open label phase of the study (Part 1) each participant aged ≥6 to <12 years received either two doses of 50 µg or 100 µg of Spikevax (COVID-19 vaccine Moderna, mRNA-1273) or placebo (0.9% sodium chloride) by intramuscular injection into the deltoid muscle or anterolateral thigh 28 days apart (i.e., Day 1 and Day 29). The protocol specified a window of +7 days for administration of the second dose.

Objectives and endpoints

The objectives that will be evaluated in this study and the endpoints associated with each objective are provided in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 vaccine administered as 2 doses 28 days apart in 3 age groups	• 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 • AESIs, including MIS-C and myocarditis and/or pericarditis, through the entire study period
• To infer the efficacy of mRNA-1273 (25, 50, and 100 µg, administered as 2 doses 28 days apart) based on immunogenicity in 3 age groups	• The proportion of participants with a serum antibody level at Day 57 ≥ antibody threshold of protection — If an accepted serum antibody threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy • The GM value of serum antibody level and seroresponse rate from Study P204 vaccine recipients at Day 57 compared with those from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301) — If a threshold is not available, efficacy will be inferred by establishing non-inferiority for each age group (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years in Study P204) compared to 18- to 25-year old participants (Study P301) by both GM value of serum antibody levels and seroresponse rate. A definition of seroresponse will be provided in the statistical analysis plan based on forthcoming information about assay performance
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 µg) administered as 2 doses 28 days apart	• The GM values of SARS-CoV-2 S protein-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)
• To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection (by serology and/or RT-PCR) post-baseline • SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline: — bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1, that becomes positive (as measured by Roche Elecsys) post-baseline, OR — Positive RT-PCR post-baseline
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) post-baseline in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with COVID-19 AND positive RT-PCR for SARS-CoV-2	• The incidence of the first occurrence of COVID-19 post-baseline, where COVID-19 is defined as symptomatic disease based on CDC case definition [1]
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence
• To describe the ratio or profile of specific S protein bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb titers in serum
• To characterise the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)
• To assess, in a subset of participants, the SARS-CoV-2 S protein-specific T-cell responses	• Magnitude, phenotype, and percentage of cytokine-producing S protein-specific T cells, as measured by flow cytometry at different time points after vaccination relative to baseline
• To explore asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; GM = geometric mean; GMFR = geometric mean fold-rise; IgG = immunoglobin; IP = investigational product; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralising antibody; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
1: The case definition of COVID-19 includes at least one of the following systemic symptoms: fever (temperature > 38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours), cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhoea, new loss of taste or smell, sore throat, abdominal pain, diarrhoea, nausea or vomiting, poor appetite or poor feeding, AND a positive test for SARS-CoV-2 by RT-PCR.

Immunogenicity assessment

Blood samples for immunogenicity assessments will be analysed for

- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus virus neutralisation assays.

- Serum bAb titer as measured by MesoScale Discovery (MSD) Multiplex assay specific to the SARS-CoV-2 S protein.
- For Part 1, testing for serologic markers for SARS-CoV-2 infection using the non-vaccine antigen-based Nucleocapsid Elecsys assay at Day 1 (prior to the first dose), Day 57, Day 209, and Day 394.

All serological assays are considered acceptably validated for use in the assessment of clinical samples.

Upon request the MAH confirmed that the assays used for the immunogenicity analyses are based on both the D614G form (neutralisation) and the Wuhan-Hu-1 strain (binding). The neutralising antibody assay utilises lentivirus particles expressing SARS-CoV-2 D614G Spike protein. The indirect binding ECL assay (MSD) utilises the V-PLEX SARS-CoV-2 Panel 2 (IgG) Kit to measure IgG antibodies to three antigens (S, N, RBD) related to SARS-CoV-2 Wuhan-Strain.

COVID-19 case definition and surveillance for COVID-19 symptoms

Cases are defined as participants meeting clinical criteria based both on symptoms for COVID-19 and on RT-PCR detection of SARS-CoV-2 from samples collected within 72 hours of the study participant reporting symptoms meeting the definition of COVID-19. The participant must have at least 1 nasal swab (or respiratory sample, if hospitalised) positive for SARS-CoV-2 by RT-PCR.

Throughout the study the following pre-specified symptoms that meet the criteria for suspicion of COVID-19 will be elicited weekly from the participant, and the presence of any one of these symptoms (in the absence of an alternative diagnosis) lasting at least 48 hours (except for fever and/or respiratory symptoms) will result in the study site staff arranging an illness visit to collect a nasal swab for SARS-CoV-2 within 72 hours. Case definition defined in study P204 are summarised below.

Endpoint	**Definition**
COVID-19 "CDC case definition"	At least 1 symptom from a pre-specified list of COVID-19 symptoms derived from the US CDC case definition Systemic symptoms: fever (temperature > 38°C/≥ 100.4°F) or chills (of any duration, including ≤ 48 hours), fatigue, headache, myalgia, nasal congestion or rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, nausea/vomiting, poor appetite/poor feeding, **OR** respiratory signs/symptoms: cough (of any duration, including ≤ 48 hours), shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours) **AND** At least 1 positive RT-PCR for SARS-CoV-2.
COVID-19 "P301 case definition"	COVID-19 case will be identified as a positive post-baseline RT-PCR test result, together with eligible symptoms as follows: A positive post-baseline PCR result **AND** At least 2 systemic symptoms: fever (≥ 38°C/≥ 100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), **OR** At least 1 of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.
SARS-CoV-2 Infection (regardless of symptoms)	A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline 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) post-baseline, **OR** Positive RT-PCR test post-baseline.

Asymptomatic SARS-CoV-2 infection	Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Absent of COVID-19 symptoms **AND** at least 1 from below: bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) post-baseline, **OR** Positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.

Abbreviations: bAb = binding antibody; CDC = Centers for Disease Control and Prevention; COVID19 = coronavirus disease 19; PCR = polymerase chain reaction; RT-PCR = reverse-transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2. Source: Study P204 protocol amendment 4 in Module 5.3.5.1.

Some of the symptoms of COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1273 (e.g. myalgia, headache, fever, and chills). During the first 7 days after vaccination, investigators should decide if a nasal swab should be collected. The collection of a nasal swab prior to the first dose on Day 1, prior to the second dose on Day 29, and then at all subsequent study visits (Day 43 [if visit is applicable], Day 57, Day 209, and Day 394) can help ensure that cases of COVID-19 are not overlooked. Any study participant who reports respiratory symptoms during the 7-day period after vaccination without an alternative diagnosis should be evaluated for COVID-19.

Surveillance for COVID-19 symptoms is conducted via biweekly telephone calls or eDiary prompts as specified in the protocol starting after participant enrolment and continuing throughout the study. If there is no response to an eDiary prompt for 2 days, the study site staff will contact the study participant by telephone.

Throughout the study the following pre-specified symptoms that meet the criteria for suspicion of COVID-19 will be elicited weekly from the participant, and the presence of any one of these symptoms (in the absence of an alternative diagnosis) lasting at least 48 hours (except for fever and/or respiratory symptoms) will result in the study site staff arranging an illness visit to collect a nasal swab for SARS-CoV-2 within 72 hours.

The CHMP endorsed the study objectives and endpoints. It is noted that the endpoint based on COVID-19 'P301 case definition' was not specified in protocol P304 (amendment 5).

Endpoints are in good correspondence with study objectives, concerns raised as regards adherence to specifics of SAP & protocol and the potential for data-driven decision-making notwithstanding. Primary analyses are stated to rely on study part 2 as per SAP v2.0 but the document also states: "*participants in Part 1 and 2 of the study and in different age groups who receive the same mRNA-1273 dose level may be combined for analysis.*"

Co-primary immunogenicity endpoints (GMT ratio & seroresponse rate) are endorsed. Definition, as well as non-inferiority margin applied (in absence of established immune correlate of protection) are acceptable for the immunobridging concept and in line with provisions as per variant RP (indent on *naïve population*) and the approach followed for the adolescent extension.

Understanding that 4-fold increase does not imply clinical surrogacy but ability to detect humoral response with sufficient certainty (i.e. technical sensitivity rather than clinical interpretability), deviating from 4-fold recommendation may be accepted in dependence of the specific assay used. (Nota bene: pre-specification as per SAP states different (lower) and assay-specific fold increases as thresholds but 4-fold data were reported in any case (and close to 100%)).

Efficacy endpoints are considered supportive and subject to accrual constraints based on study size and limited follow-up. Only descriptive summary was provided with this submission; this is considered acceptable. Given the uninterpretable low case accrual after complete 2-dose regimen at the time of readout on 6OCT, an updated readout based on a later cut-off was provided upon request.

Upon request the MAH confirmed that the pseudovirus neutralisation assays is based on the D614G form of the Wuhan strain while the MSD is based on the Wuhan-Hu1-strain spike protein.

For the secondary endpoint of antibody persistence over time and exploratory objectives, no outcome data were provided as part of this submission.

Sample size

The initial age groups in Part 1 were for estimation purposes. With approximately 750 participants (approximately 375 participants at each dose level of mRNA-1273) in the initial 6 to < 12 years age group, there was at least a 90% probability to observe at least 1 participant with an AE at a true AE rate of 1% for a given dose level. In each of the younger age groups (2 to < 6 years and 6 months to < 2 years), the safety assessment was to occur during the conduct of Part 2 after approximately 375 participants have been exposed to mRNA-1273 at the dose level selected for Part 2 by the DSMB.

The sample size in the expansion (Part 2) was to support the safety database in the paediatric participants 6 months to < 12 years of age. With up to 3,000 participants each in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years of age groups exposed to mRNA-1273 at a given dose level in Part 2, the study had at least a 95% probability to observe at least 1 participant with an AE at a true 0.1% AE rate for a given dose level.

Sample size for immunogenicity subset

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group was to be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset was to be processed, and the analysis of primary immunogenicity endpoint was to be based on the Immunogenicity PP Subset. Assuming approximately 25% of participants in the Immunogenicity Subset were not to meet the criteria to be included in the Immunogenicity PP Subset, approximately 528 participants in Part 2 (~396 receiving mRNA-1273 and ~132 receiving placebo) were to be selected for the Immunogenicity Subset from which approximately 289 participants on mRNA-1273 were to be suitable for the Immunogenicity PP Subset.

If a threshold of protection was available for the primary immunogenicity endpoint, with approximately 289 participants on mRNA-1273 in the Immunogenicity PP Subset of an age group, there was to be at least 90% power to rule out 70% with a 2-sided 95% CI (lower bound of the 95% CI > 70%) for the percentage of mRNA-1273 participants exceeding the accepted threshold if the true rate of participants exceeding the threshold is 80%.

If an acceptable antibody threshold of protection against COVID-19 was not available at the time of analysis for the primary immunogenicity endpoint, non-inferiority tests of the 2 null hypotheses based on the 2 co-primary endpoints were to be performed, respectively. The sample size calculation for each of the 2 non-inferiority tests was performed, and the larger sample size was chosen for the study.

With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and 289 young adults (18 to 25 years of age) from Study P301, there was to be 90% power to demonstrate non-inferiority of the immune response, as measured by the antibody GM value, in paediatric population at a 2-sided alpha of 0.05, compared with that in young adults (18 to 25 years of age) in Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1, a non-inferiority margin of 0.67 (or 1.5), and a point estimate minimum threshold of 0.8. The standard deviation of the natural log-transformed levels was assumed to be 1.5.

With approximately 289 participants receiving mRNA-1273 in the Immunogenicity PP Subset of each age group in Study P204 and 289 young adults (18 to 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 seroresponse rate in children at a 2-sided alpha of 0.05, compared with that in young adults 18 to 25 years of age in Study P301 receiving mRNA-1273, assuming seroresponse rate of 85% in young adults of 18 to 25 years of age from Study P301, true seroresponse rate of 85% in children (or 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 seroresponse rate difference.

In the 1273-P203 interim analysis (data snapshot on 8th May 2021), the observed seroresponse rates at Day 57 were high in both 18 to 25 years of age group from Study P301 (98.6% with 95% CI: 96.6, 99.6) and 12 to17 years of age group (98.8% with 95% CI: 97.0, 99.7), based on pseudovirus nAb ID50 titers. For this Study P204, if the true seroresponse rates were assumed to be 95% or higher in both 18 to 25 years of age group from Study P301 and an age group in children, with between-group true difference within 4%, there will be a >90% power to demonstrate non-inferiority by seroresponse rate in children compared with 18 to 25 years of age in Study P301, at a 2-sided alpha of 0.05.

Overall, the CHMP endorsed the sample size considerations, both for the overall trial size (for safety) as well as for the immunogenicity subset. For a discussion on the deviation from the primary planned sample size for immunogenicity please see the discussion on Statistical Methods below.

Randomisation

Random assignment of participants in Part 2 of the study was to be based on a centralised interactive response technology, in accordance with pre-generated randomisation schedules. Up to 4,000 participants each in the 6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years age groups were to be randomised in a 3:1 ratio to the mRNA-1273 arm (n = up to 3,000 participants in each group) or placebo arm (n = up to 1,000 participants in each group).

The CHMP noted that no details on the choice of the immunogenicity subset were provided. It seems that the immunogenicity subset was selected post-hoc based on already positive results in Part 1 in comparison to the known immunogenicity results in P301. Upon request the MAH stated that all available immunogenicity data from Part 1 (excluding the dose-finding cohort based on the first 75 subjects per dose) was used for immunogenicity analyses. This is, however, not considered as "pre-specified". With regard to Part 2 of the study randomisation of treatment allocation is endorsed.

Blinding (masking)

Part 1 of this study was planned as open label; blinding procedures were not applicable.

Part 2 of this study was to be conducted in an observer-blind manner. 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, with certain exceptions as defined in the protocol.

Statistical methods

Analyses sets

The following analysis sets were defined:

Analysis Set	Description
Randomization Set	Part 2: All participants who are randomly assigned, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	Part 1: All enrolled participants in Part 1 who receive at least 1 injection of IP. Part 2: All randomly assigned participants who receive at least 1 injection of IP.
Per-Protocol (PP) Set	All participants in the FAS who receive planned doses of IP per schedule, comply with the immunogenicity schedule, and have no major protocol deviations that impact key or critical data.
	Participants who are RT-PCR positive or seropositive at baseline will be excluded from the PP Set. The PP Set in Part 1 will be used for all analyses of immunogenicity in Part 1 unless specified otherwise.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity sampling and testing.
Per-Protocol 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 receive planned doses of IP per schedule, comply with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are RT-PCR positive or seropositive at baseline will be excluded from the PP Immunogenicity Subset, in addition to participants with HIV who are receiving highly active anti-retroviral therapy (HAART). The PP Immunogenicity Subset will be used for all analyses of immunogenicity unless specified otherwise.
Safety Set	All enrolled participants (in Part 1) and all randomly assigned participants (in Part 2) who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for solicited ARs.
Solicited Safety Set	The Solicited Safety Set consists of participants in the Safety Set who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of 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 that is not as randomized).

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; IP = investigational product; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Immunogenicity analyses

The primary analysis population for immunogenicity was to be the Immunogenicity PP Subset, unless specified otherwise. The primary objective of this study was to use the immunogenicity response to infer efficacy in participants aged 6 months to < 12 years at the dose level selected for expansion. For this objective, analyses of immunogenicity were to be performed for each paediatric age group separately at the selected dose level based on the participants in the Immunogenicity PP Subset. It was planned that for each paediatric age group, participants in Part 2 in the Immunogenicity PP Subset may be used for immunogenicity primary analysis. Further, participants from Part 1 and Part 2 who received the same mRNA-1273 dose level selected for expansion may be combined for immunogenicity analyses. If the same dose level was selected for expansion for more than one age group, these age groups may be combined for immunogenicity analyses.

If a threshold of protection against COVID-19 was available, the number and percentage of participants with antibody greater than or equal to the threshold at Day 57 would have been provided with a 2-sided 95% CI using the Clopper-Pearson method. For an age group, if the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity endpoint of this study was to be considered to be met for that age group. The number and percentage of participants with serum antibody greater than or equal to the threshold with 2-sided 95% CI was to be provided at each post-baseline time point. The CI was to be calculated using the Clopper-Pearson method.

If an accepted serum antibody threshold of protection against COVID-19 was not established, immune response as measured by GM value and seroresponse rate in each age group based on Day 57 antibody levels was to be compared to that in young adults (18 to 25 years of age) using data from Study P301. An analysis of covariance model was to be carried out with antibody at Day 57 as dependent variable and a group variable (a paediatric age group in Study P204 versus young adults [18 to 25 years of age] in Study P301) as the fixed variable for each paediatric age group. The GM values of the paediatric age group at Day 57 will 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. The corresponding 2-sided 95% CI was to be provided to assess the difference in immune response between the paediatric age group (Study P204) compared to the young adults (18 to 25 years of age) in Study P301 at Day 57. For each paediatric age group, the non-inferiority of GM value was to be considered demonstrated if:

- The lower bound of the 95% CI of the GMR is > 0.67 based on the non-inferiority margin of 1.5, AND
- The GMR point estimate > 0.8 (minimum threshold).

The number and percentage of participants with sero-response due to vaccination was to be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline time point with Day 57 being of the primary interest. The sero-response rate difference with 95% CI at Day 57 was to be provided between children receiving mRNA-1273 in Study P204 and young adults of 18 to 25 years of age receiving mRNA-1273 from Study P301. For each paediatric age group, the non-inferiority of sero-response rate was to be considered demonstrated if:

- The lower bound of the 95% CI 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 value of anti-SARS-CoV-2-specific antibody 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. For each age group, the geometric mean fold-rise of specific nAb and bAb with corresponding 95% CI at each post-baseline time point over pre-injection baseline at Day 1 was to be provided. Descriptive summary statistics including median, minimum, and maximum was also to be provided.

Multiplicity Adjustment Between Age Groups

A sequential hypothesis testing (fixed-sequence method) was to be used to adjust multiplicity to preserve the family-wise Type I error rate (alpha = 0.05), starting with the oldest age group, followed by the middle age group, and then followed by the youngest age group.

Interim analyses

Part 1: Interim analyses might have been performed after all or a subset of participants (with immunogenicity samples collected for D1 and D57) have completed Day 57 within an age group in Part 1

(one optional interim analysis for each age group, 3 interim analyses total for the 3 age groups in Part 1). Analyses of safety and immunogenicity might have been conducted at each interim analysis.

Part 2: An interim analysis of immunogenicity and safety were to be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 1 or Part 2 within an age group. This interim analysis was to be considered the primary analysis of immunogenicity for a given age group. Another interim analysis on safety might have been performed after a different subset or all participants have completed Day 57 in an age group.

Efficacy analyses

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate was to be provided by vaccination group, dose level, and age group, calculated as the number of cases divided by the total person-time. Participants in Part 1 and Part 2 of the study and in different age groups who receive the same mRNA-1273 dose level (if applicable) may be combined in the analysis.

For serologically confirmed SARS-CoV-2 infection or COVID-19, regardless of symptomatology or severity, infection rate was to be provided by vaccination group, dose level, and age group. The same analyses were to be conducted for asymptomatic SARS-CoV-2 infection.

The secondary efficacy analyses were to be performed on the PP Set, with sensitivity analyses in FAS, mITT Set, and mITT1 Set. Analyses of the efficacy endpoints in Part 2 were to be performed for the randomised blinded phase. Additional exploratory analyses were to be conducted in the blinded and unblinded phases for participants randomised to mRNA-1273 in Part 2, and in the unblinded phase for participants who are originally randomised to the placebo arm and cross-over to mRNA-1273 after use of any COVID-19 vaccine is authorised or licensed for the participant's age group.

The CHMP considered that the submitted immunogenicity data from the subset of subjects of the randomised blinded Part 2 phase support the application.

Results

Conduct of the study

The study was amended 5 times (original protocol 24th February 2021, amendments: 30 Apr 2021, 17 Jun 2021, 23 Jul 2021, 25 Aug 2021, 29 Sept 2021).

Timing of the Application

Data are available for the ≥6 years to <12 years of age group from both open-label Part 1 and blinded Part 2 with a data snapshot performed on 6th October 2021. This submission was triggered by

- the availability of immunogenicity data from Part 1 participants in the ≥ 6 years to < 12-years age group who received the selected dose of mRNA-1273 (2x 50 µg doses, 28 days apart)
- a median 2 months of follow-up after dose 2 for at least 1,000 participants who received mRNA-1273
- at least 7 days follow-up after dose 2 for at least 3,000 participants who received mRNA-1273 with a median 21 days' follow-up after dose 2.

Another IA is planned when all participants ≥6 to <12 years reach 6 months post-dose 2, at which time a full CSR will be prepared; availability of the CSR and IA data is expected by Q4 2022.

The CHMP noted that the many amendments of the study make it difficult to understand why changes in the primary analysis plan (including sample size plan) were not clearly reflected in the protocol.

Upon request the MAH informed that the further safety, immunogenicity and efficacy data are collected per protocol and proposed to submit a further interim analysis by Q1/2022 based on a 10th November 2021 data cut-off, meeting per protocol IA specification i.e. all participants ≥6 to <12 years in Part 2 reach Day 57 or had discontinued the study. This is estimated to provide a median follow-up duration of approximately 2 months post-dose 2. These data were provided following a request for further information.

Numbers analysed

The number of participants in each analysis set for Part 1 and reasons for exclusions from the PP Immunogenicity Subset are presented in Table 2. Of note, the PP Immunogenicity Subset used for immunogenicity analyses to assess non-inferiority excludes participants whose data were used for dose selection.

Table 2: Number of Participants in Each Analysis Set by Dose Level in Part 1 (FAS)

	mRNA-1273 50 µg	mRNA-1273 100 µg
FAS[a], n	380	371
Immunogenicity Subset[b], n	145	
PP Immunogenicity Subset[b], n (%)	134 (92.4)	
Excluded from PP Immunogenicity Subset	11 (7.6)	
Reason for Exclusion[c]		
Positive Baseline SARS-CoV-2 Status	10 (6.9)	
Did not Receive Dose 2 per Schedule	1 (0.7)	
Safety Set[d], n	380	371
Solicited Safety Set[d], n (%)	380 (100)	371 (100)
First Injection Solicited Safety Set	378 (99.5)	369 (99.5)
Second Injection Solicited Safety Set	379 (99.7)	371 (100)

Abbreviations: FAS = full analysis set; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
a. Numbers are based on planned treatment group.
b. Numbers are based on planned treatment group, and percentages are based on the number of participants in the Immunogenicity Subset, which includes participants in Part 1 whose data were not used in dose selection.
c. A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.
d. Numbers are based on actual treatment group, and percentages are based on the number of safety participants.
Source: Study P204 Table 14.1.2.1.1.1, Study P204 Table 14.1.2.3.1, and Study P204 Table 14.1.2.3.1.1

The number of participants in each analysis set for Part 2 and reasons for exclusion from the PP Set for Efficacy are provided in Table 3. Approximately 11% had SARS-CoV-2 positive status or had missing information at baseline in each treatment group.

Table 3: Number of Participants in Each Analysis Set by Dose Level in Part 2 (Randomisation Set)

	mRNA-1273 50 µg	Placebo
Randomization Set[a], n	3009	1002
FAS[a], n (%)	3005 (99.9)	997 (99.5)
PP Set for Efficacy[a], n (%)	2638 (87.7)	852 (85.0)
Excluded from PP Set for Efficacy, n (%)	371 (12.3)	150 (15.0)
Reason for Exclusion[b], n (%)		
Randomized but Not Dosed	4 (0.1)	5 (0.5)
Baseline SARS-CoV-2 Status Positive or Missing	315 (10.5)	117 (11.7)
Discontinued Study Treatment or Participation Without Receiving Dose 2	7 (0.2)	9 (0.9)
Did not Receive Dose 2 and Passed Window	11 (0.4)	13 (1.3)
Received Incorrect Vaccination	12 (0.4)	2 (0.2)
Received Dose 2 Out of Window	20 (0.7)	4 (0.4)
Had Other Major Protocol Deviations	2 (<0.1)	0
mITT[a], n (%)	2690 (89.4)	880 (87.8)
mITT1[a], n (%)	2678 (89.0)	878 (87.6)
Safety Set[c], n	3007	995
Solicited Safety Set[c], n (%)	3007 (100)	995 (100)
First Injection Solicited Safety Set	3005 (>99.9)	994 (99.9)
Second Injection Solicited Safety Set	2986 (99.3)	968 (97.3)

Abbreviations: FAS = full analysis set; mITT = modified intent-to-treat; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
Percentages are based on the number of participants in the Randomization Set in Part 2.
[a] Numbers are based on planned treatment group, and percentages are based on the number of randomized participants.
[b] A participant who has multiple reasons for exclusion is listed under the reason that appears earliest.
[c] Numbers are based on actual treatment group, and percentages are based on the number of safety participants.
Source: Study P204 Table 14.1.2.1.2.1 and Study P204 Table 14.1.2.5

Study Duration and Disposition

- *Part 1 – open label phase*

At the time of the data snapshot (06 October 2021), 380 participants in the 50 µg group and 371 participants in the 100 µg group received dose 1 and 379 participants in the 50 µg group and 371 participants in the 100 µg group received dose 2 (Table 4). One (0.3%) participant in the 50 µg group discontinued study vaccine due to an AE of urticaria papular following dose 1. A total of 4 (0.5%) participants withdrew from the study. One (0.3%) participant in the 50 µg group withdrew consent. In the 100 µg group, 1 (0.3%) participant was lost to follow-up and 2 (0.5%) participants withdrew consent.

Table 4: Participant Disposition by Dose Level in Part 1 (FAS)

	mRNA-1273 50 µg N=380 n (%)	mRNA-1273 100 µg N=371 n (%)	Total N=751 n (%)
Received first injection	380 (100)	371 (100)	751 (100)
Received second injection	379 (99.7)	371 (100)	750 (99.9)
Did not receive any injection	0	0	0
Completed study vaccine schedule	379 (99.7)	371 (100)	750 (99.9)
Discontinued study vaccine[a]	1 (0.3)	0	1 (0.1)
Reason for discontinuation of study vaccine			
Adverse event	1 (0.3)[b]	0	1 (0.1)
Completed study[c]	0	0	0
Withdrew from study	1 (0.3)	3 (0.8)	4 (0.5)
Reasons for withdrawal from study			
Lost to follow-up	0	1 (0.3)	1 (0.1)
Withdrawal of consent	1 (0.3)	2 (0.5)	3 (0.4)

Abbreviations: FAS = full analysis set.
Percentages are based on the number of participants enrolled in Part 1 who receive at least 1 injection of study IP.

[a.] Study Vaccine Discontinuation is defined as a participant who received the first injection but did not receive the second injection.
[b.] One participant had an adverse event of urticaria papular on Day 9 following dose 1.
[c.] Study Completion is defined as a participant who completed 12 months of follow-up after the last injection received, included participants who complete the first injection but not second injection. The study is ongoing; no participants have completed 12 months of follow-up.
Source: Study P204 Table 14.1.1.1.1

The median duration of follow-up was 140 days for the 50 µg group and 135 days for the 100 µg group after dose 1 and 111 days for the 50 µg group and 106 days for the 100 µg group after dose 2 (Table 5). In the 50 µg group, 379 (99.7%) participants have been followed for 2 months or more after dose 2.

Table 5: Summary of Study Duration by Dose Level in Part 1 (Safety Set)

	mRNA-1273 50 µg N=380	mRNA-1273 100 µg N=371	Total N=751
≥ 7 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 35 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 56 days since first injection, n (%)	380 (100)	371 (100)	751 (100)
≥ 7 days since second injection, n (%)	379 (99.7)	371 (100)	750 (99.9)
≥ 28 days since second injection, n (%)	379 (99.7)	371 (100)	750 (99.9)
≥ 56 days since second injection, n (%)	379 (99.7)	370 (99.7)	749 (99.7)
Study Duration from Dose 1, days			
Median (Min, Max)	140.0 (128, 206)	135.0 (76, 169)	138.0 (76, 206)
Study Duration from Dose 2, days			
Median (Min, Max)	111.0 (0, 177)	106.0 (41, 139)	108.0 (0, 177)

Abbreviations: Max = maximum; min = minimum.
Percentages are based on the number of participants in the Safety Set for Part 1.
Source: Study P204 Table 14.1.5.1

- ***Part 2 - randomised, blinded, placebo-controlled phase***

Table 6 displays disposition of individuals randomised in part 2 of the study. Over 99% in the vaccine group and ~97% in the placebo group received their treatment.

Table 6: Participant Disposition by Dose Level in Part 2 (Randomisation Set)

	mRNA-1273 50 µg N=3009 n (%)	Placebo N=1002 n (%)	Total N=4011 n (%)
Received first injection[a]	3005 (99.9)	997 (99.5)	4002 (99.8)
Received second injection	2985 (99.2)	971 (96.9)	3956 (98.6)
Did not receive any injection	4 (0.1)	5 (0.5)	9 (0.2)
Completed study vaccine schedule	2985 (99.2)	971 (96.9)	3956 (98.6)
Discontinued study vaccine[b]	6 (0.2)	6 (0.6)	12 (0.3)
Reason for discontinuation of study vaccine			
Adverse event	0[c]	1 (<0.1)[c]	1 (<0.1)
Physician decision	2 (<0.1)[d]	1 (<0.1)	3 (<0.1)
Withdrawal of consent	2 (<0.1)[e]	3 (0.3)	5 (0.1)
Other	2 (<0.1)[f]	1 (<0.1)	3 (<0.1)
Completed study[g]	0	0	0
Withdrew from study	9 (0.3)	11 (1.1)	20 (0.5)
Reasons for withdrawal from study			
Adverse event	1 (<0.1)[h]	0	1 (<0.1)
Physician decision	1 (<0.1)	0	1 (<0.1)
Withdrawal of consent	6 (0.2)	9 (0.9)	15 (0.4)
Other	1 (<0.1)	2 (0.2)	3 (<0.1)

Abbreviations: Max = maximum; min = minimum.

Percentages are based on the number of participants in the Randomization Set for Part 2.
[a.] Two participants who were randomized to the placebo group received mRNA-1273 50 µg due to a dosing error.
[b.] Study Vaccine Discontinuation is defined as a participant who received the first injection but did not receive the second injection.
[c.] One participant in the mRNA-1273 group had AEs of urticaria on Day 24 and wheezing on Day 29 that were coded in the AE section of the eCRF as leading to discontinuation of study vaccine d. One participant in the mRNA-1273 group discontinued study vaccine due to physician decision due to an adverse event of rash on Day 10 (Section 2.5.6.1.4.3.2). One participant discontinued study vaccine due to physician decision
[e.] Two participants in the mRNA-1273 group discontinued study vaccine due to withdrawal of consent: 1 denied nasal swab and withdrew consent and 1 no longer wanted to comply with study procedures.
[f.] Two participants in the mRNA-1273 group discontinued study vaccine for other reasons; both refused vaccination.
[g.] Study Completion is defined as a participant who completed 12 months of follow up after the last injection received, included participants who complete the first injection but not second injection.
[h.] One participant in the mRNA-1273 group withdrew from study due to an AE of inflammatory bowel disease, which was reported 21 days after dose 2. This event was assessed as not related by the investigator.
Source: Study P204 Table 14.1.1.1.2 and Study P204 Listing 16.2.7.1.2

The study duration for part 2 is summarised in Table 7. The median study duration from dose 1 was 50 days and from dose 2 20 days.

Table 7: Summary of Study Duration in Part 2 (Safety Set)

	mRNA-1273 50 µg N=3007	**Placebo N=995**	**Total N=4002**
Received first injection, n (%)	3007 (100)	995 (100)	4002 (100)
Received second injection, n (%)	2987 (99.3)	969 (97.4)	3956 (98.9)
≥ 7 days since first injection, n (%)	3007 (100)	995 (100)	4002 (100)
≥ 35 days since first injection, n (%)	3004(>99.9)	990 (99.5)	3994 (99.8)
≥ 56 days since first injection, n (%)	763 (25.4)	250 (25.1)	1013 (25.3)
≥ 7 days since second injection, n (%)	2958 (98.4)	962 (96.7)	3920 (98.0)
≥ 28 days since second injection, n (%)	474 (15.8)	165 (16.6)	639 (16.0)
Study Duration from Dose 1, days			
Median (Min, Max)	50.0 (29, 59)	50.0 (14, 59)	50.0 (14, 59)
Study Duration from Dose 2, days			
Median (Min, Max)	21.0 (0, 30)	20.0 (0, 30)	20.0 (0, 30)

Abbreviations: Max = maximum; min = minimum.
Percentages are based on the number of participants in the Safety Set for Part 2.
Source: Study P204 Table 14.1.5.2

Table 8 summarises the demographics and baseline characteristics in part 1 (dose selection) of study P204. Slightly more males were randomised to the 50 µg dose group than the 100 µg dose group (51.3% vs 46.4%). Age and weight were similar, and baseline negative SARS-CoV-2 status was comparable in both groups (86.1% and 86.8%).

Table 8: Demographics and baseline characteristics

	mRNA-1273 50 µg N=380	**mRNA-1273 100 µg N=371**	**Total N=751**
Age, years			
Mean (SD)	8.6 (1.66)	8.6 (1.62)	8.6 (1.64)
Median	9.0	9.0	9.0
Min, Max	6, 11	6, 11	6, 11
Sex, n (%)			
Male	195 (51.3)	172 (46.4)	367 (48.9)
Female	185 (48.7)	199 (53.6)	384 (51.1)
Race, n (%)			
White	266 (70.0)	284 (76.5)	550 (73.2)

Black	33 (8.7)	13 (3.5)	46 (6.1)
Asian	26 (6.8)	25 (6.7)	51 (6.8)
American Indian or Alaska Native	0	2 (0.5)	2 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (0.1)
Multiracial	39 (10.3)	31 (8.4)	70 (9.3)
Other	3 (0.8)	10 (2.7)	13 (1.7)
Not Reported	12 (3.2)	4 (1.1)	16 (2.1)
Unknown	0	2 (0.5)	2 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	72 (18.9)	69 (18.6)	141 (18.8)
Not Hispanic or Latino	304 (80.0)	296 (79.8)	600 (79.9)
Not Reported	3 (0.8)	3 (0.8)	6 (0.8)
Unknown	1 (0.3)	3 (0.8)	4 (0.5)
Race and Ethnicity Group[a], n (%)			
White, non-Hispanic	208 (54.7)	230 (62.0)	438 (58.3)
Communities of Colour	168 (44.2)	139 (37.5)	307 (40.9)
Missing	4 (1.1)	2 (0.5)	6 (0.8)
Weight, kg			
Mean (SD)	34.93 (12.472)	34.86 (11.834)	34.89 (12.153)
Median	32.05	32.27	32.18
Min, Max	16.8, 86.4	16.5, 85.6	16.5, 86.4
Baseline SARS-CoV-2 Status[b], n (%)			
Negative	327 (86.1)	322 (86.8)	649 (86.4)
Positive	28 (7.4)	30 (8.1)	58 (7.7)
Missing	25 (6.6)	19 (5.1)	44 (5.9)

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

Source: Study P204 Table 14.1.3.1.1

Participant demographics and baseline characteristics in the Part 1 PP Immunogenicity Subset are provided in Table 9 and were generally comparable to the Part 2 Safety Set (Table 10). Slightly more males than females were included in the PP Immunogenicity Subset of study P204 than in the young adult subset (59.0% vs 48.3%).

Table 9: Participant Demographics and Baseline Characteristics by Dose Level in Part 1 (Per Protocol Immunogenicity Subset)

	P204 (6-<12 years) mRNA-1273 50 µg N=134	**P301 (18-25 years) mRNA-1273 100 µg N=296**
Age, years		
Mean (SD)	8.7 (1.48)	22.4 (2.19)
Median	9.0	23.0
Min, Max	6, 11	18, 25
Sex, n (%)		
Male	79 (59.0)	143 (48.3)
Female	55 (41.0)	153 (51.7)
Race, n (%)		
White	85 (63.4)	207 (69.9)
Black	12 (9.0)	29 (9.8)

Asian	13 (9.7)	30 (10.1)
American Indian or Alaska Native	0	3 (1.0)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)
Multiracial	18 (13.4)	14 (4.7)
Other	0	8 (2.7)
Not Reported	6 (4.5)	3 (1.0)
Unknown	0	0
Ethnicity, n (%)		
Hispanic or Latino	24 (17.9)	79 (26.7)
Not Hispanic or Latino	109 (81.3)	215 (72.6)
Not Reported	1 (0.7)	0
Unknown	0	2 (0.7)
Race and Ethnicity Group[a], n (%)		
White, non-Hispanic	68 (50.7)	145 (49.0)
Communities of Colour	65 (48.5)	151 (51.0)
Missing	1 (0.7)	0
Weight, kg		
Mean (SD)	34.81 (10.714)	77.59 (19.280)
Median	32.76	73.64
Min, Max	19.4, 75.0	44.0, 158.2

Abbreviations: max = maximum; min = minimum; SD = stable disease.
Percentages are based on the number of participants in the Per Protocol Immunogenicity Subset for Part 1.
a. White non-Hispanic is defined as White and non-Hispanic, and Communities of Colour includes all the others whose race or ethnicity is not unknown, unreported, or missing.
Source: Study P204 Table 14.1.3.4.1

Participant demographics and baseline characteristics in the Part 2 Safety Set were representative of the intended target population and were generally balanced between the mRNA-1273 group and placebo group as shown in Table 10.

Table 10: Participant Demographics and Baseline Characteristics in Part 2 (Safety Set)

	mRNA-1273 50 µg N=3007 n (%)	**Placebo N=995 n (%)**	**Total N=4002 n (%)**
Age, years			
Mean (SD)	8.5 (1.65)	8.5 (1.64)	8.5 (1.65)
Median	8.0	9.0	9.0
Min, Max	6[a], 11	6, 11	6[a], 11
Sex, n (%)			
Male	1554 (51.7)	481 (48.3)	2035 (50.8)
Female	1453 (48.3)	514 (51.7)	1967 (49.2)
Race, n (%)			
White	1955 (65.0)	667 (67.0)	2622 (65.5)
Black	308 (10.2)	92 (9.2)	400 (10.0)
Asian	296 (9.8)	99 (9.9)	395 (9.9)
American Indian or Alaska Native	14 (0.5)	3 (0.3)	17 (0.4)
Native Hawaiian or Other Pacific Islander	4 (0.1)	0	4 (<0.1)
Multiracial	326 (10.8)	97 (9.7)	365 (10.8)
Other	62 (2.1)	23 (2.3)	65 (1.9)
Not Reported	28 (0.9)	12 (1.2)	40 (1.2)
Unknown	9 (0.3)	1 (0.1)	9 (0.3)
Missing	5 (0.2)	1 (0.1)	5 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	558 (18.6)	180 (18.1)	738 (18.4)
Not Hispanic or Latino	2419 (80.4)	806 (81.0)	3225 (80.6)
Not Reported	23 (0.8)	5 (0.5)	28 (0.7)
Unknown	7 (0.2)	4 (0.4)	11 (0.3)

Race and Ethnicity Group[b], n (%)			
White, non-Hispanic	1539 (51.2)	535 (53.8)	2074 (51.8)
Communities of Colour	1460 (48.6)	456 (45.8)	1916 (47.9)
Missing	8 (0.3)	4 (0.4)	12 (0.3)
Weight, kg			
Mean (SD)	33.33 (11.279)	33.52 (11.432)	33.38 (11.316)
Median	30.60	30.91	30.73
Min, Max	14.0, 112.0	14.2, 99.8	14.0, 112.0
Baseline SARS-CoV-2 Status[c], n (%)			
Negative	2692 (89.5)	878 (88.2)	3570 (89.2)
Positive	257 (8.5)	87 (8.7)	344 (8.6)
Missing	58 (1.9)	30 (3.0)	88 (2.2)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = stable disease.
Percentages are based on the number of participants in the Safety Set for Part 2.
a. One participant's age was incorrectly entered in the database as 5 years of age. The site has confirmed that the participant was indeed 6 years of age at the time of informed consent.
b. White non-Hispanic is defined as White and non-Hispanic, and Communities of Colour includes all the others whose race or ethnicity is not unknown, unreported, or missing.
c. Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.
Source: Study P204 Table 14.1.3.2

As regards baseline data, the CHMP identified no issues pertaining to selection or representativeness. Furthermore, patient characteristics are largely balanced between dose-selection cohort and part 1 as a whole. This is considered relevant in light of the question marks pertaining to the differential nAb reads between dose-selection and pivotal cohort. Patient characteristics are also balanced between the vaccine group & placebo in part 2.

A shortcoming of the submission is the median follow-up post-dose 2 in part 2 and the related inability to inform (any) supportive efficacy analyses after completed primary regimen (see next section). Safety screening is also limited accordingly.

The immunogenicity analysis set used for the confirmatory immunogenicity comparison was obtained from the expanded Part 1 50 µg group which amounted to about 50% of the newly added subjects consenting to voluntary d57 blood draws. See also discussion of statistical methods above for additional assessment of this selection approach.

Outcomes and estimation

Part 1 – Open-label phase

Dose Selection

The study began with dosing participants in the ≥ 6 to <12-year age group in Part 1 with 50 µg of mRNA-1273. After at least 75 participants had completed Day 8, an internal safety team reviewed the available safety data and agreed with the prespecified protocol plans to proceed with the 100 µg arm in Part 1 in the ≥6 to <12-year age group.

Baseline SARS-CoV-2 Status was determined as 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. All subjects in the dose definition phase were found negative at baseline.

Table 11 displays a summary of the nAb responses in children aged ≥6 to < 12 years old having received either two 50 µg or two 100 µg vaccine doses 28 days apart. In the 50 µg vaccine dose group the nAb GMT (measured by PsVNA ID50) was 1204.6 (95% CI: 1047.2, 1385.8) 28 days after dose 2 while in the 100 µg vaccine dose group a GMT of 1887.7 (95% CI: 1606.5, 2218.2) post-dose 2 was determined. All children achieved at least a 4-fold increase in nAb titers. The GMFR was 130 and 196 in the 50 µg and 100 µg dose group, respectively.

Table 11: Summary of Pseudovirus Neutralising Antibody ID50 Titers in the age group of the ≥6 to <12 years old by dose level in Part 1, Pseudovirus Neutralising Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118), Per-Protocol Immunogenicity Subset

	P204 mRNA-1273 dose group	
	50 µg (N=67)	100 µg (N=57)
Baseline (Day 1)		
GMT	9.250	9.588
95% CI	(NE, NE)	(8.923, 10.302)
Median	9.250	9.250
Min, Max	9.25, 9.25	9.25, 71.49
Post-dose 2 (Day 57)		
GMT	1204.647	1887.744
95% CI	(1047.150, 1385.831)	(1606.495, 2218.231)
GMFR	130.232	196.889
95% CI	(113.205, 149.820)	(163.316, 237.364)
Seroresponse, 4-fold increase		
n (%)	67 (100)	57 (100)
95% CI	(94.6, 100.0)	(93.7, 100.0)

GMT = geometric mean titer, CI = confidence interval, GMFR = geometric mean fold rise (post-baseline / baseline titers) (Source Table 14.2.3.1.1.1)

A review for dose selection compared the GM nAbs and seroresponse rate of the ≥6 to <12 years of age dose selection PP Immunogenicity Subset 50 µg as well as the 100 µg group in Study P204 with those from previously generated results of the immunogenicity subset of ≥18 to <25-year-old participants in the pivotal Study P301.

In children ≥6 to < 12 years old in the 50 µg dose group, the nAb GMT was 1204.647 at Day 57, 28 days after dose 2 (Table 12). All children achieved a seroresponse based on a 4-fold increase from baseline. The GMR of the paediatric 50 µg group (n=67) to young adult group (n=296) nAb titers at Day 57 was 0.93 (95% CI 0.74, 1.16). The difference in seroresponse rates between children and young adults at Day 57 was 1.4% (95% CI: -4.1%, 3.4%). The GMR of paediatric 100 µg group (n=57) to young adult group (n=296) nAb titers at Day 57 was 1.45 (95% CI 1.15, 1.84). The difference in seroresponse rates between children (Study P204) and young adults (Study P301) at Day 57 was 1.4% (95% CI: -5.0%, 3.4%).

Table 12: Part 1 Dose-Finding Analysis of Pseudovirus Neutralising Antibody Level and Seroresponse Rate at Day 57 by Pseudovirus Neutralising Assay (ID50) (Dose Selection PP Immunogenicity Subset)

	Study P204 ≥6 to < 12 Years mRNA-1273 50 µg N=67	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N=296**
Baseline GMT	9.250	9.506

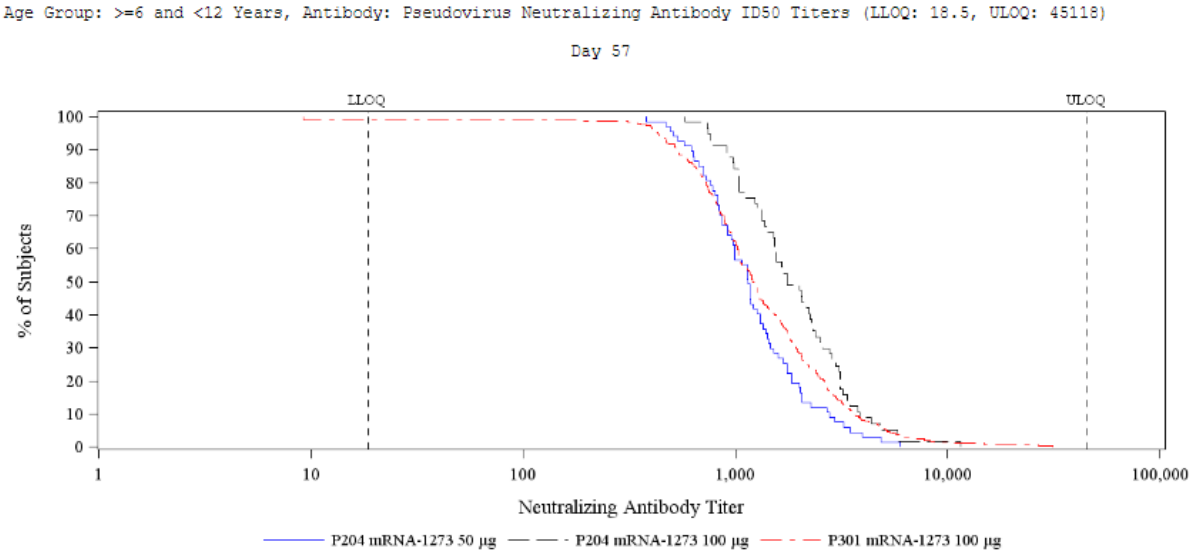
GMT Observed at Day 57	1204.647	1301.312
GMFR (95% CI)[a] at Day 57 from Baseline	130.232 (113.205, 149.820)	136.896 (122.266, 153.276)
GMT (model based) (95% CI) at Day 57	1204.647 (986.657, 1470.798)	1301.312 (1183.412, 1430.959)
GMR (P204 vs P301; model-based) (95% CI)[b]	0.93 (0.74, 1.16)	
Participants achieving seroresponse, n (%)[c] at Day 57	67 (100)	292 (98.6)
95% CI[d]	94.6, 100.0	96.6, 99.6
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	1.4 (-4.1, 3.4)	

	Study P204 ≥6 to < 12 Years mRNA-1273 100 µg N=57	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N=296**
Baseline GMT	9.588	9.506
GMT Observed at Day 57	1887.744	1301.312
GMFR (95% CI)[a] at Day 57 from Baseline	196.889 (163.316, 237.364)	136.896 (122.266, 153.276)
GMT (model based) (95% CI) at Day 57	1887.744 (1520.380, 2343.872)	1301.312 (1183.412, 1430.959)
GMR (P204 vs P301; model-based) (95% CI)[b]	1.45 (1.15, 1.84)	
Participants achieving seroresponse, n (%)[c] at Day 57	57 (100)	292 (98.6)
95% CI[d]	93.7, 100.0	96.6, 99.6
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	1.4 (-5.0, 3.4)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMFR = geometric mean fold ratio; GMR = geometric mean ratio; GMT = geometric mean titer (noted as observed or model based, which is estimated by geometric least squares mean); ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.
P301 mRNA-1273 group includes young adults (18-25 years of age).
The ULOQ for selected P301 participants tested previously was different.
Of note, one P301 participant had HIV and was included in the P301 young adults Per Protocol Immunogenicity Subset (n=296). High apparent baseline and post-immunisations values in the PsVNA ID50 are uninterpretable, likely due to highly active antiretroviral therapy. For this reason, HIV+ individuals were excluded from immunogenicity analysis by PsVNA in 301 and will be excluded in future analyses.
a. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
b. The log-transformed antibody levels are analysed using an ANCOVA model with the group variable (children in P204 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.
c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.
d. 95% CI is calculated using the Clopper-Pearson method.
e. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

The reverse cumulative distribution curves for Part 1 dose selection cohort is shown in Figure 1.

Figure 1: Reverse Cumulative Distribution Function of Pseudovirus Neutralising Antibody ID50 Titers by Age Group and Dose Level in Part 1 Dose Selection Cohort Per-Protocol Immunogenicity Subset



Based on the combined assessments of safety, reactogenicity, tolerability, and immunogenicity, the 50 µg dose was selected for further evaluation in Part 2 (randomised, placebo-controlled portion) of Study P204 in the ≥6 to <12-year age group.

Immunogenicity assessment and non-inferiority analysis

Results provided for the PP Immunogenicity Subset from Part 1 consist of all available data from the 50 µg group up until data snapshot (06 October 2021), excluding data from the dose-finding immunogenicity subset (n=67).

Table 13 summarises the analysis of serum nAb levels at Day 57 for children ≥6 years to < 12 years of age in Study P204 compared with those at Day 57 for young adults aged ≥18 to <25 years in Study P301. One P301 participant had HIV and was included in the P301 young adults Per Protocol Immunogenicity Subset (n=296) due to interference of active antiretroviral therapy with the assay.

In the PP Immunogenicity Subset (n=134), baseline nAb GMT in children ≥6 years to < 12 years old in Study P204 was below the LLOQ and GMT was 1964.6 (95% CI 1722.3, 2240.9) at Day 57, 28 days after dose 2, with 99.3% of children achieving seroresponse. The GM fold-rise from baseline at D57 was 209.4 (95% CI: 182.9, 239.8).

The pre-specified success criteria for the primary immunogenicity objective are met based on the co-primary immunogenicity endpoints. The immunobridging in children ≥6 to <12 years old in Study P204 is demonstrated as compared with young adults in Study P301. The GMR of nAb titers at Day 57 of children ≥6 to <12 years of age compared with young adults was 1.510 (95% CI: 1.263, 1.804), meeting the non-inferiority success criterion (i.e., lower bound of the 95% CI for GMR ≥0.67). In addition, the criterion on the point estimator of GMR >0.8 was also met. The difference in seroresponse rates between children and young adults at Day 57 was 0.6% (95% CI: -2.8%, 2.8%), meeting the non-inferiority success criterion (lower bound of the 95% CI of the seroresponse rate difference is > -10%).

Table 13: Co-primary Immunobridging (Pseudovirus Neutralising Antibody Level by Pseudovirus Neutralising Assay [ID50])

	Study P204	Study P301

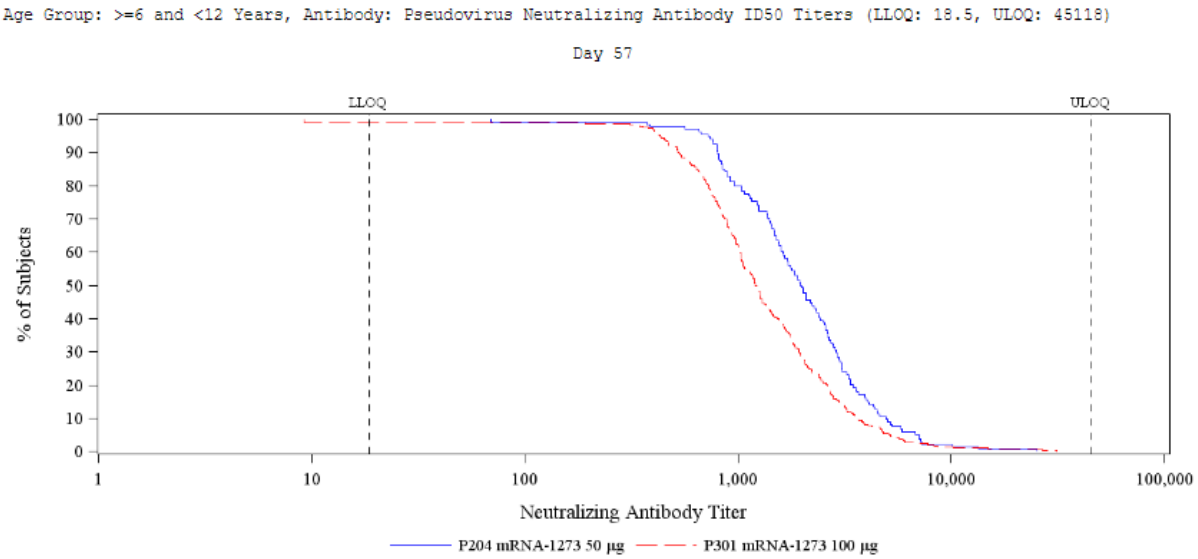
	6 to < 12 Years mRNA-1273 50 µg N=134	18 to ≤ 25 Years mRNA-1273 100 µg N=296
Baseline GMT	9.379	9.506
GMT Observed at Day 57	1964.601	1301.312
GMFR (95% CI)[a] at Day 57 from Baseline	209.466 (182.947, 239.829)	136.896 (122.266, 153.276)
GMT (model based) (95% CI) at Day 57	1964.601 (1694.578, 2277.651)	1301.312 (1178.086, 1437.427)
GMR (P204 vs P301; model-based) (95% CI)[b]	1.510 (1.263, 1.804)	
Participants achieving seroresponse, n (%)[c] at Day 57	133 (99.3)	292 (98.6)
95% CI[d]	95.9, 100.0	96.6, 99.6
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	0.6 (-2.8, 2.8)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMFR = geometric mean fold ratio; GMR = geometric mean ratio; GMT = geometric mean titer (noted as observed or model based, which is estimated by geometric least squares mean); ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.
P301 mRNA-1273 group includes young adults (18-25 years of age).
The ULOQ for selected P301 participants tested previously was different.
Of note, one P301 participant had HIV and was included in the P301 young adults Per Protocol Immunogenicity Subset (n=296). High apparent baseline and post-immunisations values in the PsVNA ID50 are uninterpretable, likely due to highly active antiretroviral therapy. For this reason, HIV+ individuals were excluded from immunogenicity analysis by PsVNA in 301 and will be excluded in future analyses.
a. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
b. The log-transformed antibody levels are analysed using an ANCOVA model with the group variable (children in P204 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.
c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.
d. 95% CI is calculated using the Clopper-Pearson method.
e. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Source: Study P204 Table 14.2.3.1.3.1, Study P204 Table 14.2.1.1.3.4.1, and Study P204 Table 14.2.1.2.3.4.1

Figure 2 displays the reverse cumulative distribution curves of the PsVNA titers for Part 1 PP immunogenicity subset. Immunogenicity data is not available for Part 1 expansion subjects at the 100 µg dose level, as only the selected dose level (50 µg) was tested as per protocol.

Figure 2: Reverse Cumulative Distribution Function of Pseudovirus Neutralising Antibody ID50 Titers by Age Group in Part 1 Expansion Per-Protocol Immunogenicity Subset



Assessment of the PsVNA results applying a cut-off of 80% inhibitory dose (ID80), showed similar results with a GMR of paediatric participants to young adults at Day 57 of 1.3 (95% CI: 1.1, 1.5) and difference in seroresponse rate again of 0.6% (95% CI: -2.8%, 2.8%) (data not shown). Anti-Spike bAb assay data using the MSD platform confirmed the findings of the analyses based on the PsVNA ID50 assay (Data not shown).

Immunogenicity results based on Part 2 PP Immunogenicity Subset samples

In both the dose-finding (N=67) and final analyses (N=134), immunogenicity of the 50 µg dose among children ≥6 to <12 years of age was significantly different to young adults in Study P301 using the PsVNA (0.9 vs 1.5). Upon request Day 57 immunogenicity analysis based on Part 2 PP Immunogenicity Subset samples were provided. The part 2 PP Immunogenicity Subset is a subset with n=320 (close to the sample size of 289 specified in the protocol for the non-inferiority testing of the coprimary endpoints) derived from the blinded, placebo-controlled phase of the study and serves as the primary analysis pre-specified to infer the effectiveness of mRNA-1273 in children.

As shown in Table 14 the Day 57 nAb GMT (measured by PsVNA ID50) was 1610.2 (95% CI 1,456.6, 1,780.0; n=319) with 99.1% of children achieving seroresponse. The GMFR in nAb from baseline to D57 was 174.0 (95% CI: 157.2, 192.5). The GMT of 1,610.2 from this larger Part 2 PP Immunogenicity Subset falls between that observed for the Part 1 dose-selection subset (1204.6: 95% CI: 1,047.2, 1,385.8; n=67) and for the Part 1 PP Immunogenicity Subset (1964.6, 95% CI: 1,722.4, 2,240.9; n=134).

As specified in the clinical P204 protocol, immunobridging between the paediatric population and the adult efficacy population was to be performed based on the Part 2 PP Immunogenicity Subset in study P204. Results from this subset successfully met non-inferiority criteria for both GMR and seroresponse rate difference compared to young adults (18 to 25 years) in the pivotal P301 study. Comparison of GMT between the Part 2 PP Immunogenicity Subset in P204 and the PP Immunogenicity Subset of young adults in P301 shows a GMR of 1.239 (95% CI: 1.072, 1.432) and a SRR difference of 0.1 (95% CI: -1.9, 2.1). These measures both successfully meet NI criteria of the 50 µg mRNA- 1273 in children 6 to <12 years compared to young adults receiving 100 µg of mRNA-1273.

Table 14: Co-primary Immunobridging at Day 57 (Pseudovirus Neutralising Antibody Level by Pseudovirus Neutralising Assay [ID50]) (PP Immunogenicity Subset for Part 2)

	Study P204 6 to < 12 years 50 µg N=319	Study P301 18 to ≤ 25 Years 100 µg N=295
Baseline GMT	9.250	9.285
GMT Observed at Day 57	1610.203	1299.855
GMFR (95% CI)[a] at Day 57 from Baseline	173.972 (157.238, 192.487)	139.990 (126.103, 155.405)
GMT (model based) (95% CI) at Day 57	1610.203 (1456.589, 1780.017)	1299.855 (1171.156, 1442.696)
GMR (P204 Part 2 vs P301; model-based) (95% CI)[b]	1.239 (1.072, 1.432)	
Participants achieving seroresponse, n (%)[c] at Day 57	313/316 (99.1)	292/295 (99.0)
95% CI[d]	(97.3, 99.8)	(97.1, 99.8)
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	0.1 (-1.9, 2.1)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMFR = geometric mean fold ratio; GMR = geometric mean ratio; GMT = geometric mean titer (noted as observed or model based, which is estimated by geometric least squares mean); ID50 = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; ULOQ = upper limit of quantification.
Antibody values reported as below the LLOQ are replaced by 0.5 × LLOQ. Values greater than ULOQ are replaced by the ULOQ if actual values are not available.
P301 mRNA-1273 group includes young adults (18-25 years of age).
The ULOQ for selected P301 participants tested previously was different.
a. 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log transformed values for GMT and GMFR, respectively, then back transformed to the original scale for presentation.
b. The log-transformed antibody levels are analysed using an ANCOVA model with the group variable (children in P204 Part 2 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.
c. Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.
d. 95% CI is calculated using the Clopper-Pearson method.
e. 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

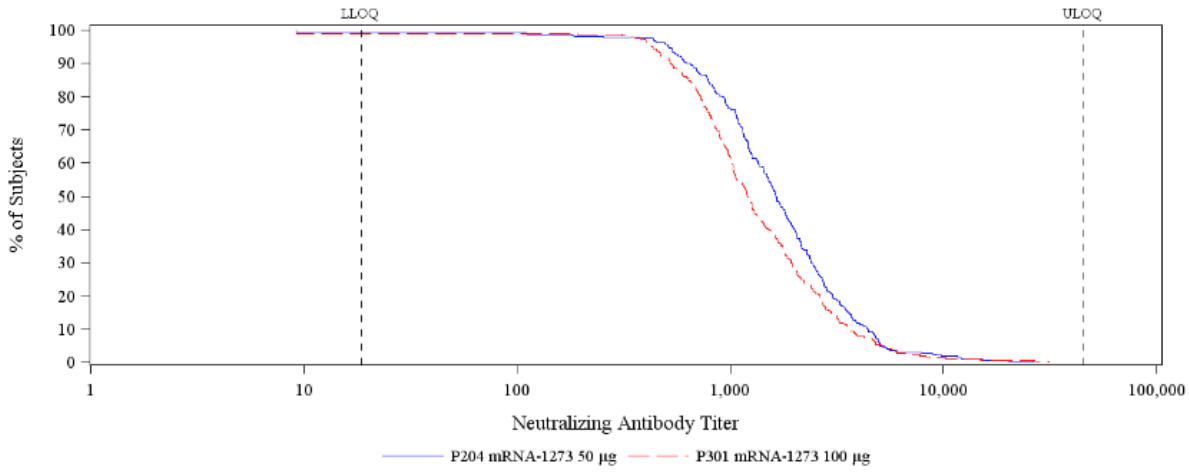
Source: Study P204 Table 14.2.3.1.1.2, Study P204 Table 14.2.1.1.3.1.2, and Study P204 Table 14.2.1.2.3.1.2

The reverse cumulative distribution curves for PsVNA titers of Part 2 subjects are presented below.

Figure 14.2.1.4.3.2
Reverse Cumulative Distribution Function of Pseudovirus Neutralizing Antibody ID50 and ID80 Titers by Age Group
Per-Protocol Immunogenicity Subset

Age Group: >=6 and <12 Years, Antibody: Pseudovirus Neutralizing Antibody ID50 Titers (LLOQ: 18.5, ULOQ: 45118)

Day 57



Results of the MSD assay show highly consistent bAb results for each of the study subsets, including the Part 2 PP immunogenicity subset. bAb results for study P204 Part 2 PP Immunogenicity Subset (295,106 [95% CI 265,272, 328,295]) agree with those observed for the dose-selection subset (333,103, 95% CI: 298,596, 371,598) and for the Part 1 PP Immunogenicity Subset (322,158, 95% CI: 292,826, 354,427).

Efficacy

- *Efficacy Analyses for Endpoints Starting 14 Days After Dose 2 in the PP Set for Efficacy*

Analysis of SARS-CoV-2 infections and COVID-19 cases occurring 14 days or more after dose 2 in the PP Set for Efficacy were secondary endpoints.

Based on the PP Set for Efficacy (data cut-off 6 Oct), there was 1 case (0.1%) of COVID-19 in the placebo group (incidence rate 8.58 per 1000 person-years) and none in the mRNA-1273 group starting 14 days after dose 2. The case in the placebo group met both the CDC case definition of COVID-19 and the P301 case definition of COVID-19. There were no cases of asymptomatic SARS-CoV-2 infection in either treatment group starting 14 days after dose 2 in the PP Set for Efficacy.

Upon request the MAH provided data from the secondary efficacy endpoint from an IA based on 10th November 2021. This data cut-off was triggered based on meeting per protocol IA specification (all participants 6 to <12 years in Part 2 reaching Day 57 or having discontinued the study). In addition, availability of an EUA allowed unblinding of any study participant and cross-over of placebo participants to either receive mRNA-1273 or withdraw from trial and seek the approved vaccine as specified on protocol P204.

Given a median follow-up of 82 days after dose 1 and 51 days after dose 2 in Part 2 blinded phase, efficacy endpoints accumulated after the first of the two doses (i.e. occurring starting 14 days PD1 and measured in the mITT1 population) greatly outnumber the efficacy endpoints accumulated after the intended, two-dose regimen (i.e. starting 14 days PD2). As shown in the table 15 below, limiting endpoint analysis to endpoints occurring 14 days PD2 (i.e. after the intended regimen) yield a total of only 7 cases. The estimated VE based on the incidence rate was 76.8% with a 95% CI of -0.373 to 0.966 (reference to Table 14.2.8.1.1.2). Similar results were obtained for the other endpoints, too few to perform meaningful analyses. It should be noted that during the study period and in the region where the study was conducted the Delta variant prevailed.

Table 15: Summary of VE analysis results starting 14 days after Dose 2 (PP Set for Efficacy)

Endpoint	**Part 2**	
	mRNA-1273 50 µg N=2644	**Placebo N=853**
CDC case definition of COVID-19		
Cases, n/N1 (%)	3/2644 (0.1)	4/853 (0.5)
Incidence rate per 1000 person-years (95% CI)[a,b]	5.043 (1.040, 14.737)	21.716 (5.917, 55.602)
P301 case definition of COVID-19		
Cases, n/N1 (%)	3/2644 (0.1)	3/853 (0.4)
Incidence rate per 1000 person-years (95% CI)	5.040 (1.039, 14.730)	16.262 (3.354, 47.524)
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	9/2644 (0.3)	10/853 (1.2)
Incidence rate per 1000 person-years (95% CI)	15.223 (6.961, 28.897)	54.930 (26.341, 101.018)
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	12/2644 (0.5)	14/853 (1.6)
Incidence rate per 1000 person-years (95% CI)	20.297 (10.488, 35.454)	76.902 (42.043, 129.028)

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; NE = not estimable; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.
N1= number of participants at risk at 14 days after dose 2 for specific efficacy endpoint

a. Person-years is defined as the total years from the first injection date for Part 1 and the randomisation date for Part 2 to the date of event (CDC Case Definition of COVID-19, P301 case definition of COVID-19, asymptomatic SARS-CoV-2 infection, or SARS-CoV-2 infection, depending upon endpoint), last date of study participation, or efficacy data cutoff date, whichever is the earliest.
b. Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
Source: Study P204 Table 14.2.8.1.1.2, Study P204 Table 14.2.7.1.1.2, Study P204 Table 14.2.6.1.1.2.1, and Study P204 Table 14.2.5.1.1.2

- *Efficacy Analyses for Endpoints Starting 14 Days After Dose 1 in the mITT1*

Table 16 summarises the descriptive analysis of SARS-CoV-2 infections and COVID-19 cases occurring at least 14 days after dose 1 in the mITT1 (data cut-off 6 Oct). The analyses of efficacy were conducted in baseline PCR and Elecsys negative participants.

VE analyses were conducted using the COVID-19 "CDC case definition," requiring only 1 symptom and reflecting the less severe disease, which is more common in paediatric patients, and a positive RT-PCR. The VE against cases occurring 14 days or more after dose 1 was based on 3 cases (0.1%) in the mRNA-1273 group and 14 cases (1.6%) in the placebo group. Vaccine efficacy was 93.0% (95% CI: 75.1%, 98.7%). Analysis of SARS-CoV-2 infection regardless of symptoms occurring 14 days or more after dose 1 showed a VE of 80.1% (95% CI: 61.5%, 90.0%) based on 16 cases (0.6%) in the mRNA-1273 group and 26 cases (3.0%) in the placebo group.

Table 16: Summary of Secondary Efficacy Endpoint Analysis Results Starting 14 Days after Dose 1 in Part 2 (mITT1; cut-off date 6 October)

Endpoint	**Part 2**	
	mRNA-1273 50 µg N=2678	**Placebo N=878**
CDC case definition of COVID-19		
Cases, n/N1 (%)	3/2672 (0.1)	14/877 (1.6)
Incidence rate per 1000 person-years (95% CI)[a,b]	11.399 (2.351, 33.313)	163.810 (89.557, 274.846)
VE based on incidence rate (95% CI)[c]	0.930 (0.751, 0.987)	
P301 case definition of COVID-19		
Cases, n/N1 (%)	0/2672 (0)	13/877 (1.5)
Incidence rate per 1000 person-years (95% CI)	0.000 (NE, 14.006)	152.027 (80.948, 259.970)
VE based on incidence rate (95% CI)	1.000 (0.893, NE)	
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	16/2672 (0.6)	26/877 (3.0)
Incidence rate per 1000 person-years (95% CI)	60.958 34.843, 98.992)	306.853 (200.447, 449.611)
VE based on incidence rate (95% CI)	0.801 (0.615, 0.900)	
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	13/2672(0.5)	12/877 (1.4)
Incidence rate per 1000 person-years (95% CI)	49.529 (26.372, 84.695)	141.625 (73.180, 247.390)
VE based on incidence rate (95% CI)	0.650 (0.161, 0.853)	

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; mITT = modified intent-to-treat; NE = not estimable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VE = vaccine efficacy.
N1= number of participants at risk at 14 days after dose 1 for specific efficacy endpoint
a. Person-years is defined as the total years from the first injection date for Part 1 and the randomisation date for Part 2 to the date of event (CDC Case Definition of COVID-19, P301 case definition of COVID-19, asymptomatic SARS-CoV-2 infection, or SARS-CoV-2 infection, depending upon endpoint), last date of study participation, or efficacy data cut-off date, whichever is the earliest.
b. Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
c. VE, 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.
Source: Study P204 Table 14.2.5.3.1.2, Study P204 Table 14.2.6.3.1.2, Study P204 Table 14.2.7.4.1.2, Study P204 Table 14.2.8.4.1.2

Based on the mITT1 population (VE starting 14 days post-dose 1) a total of 25 cases were accrued in the longer follow-up period with data cut-off on 11th November (Table 17). This allowed a more robust calculation of vaccine efficacy. The incidence of COVID-19 using the CDC case definition was 117/1000 person years in the placebo group compared to 14/1000 person years in the vaccine group, yielding a vaccine efficacy (VE) of 88% (95% CI: 70.0%, 95.8%). Using the same case definition employed in the pivotal adult efficacy trial of mRNA-1273, a VE of 91.8% was observed (95% CI: 74.2, 98.0%).

Table 17: Summary of Secondary Efficacy Endpoint Analysis Results Starting 14 Days after Dose 1 in Part 2 (mITT1; cut-off date 11th November 2021)

Endpoint	**Part 2**	
	mRNA-1273 50 µg N=2687	**Placebo N=880**
CDC case definition of COVID-19		
Cases, n/N1 (%)	7/2680 (0.3)	18/875 (2.1)
Incidence rate per 1000 person-years (95% CI)[a,b]	14.006 (5.631, 28.858)	117.096 (69.399, 185.063)
VE based on incidence rate (95% CI)[c]	0.880 (0.700, 0.958)	
P301 case definition of COVID-19		
Cases, n/N1 (%)	4/2681 (0.1)	15/877 (1.7)
Incidence rate per 1000 person-years (95% CI)	7.993 (2.178, 20.466)	97.144 (54.371, 160.225)
VE based on incidence rate (95% CI)	0.918 (0.742, 0.980)	
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	34/2678 (1.3)	40/875 (4.6)
Incidence rate per 1000 person-years (95% CI)	68.534 (47.462, 95.769)	263.995 (188.602, 359.486)
VE based on incidence rate (95% CI)	0.740 (0.579, 0.841)	
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	27/2678 (1.0)	22/875 (2.5)
Incidence rate per 1000 person-years (95% CI)	54.424 (35.866, 79.184)	145.197 (90.994, 219.830)
VE based on incidence rate (95% CI)	0.625 (0.309, 0.794)	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; mITT = modified intent-to-treat; NE = not estimable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VE = vaccine efficacy.
N1= number of participants at risk at 14 days after dose 1 for specific efficacy endpoint
a. Person-years is defined as the total years from the first injection date for Part 1 and the randomisation date for Part 2 to the date of event (CDC Case Definition of COVID-19, P301 case definition of COVID-19, asymptomatic SARS-CoV-2 infection, or SARS-CoV-2 infection, depending upon endpoint), last date of study participation, or efficacy data cut-off date, whichever is the earliest.
b. Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
c. VE, 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.
Source: Study P204 Table 14.2.5.3.1.2, Study P204 Table 14.2.6.3.1.2, Study P204 Table 14.2.7.4.1.2, Study P204 Table 14.2.8.4.1.2

Summary of main studyies

The following table (Table 18) summarises the efficacy results from the main studies 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 18 - Summary of Efficacy for trial P204

Title: A Phase 2/3, Two-Part, Open-Label, Dose-Escalation, Age De-escalation and Randomized, Observer-Blind, Placebo-Controlled Expansion Study to Evaluate the Safety, Tolerability, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Children 6 Months to Less Than 12 Years of Age			
Study identifier	mRNA-1273-P203		
Design	Part 1 open-label Part 2 randomised (3:1), 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 (P204) vs older age groups (P301) Efficacy was measured and reported with 95% CI		
Treatments groups	Active arm		Part 1 Spikevax (mRNA-1273) 50 µg, 2 doses 28 days apart, 380 subjects randomised Spikevax (mRNA-1273) 100 µg, 2 doses 28 days apart, 371 subjects randomised Part 2 Spikevax (mRNA-1273, 50 µg), 2 doses, 28 days apart, 3009 subjects randomised
	Control arm		Placebo (Saline), 2 doses, 28 days apart, 1002 subjects randomised
	Comparator group P301 immunogenicity subset		Spikevax (mRNA-1273, 100 µg), 2 doses, 28 days apart, 296 young adults randomly selected
Endpoints and definitions	Primary endpoint (Immuno-genicity)	GM value of serum nAb level	geometric mean value at 28 days post-dose 2 (day 57)
		seroresponse rate by nAb	percentage of participants with a 4-fold rise in neutralising antibody levels from day 1 prior first dose to 28 days post-dose 2
		GM value of serum bAb level by MSD	geometric mean value 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 post-baseline, where COVID-19 is defined as symptomatic disease based on CDC case definition
		VE	The incidence of SARS-CoV-2 infection including symptomatic and asymptomatic infection in SARS-CoV-2 negative subjects at baseline
		VE	The incidence of asymptomatic SARS-CoV-2 infection in participants with negative SARS-CoV-2 at baseline, in the absence of any COVID-19 symptoms
Database lock	06 October 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	6-12 years	18-25 years	
	Number of subjects	134	296	GMR (95% CI), non-inferiority (yes/no)
	GMT (95% CI) by pseudo neutralisation (ID50)	**1964.601** (1694.578, 2277.651)	**1301.312** (1178.086, 1437.427)	**1.510** (1.263, 1.804) Yes
	Number of subjects	134	296	Difference in seroresponse rates (95% CI) (yes/no)
	Seroresponse rate n, **%** (95% CI) by pseudo neutralisation (ID50)	133 **99.3** (95.9, 100)	292 **98.6** (96.6, 99.6)	**0.6** (-2.8, 2.8) Yes
	Number of subjects	133	280	GMR (95% CI), non-inferiority (yes/no)
	GLSM (95% CI) for Spike specific antibody by MSD (AU/ml)	**322157.952** (279605.198, 371186.755)	**257131.438** (233213.106, 283502.833)	**1.253** (1.055, 1.488) Yes
	Number of subjects	133	280	Difference in seroresponse rates (95% CI) (yes/no)
	Seroresponse rate n, **%** (95% CI) for Spike specific antibody by MSD (AU/ml)	133 **100** (97.3, 100)	278 **99.3** (97.4, 99.9)	**0.7** (-2.1, 2.6) Yes

Data from a larger number of subjects of the blinded part 2 confirmed that non-inferiority was met.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study mRNA-1273-P204 is a 2-part phase 2/3 study to evaluate the safety, tolerability, reactogenicity, and effectiveness of Spikevax in healthy children 6 months to less than 12 years of age separately in 3 different age groups (6 to < 12 years, 2 to < 6 years, and 6 months to < 2 years). The modified PIP including changes to the randomisation in study P204 was approved by PDCO (EMEA-002893-PIP01-20-M01). In the first open label part two doses of Spikevax in a concentration of 50 µg and of 100 µg were evaluated in children aged ≥6 to <12 years. In the subsequent randomised (3:1), observer-blind, placebo-controlled expansion study the chosen 50 µg dose level was further evaluated. The study was amended 5 times.

The sample size of both, Part 1 and Part 2 were increased during the study to allow a better safety assessment. Planned sample sizes for safety as well as immunogenicity are overall endorsed.

The analyses and analysis sets are not always unambiguously defined. For example, it is often not clear to which part of the study they belong to. The immunogenicity subset to be used for immunobridging was not well defined. No clear definition and separation between age groups and study parts (Part 1: dose finding, Part 2: dose confirmation) exists making the overall study plan rather vague. The MAH even potentially planned to combine data over age groups if the same dose was to be chosen. This is acceptable as supportive evidence but not endorsed as primary analysis.

The study plan for interim and final immunogenicity analyses is very vague and the timing of the primary analyses remains unclear. According to the protocol it seems that immunobridging was planned based on Part 2 of the study, which also is in line with the two-stage design (dose selection, dose confirmation). This was widened with a statement that "*an interim analysis of immunogenicity and safety will be performed after all or a subset of participants have completed Day 57 (1 month after the second dose) in Part 1 or Part 2 within an age group. This interim analysis will be considered the primary analysis of immunogenicity for a given age group.*" This is not fully understood in the light of the definition of interim analyses for Part 1 where it is stated that *"Interim analyses may be performed after all or a subset of participants (with immunogenicity samples collected for D1 and D57) have completed Day 57 within an age group in Part 1 (one optional interim analysis for each age group, 3 interim analyses total for the 3 age groups in Part 1)."* It is not assumed that only a first (optional) interim analysis in Part 1 would have been considered primary by the MAH at planning stage. Hence, no clear concept for interim and primary analysis was in place, which is not endorsed for a confirmatory trial.

Dose selection

In part 1 of study P204 two doses of Spikevax in a 50 µg and 100 µg concentration, respectively were evaluated in 75 subjects each. Although higher nAb levels were achieved in the 100 µg dose group compared with the 50 µg dose group (1,887.7 vs 1,204.6) all subjects in both dose selection groups reported a 4-fold increase in antibody titers based on the PP set. Comparison of the neutralising antibody responses of each of the two dosing groups with the nAb responses reported in young adults (≥18 to <25 years of age) showed a 0.93 and 1.45 fold difference in geometric mean ratio in the 50 µg and 100 µg dose group, respectively, indicating an increase in dose response with increasing concentrations. With respect to immunogenicity both concentrations result in an appropriate neutralising antibody response. Based on the reactogenicity profile the 50 µg dose was chosen for further evaluation in the ≥6 to <12-year-old participants in the subsequent randomised, observer-blinded, placebo-controlled part 2 of the study. The dose selection process – as conducted - was not pre-specified in the protocol which foresaw separate study parts for dose selection and confirmation. It was however confirmed that the enrolment of participants in the dose selection cohort occurred independent of the subsequent enrolment of the enlarged part 1 subjects for additional Part 1 safety and immunogenicity. Enrolment of these subsets occurred at non-overlapping time windows. While at the time of dose selection safety/tolerability data (post-dose 2) were available for participants receiving 50 µg or 100 µg mRNA-1273 in the dose selection part, immunogenicity data were only available for the 50 µg group in the expanded part 1 subjects. Consequently, the decision to carry the 50 µg dose forward to Part 2 occurred independent of immunogenicity data from the 100 µg Part 1 expansion cohort. As regards safety it was confirmed that data from both the 50 µg and the 100 µg dose arm were available and consequently, data from the expansion cohort could in fact have been factored into the dose selection.

Efficacy data and additional analyses

Inferring efficacy by immunobridging from adults to children 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 children and young adults following vaccination with Spikevax were assessed using two 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 immune bridging.

The immune bridging strategy to infer vaccine efficacy was based on a non-inferiority approach employing ratios of geometric mean titers (GMR) and seroresponse rates between children ≥6 to <12 years of age from study P204 and young adults ≥18 to <25 years of age from study P301. Evaluations were based on neutralising antibody (nAb) titers measured via PsVNT (ID50) at day 57 post-vaccination (Per-Protocol Immunogenicity Subset) and a 4-fold increase criterion.

The analysis presented for immunobridging was initially only based on Part 1 data and contained data on the 134 subjects which were not part of immunogenicity analyses for dose selection. This is far less than the originally planned 289 subjects for the PP immunogenicity set. The MAH clarified upon request that the "*deviation from the original protocol was considered appropriate based on the emergence of the Delta variant in summer 2021, increased pediatric hospitalization and concern for the overall well-being of school-aged children*". This is in principle endorsed. A timely protocol or SAP amendment reflecting this decision would have been preferred, though. The decision to conduct the primary immunogenicity analysis using only data from Part 1 was made based on the results in the dose selection cohort without knowledge of the immunogenicity data in the additional 134 subjects from Part 1.

Significant differences in GMTs were observed in children participating in the 50 µg group of the dose selection part and in the analyses of non-inferiority (1,204.6 vs 1,964.6) in the expanded immunogenicity set of part 1. If compared to young adults the observed discrepancy between dose-selection and the expanded ≥6 to <12 years of age immunogenicity cohorts was of concern. To exclude variability of the assay as root cause further information on assay performance was provided. A review of internal control parameters and data on assay control samples indicated that the assay performed within its validation parameters. Moreover, the MAH confirmed that there were no changes to the assay conduct or reagents used. Potential other sources for the observed differences in nAb GMT were discussed, however, no final conclusion on the root cause of these differences can be made for the time being although smaller sample size and lack of random selection of the serum samples likely contribute to the observation.

Upon request the MAH also provided further immunogenicity analyses from the (blinded) part 2 PP immunogenicity subset (N=319). An increase of neutralising antibodies was reported in children aged ≥6 to <12 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 1.5 fold higher in part 1 subjects and 1.2 fold higher in the larger cohort of part 2 subjects compared with the nAb levels observed in young adults included in the PP immunogenicity set in the pivotal efficacy study P301. Almost all children in part 1 (133/134) and part 2 (313/316) achieved at least a 4-fold increase in nAb titers after two doses of 50 µg Spikevax given 28 days apart indicating an appropriate seroresponse. Non-inferiority was demonstrated by comparison of the antibody responses in children (part 1 and part 2) to young adults. The results met the pre-specified success criteria in the neutralising antibody levels (part 1: 1.51; 95%CI: 1.263, 1.804; part 2: 1.239; 95% CI: 1.072, 1.432) and the seroresponse rates (part 1: 0.6; 95%CI: -2.8, 2.8; part 2: 0.1; 95%CI: -1.9, 2.1). Analyses based on a binding anti-Spike antibody assays confirmed these results, i.e. non-inferiority of bAb responses and response rates were established.

Lower bounds of CIs of the pivotal immunogenicity sample are well above the pre-specified margins, and direct comparisons of point estimates of GMT and SR between ≥6 to 12 years of age and young adults would support the assumption that immune response in children is at least as strong as in young adults. Despite the differences in nAb results the success criteria for immunobridging of children ≥6 to <12 years to young adults in P301 were met for the various data sets (dose selection group and expanded

immunogenicity subset of part 1). Immunogenicity analysis from a larger number of subjects who received the 50 µg dose of Spikevax or placebo in the blinded randomised part 2 of study P204 confirmed these initial results.

Vaccine efficacy was assessed as secondary endpoint in the second part of the study. In children tested SARS-CoV-2 negative at baseline and having received two doses of 50 µg Spikevax 28 days apart only 4 confirmed COVID-19 case in the placebo group and 3 cases in the vaccine group was reported 14 days post-dose 2 (data cut-off date 11 Nov). In the mITT set VE against COVID-19 starting 14 days after dose 1 was estimated to be 88% (95% CI: 70.0%, 95.8%) based on a total of 25 cases accrued (7 in the Spikevax group and 18 in the placebo group). Using the same case definition employed in the pivotal adult efficacy trial of mRNA-1273, a VE of 91.8% was observed (95% CI: 74.2, 98.0%).

Because of the very low number of confirmed COVID-19 cases and the short follow-up period of a median of 51 days post-dose 2 no reliable VE estimates are available. As SARS-CoV-2 infections in children are mostly mild and asymptomatic this is not unexpected.

In summary, and mainly building on the co-primary immunobridging endpoints, efficacy against symptomatic COVID-19 could be inferred for children ≥6 to <12 years of age.

2.4.1. Conclusions on the clinical efficacy

From the interim data available, it can be concluded that Spikevax protects children aged ≥6 to <12 years against symptomatic COVID-19 based on demonstration of non-inferior humoral immune responses compared to young adults ≥18 to <25 years. Outstanding issues were addressed appropriately and further immunogenicity results from the blinded part 2 study cohort were presented. These data support the interim results on immunobridging.

The CHMP considers the following measure (**SOB**) necessary to address issues related to clinical efficacy:

- In order to confirm the efficacy of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P204.

2.5. Clinical safety

Introduction

On 6th January 2021, Spikevax (also referred to in this report as COVID-19 Vaccine Moderna or mRNA-1273) 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. On 23rd July 2021, the indication was subsequently extended to individuals ≥12 years of age (EMEA/H/C/005791/II/0021). This procedure intends to extend the use of Spikevax to include active immunisation to prevent coronavirus disease 2019 (COVID-19) in individuals 6 years to <12 years of age. The safety assessment for the extension of indication of Spikevax to individuals 6 years to < 12 years of age is based on the submitted safety data for study mRNA-1273-P204 (hereafter referred to as P204). P204 is an ongoing Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age. The study population in P204 comprises 3 age groups (6 years to < 12 years, 2 years to < 6 years, and 6 months to < 2 years). This submission focus on children 6 years to < 12 years of age as mentioned above. Subjects in this age cohort were recruited in the USA during predominance of the Delta variant. Main exclusion criteria were hypersensitivity against any component of the vaccine, liver disease, congenital or acquired

immunodeficiency and bleeding disorders. The open-label dose selection Part 1 is evaluating up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 in each age group. It should be noted that the 25 µg dose was not tested in the age group 6 to < 12 years of age. In the blinded expansion phase (Part 2), participants receive mRNA-1273 or placebo administered as 2 IM injections approximately 28 days apart at the selected dose level.

Prior to the start of Part 2 Protocol Amendment 3 was implemented including enhanced surveillance for symptoms suggestive of possible myocarditis or pericarditis, based on individual symptoms that are components of the US CDC working case definition for myocarditis and pericarditis observed following COVID-19 vaccination (Gargano et al 2021).

Data snapshot for this analysis is 6th October 2021.

Study population

Children with chronic disease (e. g., asthma, diabetes mellitus, cystic fibrosis, human immunodeficiency virus infection) were not excluded in the trial, but the disease should be stable. Stable diseases were defined in the CTP as those which have had no change in their status in the medications required to control them in the 6 months prior to Screening Visit. Literature indicates that obesity in adults is associated with worse outcomes in COVID-19. There is a paucity of clinical data available to fully understand the risk factors and disease course in the paediatric population. In Part 1 of the trial, in both dose groups together, 14 children (1.9%) were obese with BMI>= 30 kg/m2; 6 each in mRNA-1273 and the placebo group (2.1% versus 1.6%). The proportion of obese versus non-obese participants in both vaccine groups together in part 1 was 22.5% (169 children) versus 77.5% (582 children). In part 2 of the trial, 193 children (19.4%) in the placebo and 607 in the mRNA-1273 vaccine group (20.2%) were obese. The proportion of obese/non-obese children in the 50 µg dose group, taking part 1 and part 2 together was 20.5% (696) obese versus 79.5% (2691) non-obese children. This is comparable to the proportion in the placebo group (19.4% obese children versus 80.6% non-obese children). With regard to medical history the placebo and the vaccine group in P204 were balanced, taking the 50 µg vaccine group of part 1 and part 2 together. At least one medical history was reported by 53.5% of subjects in the placebo and by 55.8% of subjects in the 50 µg mRNA-1273 vaccine group of part 1 and part 2 together (table 14.1.4.1.2). The most recorded medical histories belong to the SOC of immune system disorders (26.4% of subjects in the placebo and 28.3% in the 50 µg vaccine group). This included amongst other medical conditions seasonal allergy (21.0% versus 21.7%), drug hypersensitivity (3.7% each), one case of selective IgA immunodeficiency and 4 HIV positive children enrolled in the 50 µg vaccine group. This was followed by psychiatric disorders (14.6% versus 13.0% of subjects in the placebo and the vaccine group). Blood and lymphatic system disorders were reported by 0.5% and 0.8% of subjects in the two groups. This included individual cases of thrombocytopenia, immune thrombocytopenia, mast cell activation syndrome, anaemia, and neutropenia, all in the vaccine group. Metabolism and nutrition disorders were reported by 1.8% each (again taking the 50 µg group of part 1 and part 2 together). This included 0.5% versus 0.2% of subjects with diabetes mellitus type 1 (5 versus 8 subjects), and singular cases of metabolic syndrome and glucose tolerance impaired in the vaccine group. 0.1% (1 subject) in the placebo versus 0.3% of subjects (11) in the vaccine group had a history of cardiac disorders. 3 subjects with autoimmune thyroiditis were enrolled in the vaccine group. One subject in a vaccine group had a medical history of acute lymphocytic leukaemia.

Individuals with known history of SARS-CoV-2 infection within 2 weeks prior to administration of IP or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of IP were to be excluded, but SARS-CoV-2 seropositivity at baseline was not an exclusion criterion. In Part 1 of the trial, 86.1% of participants in the 50 µg and 86.8% in the 100 µg dose group were SARS-CoV-2 seronegative at baseline, 7.4% versus 8.1% were seropositive, and from 6.6% and 5.1% of participants in the 50 µg and the 100 µg dose group, the SARS-CoV-2 baseline

status is not known. The proportion was comparable in Part 2, were 89.5% of participants in the mRNA-1273 and 88.2% in the placebo group were SARS-CoV-2 seronegative, and 8.5% versus 8.7% seropositive. From 1.9% and 3.0% of participants in the two groups in Part 2 the SARS-CoV-2 baseline status is not known.

The CHMP noted that fewer data with regards to risk factors for severe COVID-19 outcome are available for the paediatric population compared to the adult population. Limited data suggest an increased risk of severe or critical disease in children less than one year of age and those with certain underlying medical conditions like e.g. congenital heart disease, and chronic pulmonary disease. The trial includes only individuals who are in a good health. Children with stable chronic underlying disease were however allowed to be enrolled into the trial. The proportion of obese/non-obese children in the 50 µg vaccine group (part 1 and part 2 together) was 20.5% obese versus 79.5% non-obese. This is comparable to the proportion in the placebo group (19.4% obese children versus 80.6% non-obese children). At least one medical history was reported by 53.5% of subjects in the placebo and by 55.8% of subjects in the 50 µg mRNA-1273 vaccine group (taking part 1 and part 2 together).

Patient exposure and duration of follow-up

First interim analysis with data cut-off 6th October 2021

The data cut-off for the first interim analysis submitted to support the extension of indication to children 6-<12 years of age was 6th October 2021. For this cut-off, the safety sets include data from 4753 participant (data snapshot 6th October 2021), including 3,758 participants who received at least 1 dose of either 50 µg or 100 µg mRNA-1273 and from 995 participants who received at least 1 dose of placebo. The size of the submitted safety database supports detection of an AE occurring at a rate of 0.1% with a 95% probability. Overall, 1,374 participants had received at least one dose of 50 µg mRNA-1273, which is the final selected dose for the paediatric population 6-<12 years of age.

At the data snapshot performed on 6th October 2021, in Part 1, the median duration of follow-up was 140 days for the 50 µg group (n=380) and 135 days for the 100 µg group (n=371) after dose 1, and 111 days for the 50 µg group (n=380) and 106 days for the 100 µg group after dose 2 (n=371). In Part 2, the median follow-up post-dose 2 was 21 days for the 50 µg group and 20 days for the placebo group. At the time of data snapshot, no participants had been followed for ≥ 56 days after the second dose. A safety follow-up of at 28 days after dose 2 was performed for 853 participants who had received at least one dose of 50 µg mRNA-1273. Safety follow-up for 3 months post-dose 2 was provided for 749 subjects who had received at least one dose of either 50 µg or 100 µg mRNA-1273 (in Part 1). 379 children in the 50 µg group in Part 1 provided at least 56 days of follow-up, and only 474 children in the 50 µg group of Part 2 provide at least 28 days post-dose 2. The time-window foreseen for collection of unsolicited AEs, SAEs, MAAEs, AESIs is up to 28 days after each injection, this means that a meaningful short term follow-up is only available for a minority of subjects, i.e. 18.8% in the main Part 2. An overview of the sample size and duration of follow-up for Part 1, Part 2 and for Part 1 and Part 2 together (i.e. for the 100 µg and the 50 µg dose recipients) is provided in Tables 19, 20 and 21.

Table 19: Summary of Study Duration by Age Group and Dose Level in Part 1 Safety Set, source: Table 14.1.5.1

Age Group: >=6 and <12 Years

	mRNA-1273		
	50 µg (N=380)	100 µg (N=371)	Total (N=751)
Number of Subjects, n (%)			
Received First Injection	380 (100)	371 (100)	751 (100)
Received Second Injection	379 (99.7)	371 (100)	750 (99.9)
>= 7 Days Since First Injection	380 (100)	371 (100)	751 (100)
>= 35 Days Since First Injection	380 (100)	371 (100)	751 (100)
>= 56 Days Since First Injection	380 (100)	371 (100)	751 (100)
>= 7 Days Since Second Injection	379 (99.7)	371 (100)	750 (99.9)
>= 21 Days Since Second Injection	379 (99.7)	371 (100)	750 (99.9)
>= 28 Days Since Second Injection	379 (99.7)	371 (100)	750 (99.9)
>= 28 and < 56 Days Since Second Injection	0	1 (0.3)	1 (0.1)
>= 56 Days Since Second Injection	379 (99.7)	370 (99.7)	749 (99.7)
Study Duration from First Injection (Days)			
n	380	371	751
Mean (SD)	148.5 (22.08)	140.7 (11.91)	144.6 (18.21)
Median	140.0	135.0	138.0
Q1, Q3	134.0, 145.0	133.0, 143.0	133.0, 145.0
Min, Max	128, 206	76, 169	76, 206
Person-years from First Injection [1]	154.45	142.91	297.36

Table 20 Summary of Study Duration by Age Group and Dose Level in Part 2 Safety Set, source: table 14.1.5.2

Age Group: >=6 and <12 Years

	Part 2			Part 1 + Part 2
	Placebo (N=995)	mRNA-1273 50 µg (N=3007)	Total (N=4002)	mRNA-1273 50 µg (N=3387)
Number of Subjects, n (%)				
Received First Injection	995 (100)	3007 (100)	4002 (100)	3387 (100)
Received Second Injection	969 (97.4)	2987 (99.3)	3956 (98.9)	3366 (99.4)
>= 7 Days Since First Injection	995 (100)	3007 (100)	4002 (100)	3387 (100)
>= 35 Days Since First Injection	990 (99.5)	3004 (>99.9)	3994 (99.8)	3384 (>99.9)
>= 56 Days Since First Injection	250 (25.1)	763 (25.4)	1013 (25.3)	1143 (33.7)
>= 7 Days Since Second Injection	962 (96.7)	2958 (98.4)	3920 (98.0)	3337 (98.5)
>= 21 Days Since Second Injection	489 (49.1)	1509 (50.2)	1998 (49.9)	1888 (55.7)
>= 28 Days Since Second Injection	165 (16.6)	474 (15.8)	639 (16.0)	853 (25.2)
>= 28 and < 56 Days Since Second Injection	165 (16.6)	474 (15.8)	639 (16.0)	474 (14.0)
>= 56 Days Since Second Injection	0	0	0	379 (11.2)
Study Duration from Randomization (Days)				
n	995	3007	4002	3387
Mean (SD)	49.9 (5.96)	50.0 (5.78)	50.0 (5.83)	61.0 (32.41)
Median	50.0	50.0	50.0	51.0
Q1, Q3	45.0, 56.0	45.0, 56.0	45.0, 56.0	45.0, 57.0
Min, Max	14, 59	29, 59	14, 59	29, 206

Table 21: Overview of Participant Disposition and Duration Part 1 and Part 2 (Safety Set), 06-Oct-2021 data snapshot

	mRNA-1273 (50 µg and 100 µg) (n=3758)	**Placebo (n=995)**	**Total**
Received Dose 1	3758	995	4753
Received Dose 2	3737	969	4706
Follow-up post-dose 2:			
≥7 days	3708	962	4670[a]
≥21 days	2259	489	2748
≥1 month	1224	165	1389[b]
≥2 months	749	0	749
≥3 months	749	0	749

Second interim analysis (IA) with cut-off date 10th November 2021

Upon request, the MAH submitted additional safety data from a protocol specified Interim Analysis (IA) performed on 10th November 2021, at the time at which each participant according to the protocol had either completed study Day 57 or had discontinued study.

For the part 2 trial follow-up it must be considered, that on 29th October 2021, a competitor's COVID-19 vaccine became available for that age group via EUA by the FDA. Per Protocol Amendment 5, if a child becomes eligible for a COVID-19 vaccine outside of the study, it becomes eligible to unblind and, if having received placebo, also eligible to receive comparator vaccine or to cross-over to receive 2 doses of mRNA-1273. Unblinding and cross-over vaccinations for the 6 to <12-year-old age group in Part 2 started on 1st November 2021, 9 days before the data cut-off date for the pre-specified IA, marking the ending of the blinded follow-up for this age group. Data collected after participant unblinding are not included in the blinded phase analyses. Only 80 /1000 placebo participants have left the trial to date to seek an alternative vaccine. The vast majority of placebo recipients have crossed over to mRNA-1273 and contribute to additional safety follow-up, albeit unblinded.

Duration of follow-up in the 2nd IA

In Part 1, post-dose 1 the median duration of follow-up was 175 and 170 days, respectively, for the 50 and the 100 µg groups, post-dose 2 it was 146 and 141 days, respectively for the 2 dose groups.

379 (99.7%) participants in the 50 µg group and 370 (99.7%) participants in the 100 µg group have been followed for 2 months (56 days) or more after dose 2.

In Part 2, the median duration of follow-up was 82 days after dose 1 and 51 days after dose 2 in the blinded phase prior to unblinding or cross-over. In Part 2 blinded phase, 2981 (99.1 %) participants in the mRNA-1273 group and 966 (97.1 %) participants in the placebo group have been followed for 28 days or more after dose 2. In the blinded phase, 1066 (35.5%) participants in the mRNA-1273 group and 218 (21.9%) participants in the placebo group have been followed for 56 days or more after dose 2.

Table 22: Summary of Study Duration in Part 2 Blinded Phase (Safety Set), source: Table 3 response document

Blinded phase	mRNA-1273 50 µg N=3007	Placebo N=995	Total N=4002
Received first injection, n (%)	3007 (100)	995 (100)	4002 (100)
Received second injection, n (%)	2990 (99.4)	971 (97.6)	3961 (99.0)
≥ 7 days since first injection, n (%)	3007 (100)	995 (100)	4002 (100)
≥ 56 days since first injection, n (%)	2995 (99.6)	986 (99.1)	3981 (99.5)
≥ 7 days since second injection, n (%)	2990 (99.4)	971 (97.6)	3961 (99.0)
≥ 28 days since second injection, n (%)	2981 (99.1)	966 (97.1)	3947 (98.6)
≥ 56 days since second injection, n (%)	1066 (35.5)	218 (21.9)	1284 (32.1)
Study duration from dose 1, days			
Median (Min, Max)	83.0 (29, 94)	79.0 (14, 94)	82.0 (14, 94)
Study duration from dose 2, days			
Median (Min, Max)	52.0 (0, 65)	49.0 (0, 65)	51.0 (0, 65)
Min, Max	0, 65	0, 65	0, 65

Abbreviations: Max = maximum; min = minimum.
Percentages are based on the number of participants in the Safety Set for Part 2.
Source: Study P204 Table 14.1.5.2

Taking blinded phase and open-label phase together, there are 2984 (99.2 %) participants in the mRNA-1273 group and 967 (97.2 %) participants in the placebo group who have been followed for 28 days or more after dose 2. 1498 (49.8%) participants in the mRNA-1273 group and 456 (45.8%) participants in the placebo group have been followed for 56 days or more after dose 2.

The CHMP noted that the first data snapshot supporting the extension of indication to the paediatric population from 6-<12 years of age is 6th October 2021. The safety sets include data from 4,753 participant (data snapshot 6th October 2021), including 3,758 participants who received at least 1 dose of either 50 µg or 100 µg mRNA-1273 and from 995 participants who received at least 1 dose of placebo. Overall, 3,387 participants had received at least one dose of 50 µg mRNA-1273, which is the final selected dose for the paediatric population 6-<12 years of age. Follow-up time is rather short. A safety follow-up of at least 28 days after dose 2 was performed for 853 participants who had received at least one dose of 50 µg mRNA-1273. Safety follow-up for 3 months post-dose 2 was provided for 749 subjects who had received at least one dose of either 50 µg or 100 µg mRNA-1273 (in Part 1).

The time-window foreseen for collection of unsolicited AEs, SAEs, MAAEs, and AESIs is up to 28 days after each injection, this means that a meaningful short term follow-up is only available for a minority of subjects, i.e. 18.8% in the main Part 2. The MAH stated that follow-up safety data for a later time point (e.g. 22nd November 2021) was, that not possible within this procedure. The MAH proposed to conduct another interim analysis (IA) based on a 10th November 2021 data cut-off, meeting per protocol IA specification (all participants 6 to <12 years in Part 2 reach Day 57 or had discontinued the study). The 2nd IA was submitted as requested. Almost all subjects in both phases have follow-up of 28 days post-dose 2. However, still not all subjects had a follow-up of 56 days or longer post-dose 2, neither in the blinded phase (below 40% of subjects) nor taking blinded and unblinded phase together (less than 50%). Day 56 follow-up post-dose 2 is available for 1,066 subjects in the blinded phase and for 1,498 subjects in the blinded/unblinded phase. Unblinding and cross-over vaccinations for the 6 to <12-year-old age group in Part 2 started on 1st November 2021, 9 days before the data cut-off date for the pre-specified IA, marking the ending of the blinded follow-up for this age group. This was necessary because of a COVID-19 vaccine became available via EUA. This is acknowledged.

Disposition

Part 1

In Part 1, at the time of the data snapshot (06 October 2021), 380 participants (100%) in the 50 µg group and 371 participants (100%) in the 100 µg group had received dose 1; 379 participants (99.7%) in the 50 µg group and 371 participants (100%) in the 100 µg group had received dose 2. One subject (in the 50 µg dose group) discontinued study vaccination due to an adverse event of urticaria papular on Day 9 following dose 1. Details are described in the AE section below. One subject in the 100 µg dose group withdraw from the study because of lost to follow-up. 3 subjects (0.4%), 1 in the 50 µg dose group and 2 in the 100 µg dose group withdraw consent.

Details are provided in Table 23.

Table 23: Participant Disposition by Dose Level in Part 1 (FAS), source: table 7 Clinical overview

	mRNA-1273 50 µg N=380 n (%)	**mRNA-1273 100 µg N=371 n (%)**	**Total N=751 n (%)**
Received first injection	380 (100)	371 (100)	751 (100)
Received second injection	379 (99.7)	371 (100)	750 (99.9)
Did not receive any injection	0	0	0
Completed study vaccine schedule	379 (99.7)	371 (100)	750 (99.9)
Discontinued study vaccine[a]	1 (0.3)	0	1 (0.1)
Reason for discontinuation of study vaccine			
Adverse event	1 (0.3)[b]	0	1 (0.1)
Completed study[c]	0	0	0
Withdrew from study	1 (0.3)	3 (0.8)	4 (0.5)
Reasons for withdrawal from study			
Lost to follow-up	0	1 (0.3)	1 (0.1)
Withdrawal of consent	1 (0.3)	2 (0.5)	3 (0.4)

Abbreviations: FAS = full analysis set.
Percentages are based on the number of participants enrolled in Part 1 who receive at least 1 injection of study IP.
[a.] Study Vaccine Discontinuation is defined as a participant who received the first injection but did not receive the second injection.
[b.] One participant had an adverse event of urticaria papular on Day 9 following dose 1.
[c.] Study Completion is defined as a participant who completed 12 months of follow-up after the last injection received, included participants who complete the first injection but not second injection. The study is ongoing; no participants have completed 12 months of follow-up.
Source: Study P204 Table 14.1.1.1.1

Part 2

In Part 2, at the time of the data snapshot (06 October 2021), 3007 participants in the mRNA-1273 group and 995 participants in the placebo group had received dose 1 and 2987 participants in the mRNA-1273 group and 969 participants in the placebo group had received dose 2. A total of 12 (0.3%) participants discontinued study vaccine, 6 participants each in the mRNA-1273 group (0.2%) and the placebo group (0.6%). Reasons for discontinuation of study vaccine in the mRNA-1273 group for 2 participants each (<0.1%) were physician decision, withdrawal of consent and other. Although none of the participants were coded as discontinuing due to an AE, 1 of the 2 participants who discontinued study vaccination due to physician decision had an AE of rash, on Day 10. In addition to the 12 participants coded as discontinuing study vaccine, an additional participant had AEs of urticaria on Day 24 and wheezing on Day 29 that were coded in the AE section of the electronic case report form (eCRF) as leading to discontinuation of study vaccine.

Overall, 20 subjects (0.5%) withdraw from the study, 9 participants (0.3%) in the mRNA-1273 group and 11 (1.1%) in the placebo group. Reasons for study withdrawal in the mRNA-1273 group were withdrawal of consent for 6 participants (0.2%). One subject each withdraw due to an event of moderate AE (inflammatory bowel disease), due to physician decision, and because of other not specified reasons. The AE of inflammatory bowel disease was not considered being vaccine related by the investigator and is described in the section "Discontinuation due to adverse events" in this AR. The new possible diagnosis for this event after follow-up investigation is Common Variable Immunodeficiency (CVID). No further information is provided for the subjects who discontinued due to physician decision. A summary of the participant disposition is provided in Table 24.

Table 24: Participant Disposition by Dose Level in Part 2 (Randomisation Set)

	mRNA-1273 50 µg N=3009 n (%)	**Placebo N=1002 n (%)**	**Total N=4011 n (%)**
Received first injection[a]	3005 (99.9)	997 (99.5)	4002 (99.8)
Received second injection	2985 (99.2)	971 (96.9)	3956 (98.6)
Did not receive any injection	4 (0.1)	5 (0.5)	9 (0.2)
Completed study vaccine schedule	2985 (99.2)	971 (96.9)	3956 (98.6)
Discontinued study vaccine[b]	6 (0.2)	6 (0.6)	12 (0.3)
Reason for discontinuation of study vaccine			
Adverse event	0[c]	1 (<0.1)[c]	1 (<0.1)
Physician decision	2 (<0.1)[d]	1 (<0.1)	3 (<0.1)
Withdrawal of consent	2 (<0.1)[e]	3 (0.3)	5 (0.1)
Other	2 (<0.1)[f]	1 (<0.1)	3 (<0.1)
Completed study[g]	0	0	0
Withdrew from study	9 (0.3)	11 (1.1)	20 (0.5)
Reasons for withdrawal from study			
Adverse event	1 (<0.1)[h]	0	1 (<0.1)
Physician decision	1 (<0.1)	0	1 (<0.1)
Withdrawal of consent	6 (0.2)	9 (0.9)	15 (0.4)
Other	1 (<0.1)	2 (0.2)	3 (<0.1)

Abbreviations: Max = maximum; min = minimum.
Percentages are based on the number of participants in the Randomization Set for Part 2.
[a.] Two participants who were randomized to the placebo group received mRNA-1273 50 µg due to a dosing error.
[b.] Study Vaccine Discontinuation is defined as a participant who received the first injection but did not receive the second injection.
[c.] One participant in the mRNA-1273 group had AEs of urticaria on Day 24 and wheezing on Day 29 that were coded in the AE section of the eCRF as leading to discontinuation of study vaccine d. One participant in the mRNA-1273 group discontinued study vaccine due to physician decision due to an adverse event of rash on Day 10 (Section 2.5.6.1.4.3.2). One participant discontinued study vaccine due to physician decision.
[e.] Two participants in the mRNA-1273 group discontinued study vaccine due to withdrawal of consent: 1 denied nasal swab and withdrew consent and 1 no longer wanted to comply with study procedures.
[f.] Two participants in the mRNA-1273 group discontinued study vaccine for other reasons; both refused vaccination.
[g.] Study Completion is defined as a participant who completed 12 months of follow up after the last injection received, included participants who complete the first injection but not second injection.
[h.] One participant in the mRNA-1273 group withdrew from study due to an AE of inflammatory bowel disease, which was reported 21 days after dose 2. This event was assessed as not related by the investigator.
Source: Study P204 Table 14.1.1.1.2 and Study P204 Listing 16.2.7.1.2

Study disposition in the 2nd IA

In Part 1, at the time of the IA, 380 participants in the 50 µg group and 371 participants in the 100 µg group received dose 1 and 379 participants in the 50 µg group and 371 participants in the 100 µg group

received dose 2. As of 10th November 2021, no additional participants have been withdrawn due to TEAE in Part 1.

In Part 2, a total of 4,002 participants had received dose 1 (3007 in mRNA-1273 group and 995 in placebo group) and a total of 3,961 participants had received dose 2 (2,988 in the mRNA-1273 group and 973 in placebo group. The proportion of subjects who discontinued through 10th November 2021 was comparable to the first interim analyses. A total of 13 subjects (0.4%) in the mRNA-1273 vaccine group discontinued from vaccination. One subject discontinued due to an AE, and 2 due to physician decision (no change compared with the 1st interim analysis). 6 subjects in the mRNA-1273 vaccine group withdrew consent (i.e. 0.2% compared with 0.1% in the 1st interim analysis), 3 subjects entered cross-over phase and 1 subject discontinued due to other not further specified reason.

In summary, in the 10th November 2021 IA safety analysis, a median follow-up of 56 days post-dose 2 is provided for a total of 3,387 participants exposed to 50 µg mRNA-1273 across study Parts 1 and 2 from the blinded and open label phases. From Part 2, median follow-up of 55 days post-dose 2 is provided for 4,002 participants (3,007 exposed to 50 µg of mRNA-1273 and 995 to placebo).

Demography

Part 1

The proportion of female and male participants was overall balanced in in Part 1 of the trial. In total, 51.1% of subjects were female and 48.9% male. In the 100 µg dose group slightly more females (53.6%) than males (46.4%) were included, vice versa in the 50 µg dose group (48.7% females and 51.3% males). The two dose groups were also balanced with regards to age, weight, and SARS-CoV-2 baseline serostatus. Mean age is 8.6 years in both dose groups, the mean weight 34.93 and 34.86 kg. 86.1% of participants in the 50 µg and 86.8% in the 100 µg dose group were SARS-CoV-2 seronegative at baseline, 7.4% versus 8.1% were seropositive, and from 6.6% and 5.1% of participants in the 50 µg and the 100 µg dose group, the SARS-CoV-2 baseline status is not known.

Table 25: Participant Demographics and Baseline Characteristics by Dose Level in Part 1 (Safety Set), source: Table 11, Clinical overview

	mRNA-1273 50 µg N=380	mRNA-1273 100 µg N=371	Total N=751
Age, years			
Mean (SD)	8.6 (1.66)	8.6 (1.62)	8.6 (1.64)
Median	9.0	9.0	9.0
Min, Max	6, 11	6, 11	6, 11
Sex, n (%)			
Male	195 (51.3)	172 (46.4)	367 (48.9)
Female	185 (48.7)	199 (53.6)	384 (51.1)
Race, n (%)			
White	266 (70.0)	284 (76.5)	550 (73.2)
Black	33 (8.7)	13 (3.5)	46 (6.1)
Asian	26 (6.8)	25 (6.7)	51 (6.8)
American Indian or Alaska Native	0	2 (0.5)	2 (0.3)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0	1 (0.1)
Multiracial	39 (10.3)	31 (8.4)	70 (9.3)
Other	3 (0.8)	10 (2.7)	13 (1.7)
Not Reported	12 (3.2)	4 (1.1)	16 (2.1)
Unknown	0	2 (0.5)	2 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	72 (18.9)	69 (18.6)	141 (18.8)
Not Hispanic or Latino	304 (80.0)	296 (79.8)	600 (79.9)
Not Reported	3 (0.8)	3 (0.8)	6 (0.8)
Unknown	1 (0.3)	3 (0.8)	4 (0.5)

	mRNA-1273 50 µg N=380	mRNA-1273 100 µg N=371	Total N=751
Race and Ethnicity Group[a], n (%)			
White, non-Hispanic	208 (54.7)	230 (62.0)	438 (58.3)
Communities of Color	168 (44.2)	139 (37.5)	307 (40.9)
Missing	4 (1.1)	2 (0.5)	6 (0.8)
Weight, kg			
Mean (SD)	34.93 (12.472)	34.86 (11.834)	34.89 (12.153)
Median	32.05	32.27	32.18
Min, Max	16.8, 86.4	16.5, 85.6	16.5, 86.4
Baseline SARS-CoV-2 Status[b], n (%)			
Negative	327 (86.1)	322 (86.8)	649 (86.4)
Positive	28 (7.4)	30 (8.1)	58 (7.7)
Missing	25 (6.6)	19 (5.1)	44 (5.9)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = standard deviation.

Percentages are based on the number of participants in the Safety Set for Part 1.

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

[b.] Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

Source: Study P204 Table 14.1.3.1.1

Part 2

Demography and baseline characteristics in Part 2 are not notably different from Part 1. Demographics and baseline characteristics were balanced between the mRNA-1273 group and the placebo group. In total, 49.2% of subjects were female and 50.8% male. In the mRNA-1273 group slightly more males (51.7%) than females (48.3%) were included, vice versa in the placebo group (48.3% males and 51.7%

females). Like in Part 1, the two study groups were also balanced with regards to age, weight, and SARS-CoV-2 baseline serostatus. Mean age is 8.5 years in the mRNA-1273 and the placebo group, the mean weight is 33.33 and 33.52 kg. 89.5% of participants in the mRNA-1273 and 88.2% in the placebo group were SARS-CoV-2 seronegative, 8.5% versus 8.7% seropositive, from 1.9% and 3.0% of participants in the two groups the SARS-CoV-2 baseline status is not known.

Table 26: Participant Demographics and Baseline Characteristics in Part 2 (Safety Set), source: Table 13, Clinical overview

	mRNA-1273 50 µg N=3007 n (%)	**Placebo N=995 n (%)**	**Total N=4002 n (%)**
Age, years			
Mean (SD)	8.5 (1.65)	8.5 (1.64)	8.5 (1.65)
Median	8.0	9.0	9.0
Min, Max	6[a], 11	6, 11	6[a], 11
Sex, n (%)			
Male	1554 (51.7)	481 (48.3)	2035 (50.8)
Female	1453 (48.3)	514 (51.7)	1967 (49.2)
Race, n (%)			
White	1955 (65.0)	667 (67.0)	2622 (65.5)
Black	308 (10.2)	92 (9.2)	400 (10.0)
Asian	296 (9.8)	99 (9.9)	395 (9.9)
American Indian or Alaska Native	14 (0.5)	3 (0.3)	17 (0.4)
Native Hawaiian or Other Pacific Islander	4 (0.1)	0	4 (<0.1)
Multiracial	326 (10.8)	97 (9.7)	365 (10.8)
Other	62 (2.1)	23 (2.3)	65 (1.9)
Not Reported	28 (0.9)	12 (1.2)	40 (1.2)
Unknown	9 (0.3)	1 (0.1)	9 (0.3)
Missing	5 (0.2)	1 (0.1)	5 (0.1)

	mRNA-1273 50 µg N=3007 n (%)	Placebo N=995 n (%)	Total N=4002 n (%)
Ethnicity, n (%)			
Hispanic or Latino	558 (18.6)	180 (18.1)	738 (18.4)
Not Hispanic or Latino	2419 (80.4)	806 (81.0)	3225 (80.6)
Not Reported	23 (0.8)	5 (0.5)	28 (0.7)
Unknown	7 (0.2)	4 (0.4)	11 (0.3)
Race and Ethnicity Group[b], n (%)			
White, non-Hispanic	1539 (51.2)	535 (53.8)	2074 (51.8)
Communities of Color	1460 (48.6)	456 (45.8)	1916 (47.9)
Missing	8 (0.3)	4 (0.4)	12 (0.3)
Weight, kg			
Mean (SD)	33.33 (11.279)	33.52 (11.432)	33.38 (11.316)
Median	30.60	30.91	30.73
Min, Max	14.0, 112.0	14.2, 99.8	14.0, 112.0
Baseline SARS-CoV-2 Status[c], n (%)			
Negative	2692 (89.5)	878 (88.2)	3570 (89.2)
Positive	257 (8.5)	87 (8.7)	344 (8.6)
Missing	58 (1.9)	30 (3.0)	88 (2.2)

Abbreviations: COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; RT-PCR = reverse transcription polymerase chain ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = stable disease.

Percentages are based on the number of participants in the Safety Set for Part 2.

[a.] One participant's age was incorrectly entered in the database as 5 years of age. The site has confirmed that the participant was indeed 6 years of age at the time of informed consent.

[b.] 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.

[c.] Baseline SARS-CoV-2 Status: Positive if there is immunologic or virologic evidence of prior COVID-19, defined as positive RT-PCR test or positive Elecsys result at Day 1. Negative is defined as negative RT-PCR test and negative Elecsys result at Day 1.

Source: Study P204 Table 14.1.3.2

The CHMP considered that the demographics and baseline characteristics were balanced between the two dose groups in Part 1 and between the mRNA-1273 and the placebo group in Part 2. Part 1 and Part 2 were also comparable with regards to Demographics and baseline characteristics. The majority of participants in both parts of the study were SARS-CoV-2 seronegative at baseline (86.4% in Part 1 and 89.2% in Part 2).

Safety analysis set

All safety analyses in Part 1 and Part 2 of the study are based on the Safety Set, except summaries of solicited ARs, which are based on the Solicited Safety Set. The safety set consists of all enrolled participants (in Part 1) and all randomly assigned participants (in Part 2) who receive at least 1 dose of IP. The Solicited Safety Set consists of participants in the Safety Set who contributed any solicited AR data. Beside the Solicited Safety Set there are two more Solicited Safety Sets. The first Injection Solicited Safety Set comprises of all participants in the Solicited Safety Set who have received the first study injection and have contributed any solicited AR data from the time of first study injection through the following 6 days. The Second Injection Solicited Safety Set includes all participants in the Solicited Safety Set who have received the second study injection and have contributed any solicited AR data from the time of second study injection through the following 6 days.

Adverse events

The P204 paediatric study evaluates the collection of solicited local and systemic adverse reactions (ARs) for 7 days following each and any dose. All unsolicited adverse events (AEs) were to be collected for 28 days following each injection and serious adverse events (SAEs), medically attended AEs (MAAEs), AEs of special interest (AESIs), and AEs leading to withdrawals are collected for the study duration. At each injection visit, participants' parent(s) were to be instructed on thermometer (oral/tympanic) usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and assessment for localised axillary swelling or tenderness on the same side as the injection arm/thigh. AEs were to be recorded by the participants' parent(s) via eDiary. The eDiary was adapted for use in paediatric populations from the eDiary used in the Study P301 submission for adults ≥ 18 years of age. Severity assessment of solicited ARs was to be performed according to Guidance for industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) modified for use in children 37 months to < 12 years of age. The determination of severity for all unsolicited AEs was to be performed upon medical judgment based on pre-defined severity definitions in the CTP. Per protocol, all solicited ARs (local and systemic) were to be considered vaccine related. For unsolicited AEs causality assessment was to be performed by the investigator according to classification pre-defined in the CTP.

Solicited adverse reactions

Solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness. Solicited systemic ARs assessed included fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting. Toxicity grades for injection site erythema (redness) or swelling (hardness) are defined as: grade 1: 25-50 mm, grade 2; 51-100 mm, grade 3: >100 mm, and grade 4: necrosis or exfoliative dermatitis. Toxicity grades for injection site pain and for axillary (or groin) swelling or tenderness is defined as: grade 1: no interference with activity, grade 2: some interference with activity, grade 3: prevents daily activity, and grade 4: emergency room visit or hospitalisation. Toxicity grades for fever are defined as: grade 1: 38.0-38.4°C, grade 2: 38.5-38.9°C, grade 3: 39.0-40.0°C, and grade 4: >40.0°C. Toxicity grades for other solicited systemic ARs are defined as: grade 1: no interference with activity (or, for nausea/vomiting: 1-2 episodes/24 hours), grade 2: some interference with activity (or, for nausea/vomiting: >2 episodes/24 hours), grade 3: prevents daily activity, and grade 4: emergency room visit or hospitalisation. Any solicited AR that meets either of the following criteria was also included in the analysis of unsolicited AEs: 1) solicited local or systemic AR lasting beyond 7 days post-injection 2) solicited local or systemic AR meeting SAE criteria. These events appear in both solicited AR and unsolicited AE tables.

Very minor changes in the incidence of solicited ARs were noted for part 1 and part 2 in the 2nd analysis with cut-off date 10th November 2021. Upon request, the MAH confirmed, that the root cause for these changes is that additional subjects having completed ≥ 7 days since second injection, which is the period for collection of SARs via eDiary in Part 2:

- 6th October 2021 Data snapshot: n (%): 2958 (98.4) mRNA-1273; and 962 (96.7) Placebo (Source: Study P204 Table 14.1.5.2)
- 10th November 2021 Interim Analysis: n (%): 2990 (99.4) mRNA-1273; and 971 (97.6) Placebo (Source: Study P204 Table 14.1.5.2)

Moreover, with the on-going nature of the study additional queries were closed, and further activities regarding data cleaning were conducted, which may contribute. The minor changes in the incidence of solicited ARs do not impact the benefit-risk balance of Spikevax.

The CHMP considered that the procedures implemented in the CTP are adequate for the collection and evaluation of the safety and reactogenicity profile of the vaccine the in the target population (i.e. the paediatric population from 6 to below 12 years of age.

Solicited local ARs

Part 1

The study began with dosing participants in the 6 years to < 12-year age group in Part 1 with 50 µg of mRNA-1273. After at least 75 participants had completed Day 8 (1 week after dose 1 of mRNA-1273 50 µg), an internal safety team reviewed the available safety data and agreed with the pre-specified protocol plans to proceed with the 100 µg arm in Part 1 in the 6 years to < 12-year age group.

In summary, the review of the reactogenicity profile of the 50 µg dose was comparable to what had been observed in young adults 18 to 25 years of age who had received 100 µg in Study P301. The 100 µg dose was more reactogenic in 6 years to < 12-year-old participants than in the older populations as evidenced by an increased fever rate.

Solicited local ARs occurred in a lower incidence in the 50 µg dose group compared with the 100 µg dose group after each dose. The incidence of solicited local ARs in both dose groups was, as previously observed in other mRNA-1273 clinical trials higher post-dose 2 compared with post-dose 1. The difference in reactogenicity post-each dose was less pronounced for pain in both dose groups than for the other solicited local ARs. The incidence of local solicited ARs after each dose is presented in Table27. The incidence of any solicited local AR after any dose was slightly lower in the 50 µg dose group (97.4% of subjects) compared with the 100 µg dose group (98.1%). The most often reported solicited local AR in both dose groups after any dose was pain reported by 96.8% of subjects in the 50 µg and by 97.6% in the 100 µg dose group. This was followed by erythema (26.1% versus 37.2%), swelling (25.0% versus 32.6%), and axillary (or groin) swelling or tenderness (18.9% versus 25.9%). The majority of solicited local ARs was reported as mild to moderate in both groups. Again, the incidence of severe ARs was higher in the 100 µg group compared with the 50 µg group. The most frequently reported grade 3 local solicited AR after any dose in both groups was pain, reported by 2.6% of subjects in the 50 µg and by 6.2% in the 100 µg dose group. Grade 3 erythema was reported by 1.1% versus 4.3% of subjects, and grade 3 swelling by 0.8% versus 1.9%. No grade 3 axillary (or groin) swelling or tenderness was reported in the 50 µg group, but by 2 subjects in the 100 µg group. No grade 4 solicited local ARs reported in the 50 µg and the 100 µg dose group. The incidence of solicited local ARs after any injection is provided in Table 28. Solicited local ARs in participants in both dose groups had after any dose a median onset of 1 day and generally persisted for a median of 3 days after any injection in both groups. Any solicited local AR persisting beyond 7 days after any injection was reported by 5.3% of subjects in the 50 µg and by 4.3% in the 100 µg dose group. The most frequently reported solicited local AR persisting beyond 7 days after any injection was erythema (2.6% of subjects), followed by axillary (or groin) swelling or tenderness (2.4% of subjects, respectively). In the 50 µg group, the most common solicited local ARs persisting beyond 7 days after dose 1 include erythema (2.4%) and axillary (or groin) swelling or tenderness (2.1%). Solicited local ARs persisting beyond 7 days after dose 2 included injection site pain (1.1% of participants), erythema (0.3%), injection site swelling (0.5%), and axillary (or groin) swelling or tenderness (0.5%). Late onset solicited local ARs starting after day 7 post-dose 1 were reported by 3.9% of participants in the 50 µg dose group and by 2.7% in the 100 µg dose group. The ARs reported in the 50 µg dose were injection site erythema in 3.9% and injection site swelling in 0.5% of participants. The ARs reported after dose 1 in the 100 µg dose were injection site erythema in 2.7% and injection site swelling in 0.8% of participants, respectively. No late onset local solicited ARs were reported after dose 2.

Table 27: Summary of Local Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set), source: Table 23 Clinical overview

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	**mRNA-1273 100 µg (N=369) n (%)**	**mRNA-1273 50 µg (N=379) n (%)**	**mRNA-1273 100 µg (N=371) n (%)**
Solicited local adverse reactions – N1	378	369	379	371
Any solicited local adverse reactions	339 (89.7)	347 (94.0)	355 (93.7)	348 (93.8)
95% CI	86.2, 92.6	91.1, 96.2	90.7, 95.9	90.8, 96.0
Grade 1	237 (62.7)	176 (47.7)	201 (53.0)	157 (42.3)
Grade 2	98 (25.9)	159 (43.1)	144 (38.0)	161 (43.4)
Grade 3	4 (1.1)	12 (3.3)	10 (2.6)	30 (8.1)
Grade 4	0	0	0	0
Grade 3 or above	4 (1.1)	12 (3.3)	10 (2.6)	30 (8.1)
Pain – N1	378	369	379	371
Any	336 (88.9)	341 (92.4)	350 (92.3)	346 (93.3)
Grade 1	252 (66.7)	193 (52.3)	233 (61.5)	197 (53.1)
Grade 2	82 (21.7)	138 (37.4)	109 (28.8)	135 (36.4)
Grade 3	2 (0.5)	10 (2.7)	8 (2.1)	14 (3.8)
Grade 4	0	0	0	0
Grade 3 or above	2 (0.5)	10 (2.7)	8 (2.1)	14 (3.8)
Erythema (redness) – N1	378	369	379	371
Any	44 (11.6)	66 (17.9)	81 (21.4)	108 (29.1)
Grade 1	29 (7.7)	35 (9.5)	36 (9.5)	34 (9.2)
Grade 2	13 (3.4)	31 (8.4)	43 (11.3)	58 (15.6)
Grade 3	2 (0.5)	0	2 (0.5)	16 (4.3)
Grade 4	0	0	0	0
Grade 3 or above	2 (0.5)	0	2 (0.5)	16 (4.3)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	mRNA-1273 100 µg (N=369) n (%)	mRNA-1273 50 µg (N=379) n (%)	mRNA-1273 100 µg (N=371) n (%)
Swelling (hardness) – N1	378	369	379	371
Any	40 (10.6)	57 (15.4)	81 (21.4)	92 (24.8)
Grade 1	28 (7.4)	34 (9.2)	50 (13.2)	50 (13.5)
Grade 2	10 (2.6)	21 (5.7)	30 (7.9)	36 (9.7)
Grade 3	2 (0.5)	2 (0.5)	1 (0.3)	6 (1.6)
Grade 4	0	0	0	0
Grade 3 or above	2 (0.5)	2 (0.5)	1 (0.3)	6 (1.6)
Axillary (or groin) swelling or tenderness – N1	378	369	379	371
Any	41 (10.8)	54 (14.6)	46 (12.1)	63 (17.0)
Grade 1	34 (9.0)	43 (11.7)	40 (10.6)	46 (12.4)
Grade 2	7 (1.9)	10 (2.7)	6 (1.6)	16 (4.3)
Grade 3	0	1 (0.3)	0	1 (0.3)
Grade 4	0	0	0	0
Grade 3 or above	0	1 (0.3)	0	1 (0.3)

Abbreviations: CI=confidence interval; N1=number of participants who submitted any data for the event; Any=grade 1 or higher.

Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). 95% CI is calculated using the Clopper-Pearson method. Pain is injection site pain. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: grade 1=25-50 mm; grade 2=51-100 mm; grade 3=>100 mm; grade 4=necrosis or exfoliative dermatitis. Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: grade 1=no interference with activity; grade 2=some interference with activity; grade 3=prevents daily activity; grade 4=emergency room visit or hospitalization.

Source: Study P204 Table 14.3.1.1.1.1 and Table 14.3.1.1.2.1

Table 29: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Grade, Age Group and Dose Level in Part 1 Solicited Safety Set, source: Table 14.3.1.1.3.1

Age Group: >=6 and <12 Years

Solicited Adverse Reaction Category Grade	mRNA-1273 50 µg (N=380) n (%)	 100 µg (N=371) n (%)	 Total (N=751) n (%)
Solicited Adverse Reactions - N1	380	371	751
Any Solicited Adverse Reactions	374 (98.4)	367 (98.9)	741 (98.7)
95% CI	96.6, 99.4	97.3, 99.7	97.6, 99.4
Grade 1	118 (31.1)	69 (18.6)	187 (24.9)
Grade 2	200 (52.6)	194 (52.3)	394 (52.5)
Grade 3	56 (14.7)	102 (27.5)	158 (21.0)
Grade 4	0	2 (0.5)	2 (0.3)
Grade 3 or Above	56 (14.7)	104 (28.0)	160 (21.3)
Solicited Local Adverse Reactions - N1	380	371	751
Any Solicited Local Adverse Reactions	370 (97.4)	364 (98.1)	734 (97.7)
95% CI	95.2, 98.7	96.2, 99.2	96.4, 98.7
Grade 1	180 (47.4)	116 (31.3)	296 (39.4)
Grade 2	176 (46.3)	209 (56.3)	385 (51.3)
Grade 3	14 (3.7)	39 (10.5)	53 (7.1)
Grade 4	0	0	0
Grade 3 or Above	14 (3.7)	39 (10.5)	53 (7.1)
Pain - N1	380	371	751
Any	368 (96.8)	362 (97.6)	730 (97.2)
Grade 1	213 (56.1)	155 (41.8)	368 (49.0)
Grade 2	145 (38.2)	184 (49.6)	329 (43.8)
Grade 3	10 (2.6)	23 (6.2)	33 (4.4)
Grade 4	0	0	0
Grade 3 or Above	10 (2.6)	23 (6.2)	33 (4.4)
Erythema (Redness) - N1	380	371	751
Any	99 (26.1)	138 (37.2)	237 (31.6)
Grade 1	48 (12.6)	49 (13.2)	97 (12.9)
Grade 2	47 (12.4)	73 (19.7)	120 (16.0)
Grade 3	4 (1.1)	16 (4.3)	20 (2.7)
Grade 4	0	0	0
Grade 3 or Above	4 (1.1)	16 (4.3)	20 (2.7)
Swelling (Hardness) - N1	380	371	751
Any	95 (25.0)	121 (32.6)	216 (28.8)
Grade 1	58 (15.3)	66 (17.8)	124 (16.5)
Grade 2	34 (8.9)	48 (12.9)	82 (10.9)
Grade 3	3 (0.8)	7 (1.9)	10 (1.3)
Grade 4	0	0	0
Grade 3 or Above	3 (0.8)	7 (1.9)	10 (1.3)
Axillary (or Groin) Swelling or Tenderness - N1	380	371	751
Any	72 (18.9)	96 (25.9)	168 (22.4)
Grade 1	62 (16.3)	73 (19.7)	135 (18.0)
Grade 2	10 (2.6)	21 (5.7)	31 (4.1)
Grade 3	0	2 (0.5)	2 (0.3)
Grade 4	0	0	0
Grade 3 or Above	0	2 (0.5)	2 (0.3)

Solicited systemic ARs

Part 1

Solicited systemic ARs occurred with a lower incidence in the 50 µg dose group compared to the 100 µg dose group after each dose. The incidence of systemic ARs in both dose groups was higher post-dose 2 compared with post-dose 1. The difference in reactogenicity post- each dose was more pronounced for systemic ARs compared with local ARs. This is in line to what has been observed in previous Spikevax clinical trials. The incidence of systemic solicited ARs after each dose is presented in Table 30. The incidence of any solicited systemic AR after any dose was slightly lower in the 50 µg dose group (82.6% of subjects) compared with the 100 µg dose group (89.5%). The most often reported solicited systemic AR in the 50 µg dose group after any dose was fatigue reported by 68.9% of subjects in the 50 µg and by 74.7% in the 100 µg dose group. This was followed by headache (60.0% versus 68.5%), myalgia (28.7%

versus 38.8%), nausea (26.3% versus 32.6%), chills (25.8% versus 39.9%), fever (23.4% versus 31.8%), and arthralgia (16.1% versus 24.5%). The majority of solicited systemic ARs was reported as mild to moderate in both groups. Again, the incidence of severe ARs was higher in the 100 µg group compared with the 50 µg group. The most frequently reported grade 3 systemic solicited AR after any dose in the 50 µg dose group was fatigue, reported by 7.9% of subjects in the 50 µg and by 12.4% in the 100 µg dose group. Grade 3 headache was reported by 3.7% versus 6.7% of subjects, and grade 3 fever by 2.9% versus 5.7% of subjects. Grade 3 myalgia was reported by 1.8% versus 5.1% of subjects. Other grade 3 solicited systemic ARs were reported by not more than 0.5% of subjects in the 50 µg dose group. No grade 4 solicited systemic ARs were reported in the 50 µg dose group, but by 2 subjects in the 100 µg group (both reported grade 4 fever). The incidence of solicited systemic ARs after any dose is provided in Table 31. Solicited systemic ARs in participants in both dose groups had after any dose a median onset of 1 day and generally persisted for a median of 2 days after any injection in both groups. The incidence of any solicited systemic AR persisting beyond 7 days after any injection was 3.2% each in the 50 µg and the 100 µg dose group. The most often reported systemic solicited ARs persisting beyond day 7 in the 50 µg group were fatigue (reported by 1.8% of subjects), headache (1.3%), and nausea (1.1%). For all other solicited systemic ARs only 0.3% of subjects reported persisting events. Late onset solicited systemic ARs starting after day 7 post-dose 1 were not reported in the 50 µg dose group after dose 1. Only 1 subject reported persisting fever after dose 2.

Table 30: Summary of Solicited Systemic Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set), source: table 25, Clinical overview

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=378) n (%)	mRNA-1273 100 µg (N=369) n (%)	mRNA-1273 50 µg (N=379) n (%)	mRNA-1273 100 µg (N=371) n (%)
Solicited systemic adverse reactions – N1	378	369	379	371

95% CI	49.6, 59.9	55.2, 65.5	70.3, 79.2	80.3, 87.9
Grade 1	135 (35.7)	120 (32.5)	112 (29.6)	111 (29.9)
Grade 2	64 (16.9)	86 (23.3)	136 (35.9)	136 (36.7)
Grade 3	8 (2.1)	17 (4.6)	36 (9.5)	64 (17.3)
Grade 4	0	0	0	2 (0.5)
Grade 3 or above	8 (2.1)	17 (4.6)	36 (9.5)	66 (17.8)
Fever – N1	378	369	379	371
Any	11 (2.9)	24 (6.5)	78 (20.6)	110 (29.6)
Grade 1	6 (1.6)	15 (4.1)	39 (10.3)	50 (13.5)
Grade 2	4 (1.1)	7 (1.9)	29 (7.7)	39 (10.5)
Grade 3	1 (0.3)	2 (0.5)	10 (2.6)	19 (5.1)
Grade 4	0	0	0	2 (0.5)
Grade 3 or above	1 (0.3)	2 (0.5)	10 (2.6)	21 (5.7)
Headache – N1	378	369	379	371
Any	109 (28.8)	129 (35.0)	188 (49.6)	226 (60.9)
Grade 1	72 (19.0)	81 (22.0)	87 (23.0)	113 (30.5)
Grade 2	33 (8.7)	42 (11.4)	91 (24.0)	94 (25.3)
Grade 3	4 (1.1)	6 (1.6)	10 (2.6)	19 (5.1)
Grade 4	0	0	0	0
Grade 3 or above	4 (1.1)	6 (1.6)	10 (2.6)	19 (5.1)
Fatigue – N1	378	369	379	371
Any	154 (40.7)	167 (45.3)	216 (57.0)	236 (63.6)
Grade 1	102 (27.0)	97 (26.3)	93 (24.5)	93 (25.1)
Grade 2	48 (12.7)	60 (16.3)	97 (25.6)	107 (28.8)
Grade 3	4 (1.1)	10 (2.7)	26 (6.9)	36 (9.7)
Grade 4	0	0	0	0
Grade 3 or above	4 (1.1)	10 (2.7)	26 (6.9)	36 (9.7)
Myalgia – N1	378	369	379	371
Any	40 (10.6)	58 (15.7)	89 (23.5)	112 (30.2)
Grade 1	27 (7.1)	34 (9.2)	53 (14.0)	47 (12.7)
Grade 2	13 (3.4)	18 (4.9)	29 (7.7)	52 (14.0)
Grade 3	0	6 (1.6)	7 (1.8)	13 (3.5)
Grade 4	0	0	0	0
Grade 3 or above	0	6 (1.6)	7 (1.8)	13 (3.5)
Arthralgia – N1	378	369	379	371
Any	27 (7.1)	39 (10.6)	43 (11.3)	68 (18.3)

Table 31: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Grade, Age Group and Dose Level in Part 1 Solicited Safety Set, source: Table 14.3.1.1.3.1

Age Group: >=6 and <12 Years

Solicited Adverse Reaction Category Grade	mRNA-1273 50 µg (N=380) n (%)	mRNA-1273 100 µg (N=371) n (%)	Total (N=751) n (%)
Solicited Systemic Adverse Reactions - N1	380	371	751
Any Solicited Systemic Adverse Reactions	314 (82.6)	332 (89.5)	646 (86.0)
95% CI	78.4, 86.3	85.9, 92.4	83.3, 88.4
Grade 1	115 (30.3)	100 (27.0)	215 (28.6)
Grade 2	155 (40.8)	152 (41.0)	307 (40.9)
Grade 3	44 (11.6)	78 (21.0)	122 (16.2)
Grade 4	0	2 (0.5)	2 (0.3)
Grade 3 or Above	44 (11.6)	80 (21.6)	124 (16.5)
Fever - N1	380	371	751
Any	89 (23.4)	118 (31.8)	207 (27.6)
Grade 1	45 (11.8)	51 (13.7)	96 (12.8)
Grade 2	33 (8.7)	44 (11.9)	77 (10.3)
Grade 3	11 (2.9)	21 (5.7)	32 (4.3)
Grade 4	0	2 (0.5)	2 (0.3)
Grade 3 or Above	11 (2.9)	23 (6.2)	34 (4.5)
Headache - N1	380	371	751
Any	228 (60.0)	254 (68.5)	482 (64.2)
Grade 1	109 (28.7)	118 (31.8)	227 (30.2)
Grade 2	105 (27.6)	111 (29.9)	216 (28.8)
Grade 3	14 (3.7)	25 (6.7)	39 (5.2)
Grade 4	0	0	0
Grade 3 or Above	14 (3.7)	25 (6.7)	39 (5.2)
Fatigue - N1	380	371	751
Any	262 (68.9)	277 (74.7)	539 (71.8)
Grade 1	114 (30.0)	109 (29.4)	223 (29.7)
Grade 2	118 (31.1)	122 (32.9)	240 (32.0)
Grade 3	30 (7.9)	46 (12.4)	76 (10.1)
Grade 4	0	0	0
Grade 3 or Above	30 (7.9)	46 (12.4)	76 (10.1)
Myalgia - N1	380	371	751
Any	109 (28.7)	144 (38.8)	253 (33.7)
Grade 1	65 (17.1)	63 (17.0)	128 (17.0)
Grade 2	37 (9.7)	62 (16.7)	99 (13.2)
Grade 3	7 (1.8)	19 (5.1)	26 (3.5)
Grade 4	0	0	0
Grade 3 or Above	7 (1.8)	19 (5.1)	26 (3.5)
Arthralgia - N1	380	371	751
Any	61 (16.1)	91 (24.5)	152 (20.2)
Grade 1	41 (10.8)	55 (14.8)	96 (12.8)
Grade 2	18 (4.7)	28 (7.5)	46 (6.1)
Grade 3	2 (0.5)	8 (2.2)	10 (1.3)
Grade 4	0	0	0
Grade 3 or Above	2 (0.5)	8 (2.2)	10 (1.3)
Nausea/Vomiting - N1	380	371	751
Any	100 (26.3)	121 (32.6)	221 (29.4)
Grade 1	77 (20.3)	93 (25.1)	170 (22.6)
Grade 2	21 (5.5)	24 (6.5)	45 (6.0)
Grade 3	2 (0.5)	4 (1.1)	6 (0.8)
Grade 4	0	0	0
Grade 3 or Above	2 (0.5)	4 (1.1)	6 (0.8)
Chills - N1	380	371	751
Any	98 (25.8)	148 (39.9)	246 (32.8)
Grade 1	52 (13.7)	74 (19.9)	126 (16.8)
Grade 2	45 (11.8)	71 (19.1)	116 (15.4)
Grade 3	1 (0.3)	3 (0.8)	4 (0.5)
Grade 4	0	0	0
Grade 3 or Above	1 (0.3)	3 (0.8)	4 (0.5)

Part 2

Solicited local ARs

Solicited local ARs occurred in a higher incidence in the mRNA-1273 group compared with the placebo group, as it can be expected. The incidence of solicited local ARs in the mRNA-1273 group was, as previously observed in Part 1 and in other mRNA-1273 clinical trials higher post-dose 2 compared with

post-dose 1. The incidence of local solicited ARs after each dose is presented in Table 31. The incidence of any solicited local AR after any dose was reported by 98.6% of subjects in the mRNA-1273 group and by 65.2% in the placebo group. The most often reported solicited local AR in the mRNA-1273 group after any dose was pain reported by 98.4% of subjects in the mRNA-1273 versus 64.1% in the placebo group. This was followed by axillary (or groin) swelling or tenderness (26.9% versus 12.6%), erythema (24.3.0% versus 2.0%), and injection site swelling (22.5% versus 2.0%). The majority of solicited local ARs was reported as mild to moderate in both groups. Again, the incidence of severe ARs was higher in the mRNA-1273 compared with the placebo group. The most frequently reported grade 3 local solicited AR after any dose in the mRNA-1273 group was pain, reported by 3.3% of subjects. Grade 3 erythema was reported by 1.6%, and grade 3 injection site swelling by 1.3% of subjects. Grade 3 axillary (or groin) swelling or tenderness was reported for only 0.2% of subjects. No grade 4 solicited local ARs was reported in the mRNA-1273 vaccine group. The incidence of solicited local ARs after any is provided in Table 32. The majority of the solicited local ARs in the mRNA-1273 group in Part 2 occurred within Day 1 (94.8%) to day 2 (3.6%) after any dose and persisted for a median of 3 days. Any solicited local AR persisting beyond 7 days after any injection was reported by 4.6% of subjects in the vaccine and by 2.4% of subjects in the placebo group. The most frequently reported solicited local AR persisting beyond 7 days after any injection in the mRNA-1273 group was axillary (or groin) swelling or tenderness reported by 2.2% of subjects, followed by injection site pain and injection site erythema reported by 1.4% of subjects each in the vaccine group. Persisting injection site swelling was reported by 0.9% of subjects in the vaccine group. Late onset solicited local ARs starting after day 7 in the mRNA-1273 group were reported by 2.7% of subjects in the mRNA-1273 vaccine group post-dose 1, but only by < 0.1% of participants (3) post-dose 2. The ARs reported after any dose were injection site swelling (0.7%) participants), injection site pain (0.5%), erythema (2.1%), and axillary (or groin) swelling or tenderness (< 0.1%) of participants.

Table 32: Summary of Solicited Local Adverse Reactions (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set), source: Table 24 Clinical overview

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	Placebo (N=994) n (%)	mRNA-1273 50 µg (N=2986) n (%)	Placebo (N=968) n (%)
Solicited local adverse reactions – N1	3005	994	2986	968
Any solicited local adverse reactions	2818 (93.8)	481 (48.4)	2847 (95.3)	491 (50.7)
95% CI	92.9, 94.6	45.2, 51.5	94.5, 96.1	47.5, 53.9
Grade 1	1934 (64.4)	450 (45.3)	1494 (50.0)	446 (46.1)
Grade 2	830 (27.6)	28 (2.8)	1232 (41.3)	40 (4.1)
Grade 3	54 (1.8)	3 (0.3)	121 (4.1)	5 (0.5)
Grade 4	0	0	0	0
Grade 3 or above	54 (1.8)	3 (0.3)	121 (4.1)	5 (0.5)
Pain – N1	3005	994	2986	968
Any	2798 (93.1)	994	2830 (94.8)	481 (49.7)
Grade 1	2022 (67.3)	466 (46.9)	1695 (56.8)	446 (46.1)
Grade 2	748 (24.9)	441 (44.4)	1055 (35.3)	33 (3.4)
Grade 3	28 (0.9)	25 (2.5)	80 (2.7)	2 (0.2)
Grade 4	0	0	0	0
Grade 3 or above	28 (0.9)	0	80 (2.7)	2 (0.2)
Erythema (redness) – N1	3005	994	2986	968
Any	359 (11.9)	12 (1.2)	561 (18.8)	11 (1.1)
Grade 1	242 (8.1)	9 (0.9)	267 (8.9)	7 (0.7)
Grade 2	101 (3.4)	2 (0.2)	261 (8.7)	3 (0.3)
Grade 3	16 (0.5)	1 (0.1)	33 (1.1)	1 (0.1)
Grade 4	0	0	0	0
Grade 3 or above	16 (0.5)	1 (0.1)	33 (1.1)	1 (0.1)
Swelling (hardness) – N1	3005	994	2986	968
Any	362 (12.0)	11 (1.1)	510 (17.1)	12 (1.2)
Grade 1	261 (8.7)	9 (0.9)	316 (10.6)	12 (1.2)
Grade 2	82 (2.7)	1 (0.1)	174 (5.8)	0
Grade 3	19 (0.6)	1 (0.1)	20 (0.7)	0
Grade 4	0	0	0	0
Grade 3 or above	19 (0.6)	1 (0.1)	20 (0.7)	0
Axillary (or groin) swelling or tenderness – N1	3005	994	2986	968
Any	467 (15.5)	85 (8.6)	536 (18.0)	65 (6.7)
Grade 1	401 (13.3)	82 (8.2)	409 (13.7)	55 (5.7)
Grade 2	63 (2.1)	2 (0.2)	124 (4.2)	8 (0.8)

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	Placebo (N=994) n (%)	mRNA-1273 50 µg (N=2986) n (%)	Placebo (N=968) n (%)
Grade 3	3 (<0.1)	1 (0.1)	3 (0.1)	2 (0.2)
Grade 4	0	0	0	0
Grade 3 or above	3 (<0.1)	1 (0.1)	3 (0.1)	2 (0.2)

Abbreviations: CI=confidence interval; N1=number of participants who submitted any data for the event; Any=grade 1 or higher.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). 95% CI is calculated using the Clopper-Pearson method. Pain is injection site pain. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: grade 1=25-50 mm; grade 2=51-100 mm; grade 3=>100 mm; grade 4=necrosis or exfoliative dermatitis. Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: grade 1=no interference with activity; grade 2=some interference with activity; grade 3=prevents daily activity; grade 4=emergency room visit or hospitalization.
Sources: Table 14.3.1.1.1.2.1 and Table 14.1.1.2.2.1

Table 33: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade, Solicited Safety Set, source: table 14.3.1.1.3.2.1

	Part 2			Part 1 + Part 2
Solicited Adverse Reaction Category Grade	Placebo (N=995) n (%)	mRNA-1273 50 µg (N=3007) n (%)	Total (N=4002) n (%)	mRNA-1273 50 µg (N=3387) n (%)
Solicited Adverse Reactions - N1	995	3007	4002	3387
Any Solicited Adverse Reactions	824 (82.8)	2985 (99.3)	3809 (95.2)	3359 (99.2)
95% CI	80.3, 85.1	98.9, 99.5	94.5, 95.8	98.8, 99.4
Grade 1	522 (52.5)	788 (26.2)	1310 (32.7)	906 (26.7)
Grade 2	269 (27.0)	1688 (56.1)	1957 (48.9)	1888 (55.7)
Grade 3	32 (3.2)	509 (16.9)	541 (13.5)	565 (16.7)
Grade 4	1 (0.1)	0	1 (<0.1)	0
Grade 3 or Above	33 (3.3)	509 (16.9)	542 (13.5)	565 (16.7)
Solicited Local Adverse Reactions - N1	995	3007	4002	3387
Any Solicited Local Adverse Reactions	649 (65.2)	2964 (98.6)	3613 (90.3)	3334 (98.4)
95% CI	62.2, 68.2	98.1, 99.0	89.3, 91.2	98.0, 98.8
Grade 1	581 (58.4)	1334 (44.4)	1915 (47.9)	1514 (44.7)
Grade 2	60 (6.0)	1464 (48.7)	1524 (38.1)	1640 (48.4)
Grade 3	8 (0.8)	166 (5.5)	174 (4.3)	180 (5.3)
Grade 4	0	0	0	0
Grade 3 or Above	8 (0.8)	166 (5.5)	174 (4.3)	180 (5.3)
Pain - N1	995	3007	4002	3387
Any	638 (64.1)	2958 (98.4)	3596 (89.9)	3326 (98.2)
Grade 1	585 (58.8)	1568 (52.1)	2153 (53.8)	1781 (52.6)
Grade 2	51 (5.1)	1290 (42.9)	1341 (33.5)	1435 (42.4)
Grade 3	2 (0.2)	100 (3.3)	102 (2.5)	110 (3.2)
Grade 4	0	0	0	0
Grade 3 or Above	2 (0.2)	100 (3.3)	102 (2.5)	110 (3.2)

Note: Footnotes are listed on the last page.
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Erythema (Redness) - N1	995	3007	4002	3387
Any	20 (2.0)	730 (24.3)	750 (18.7)	829 (24.5)
Grade 1	13 (1.3)	371 (12.3)	384 (9.6)	419 (12.4)
Grade 2	5 (0.5)	310 (10.3)	315 (7.9)	357 (10.5)
Grade 3	2 (0.2)	49 (1.6)	51 (1.3)	53 (1.6)
Grade 4	0	0	0	0
Grade 3 or Above	2 (0.2)	49 (1.6)	51 (1.3)	53 (1.6)
Swelling (Hardness) - N1	995	3007	4002	3387
Any	20 (2.0)	677 (22.5)	697 (17.4)	772 (22.8)
Grade 1	18 (1.8)	412 (13.7)	430 (10.7)	470 (13.9)
Grade 2	1 (0.1)	226 (7.5)	227 (5.7)	260 (7.7)
Grade 3	1 (0.1)	39 (1.3)	40 (1.0)	42 (1.2)
Grade 4	0	0	0	0
Grade 3 or Above	1 (0.1)	39 (1.3)	40 (1.0)	42 (1.2)
Axillary (or Groin) Swelling or Tenderness - N1	995	3007	4002	3387
Any	125 (12.6)	810 (26.9)	935 (23.4)	882 (26.0)
Grade 1	112 (11.3)	627 (20.9)	739 (18.5)	689 (20.3)
Grade 2	10 (1.0)	177 (5.9)	187 (4.7)	187 (5.5)
Grade 3	3 (0.3)	6 (0.2)	9 (0.2)	6 (0.2)
Grade 4	0	0	0	0
Grade 3 or Above	3 (0.3)	6 (0.2)	9 (0.2)	6 (0.2)

Solicited systemic ARs

Solicited systemic ARs also occurred in a higher incidence in the mRNA-1273 group compared with the placebo group. The incidence of solicited systemic ARs in the mRNA-1273 group was again notably higher post-dose 2 compared with post-dose 1. The difference in reactogenicity post- each dose was again more distinct for systemic than for local ARs. The incidence of systemic solicited ARs after each dose is presented in Table 34. The incidence of any solicited systemic AR after any dose was reported by 86.5% of subjects in the mRNA-1273 group and by 67.2% in the placebo group. The most often reported solicited systemic AR in the mRNA-1273 group after any dose was fatigue reported by 73.0% of subjects in the mRNA-1273 versus 47.2% in the placebo group. This was followed by headache (62.0% versus 43.7%), myalgia (35.2% versus 17.3%), chills (34.6% versus 11.8), nausea (29.2% versus 17.8%), fever (25.9% versus 3.6%), and arthralgia (21.2% versus 13.4%). The majority of solicited systemic ARs was reported as mild to moderate in both groups. Again, the incidence of severe ARs was higher in the mRNA-1273 compared with the placebo group. The most frequently reported grade 3 systemic solicited AR after any dose in the mRNA-1273 group was fatigue, reported by 7.1% of subjects. Grade 3 headache was reported by 4.4%, and grade 3 fever by 4.2%. Grade 3 myalgia was reported by 2.7% of subjects. All other solicited systemic ARs were reported by not more than 0.9% of subjects in the mRNA-1273 group after any dose. No grade 4 solicited systemic AR was reported in the mRNA-1273 vaccine group. The incidence of solicited local ARs after any dose is provided in Table 35. The majority of the solicited systemic ARs in participants in the mRNA-1273 group in Part 2 after any dose occurred within day 1 (57.1%) to day 2 (25.9%) and persisted for a median of 2 days. Any solicited systemic AR persisting beyond 7 days after any injection was reported by 4.0% of subjects in the vaccine and by 4.4% of subjects in the placebo group. The most frequently reported solicited systemic AR persisting beyond 7 days after any injection in the mRNA-1273 group was headache reported by 2.2% of subjects, followed by fatigue reported by 1.8% of subjects in the vaccine group. All other persisting solicited systemic ARs were reported by not more than 0.5% of subjects after any dose in the vaccine group. Late onset solicited systemic ARs starting after day 7 in the mRNA-1273 group were reported by only 0.5% of subjects in the mRNA-1273 vaccine group after any dose (by 0.4% of subjects after dose 1 and by 0.1% after dose 2).

Table 34: Summary of Solicited Systemic Adverse Reactions (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set), source: table 26, Clinical overview

	Dose 1		Dose 2	
	mRNA-1273 50 µg (N=3005) n (%)	Placebo (N=994) n (%)	mRNA-1273 50 µg (N=2986) n (%)	Placebo (N=968) n (%)
Solicited systemic adverse reactions – N1	3005	994	2986	968
Any solicited systemic adverse reactions	1743 (58.0)	519 (52.2)	2332 (78.1)	485 (50.1)
95% CI	56.2, 59.8	49.1, 55.4	76.6, 79.6	46.9, 53.3
Grade 1	1104 (36.7)	348 (35.0)	828 (27.7)	323 (33.4)
Grade 2	586 (19.5)	158 (15.9)	1143 (38.3)	148 (15.3)
Grade 3	53 (1.8)	12 (1.2)	361 (12.1)	14 (1.4)
Grade 4	0	1 (0.1)[a]	0	0
Grade 3 or above	53 (1.8)	13 (1.3)	361 (12.1)	14 (1.4)
Fever – N1	3004	994	2986	968
Any	102 (3.4)	15 (1.5)	719 (24.1)	21 (2.2)
Grade 1	57 (1.9)	10 (1.0)	385 (12.9)	14 (1.4)
Grade 2	28 (0.9)	2 (0.2)	222 (7.4)	5 (0.5)
Grade 3	17 (0.6)	2 (0.2)	112 (3.8)	2 (0.2)
Grade 4	0	1 (0.1)[a]	0	0
Grade 3 or above	17 (0.6)	3 (0.3)	112 (3.8)	2 (0.2)
Headache – N1	3002	993	2983	967

Any	938 (31.2)	306 (30.8)	1617 (54.2)	275 (28.4)
Grade 1	672 (22.4)	227 (22.9)	759 (25.4)	187 (19.3)
Grade 2	248 (8.3)	75 (7.6)	740 (24.8)	80 (8.3)
Grade 3	18 (0.6)	4 (0.4)	118 (4.0)	8 (0.8)
Grade 4	0	0	0	0
Grade 3 or above	18 (0.6)	4 (0.4)	118 (4.0)	8 (0.8)
Fatigue – N1	3002	993	2983	967
Any	1299 (43.3)	334 (33.6)	1921 (64.4)	334 (34.5)
Grade 1	853 (28.4)	215 (21.7)	800 (26.8)	226 (23.4)
Grade 2	415 (13.8)	111 (11.2)	932 (31.2)	100 (10.3)
Grade 3	31 (1.0)	8 (0.8)	189 (6.3)	8 (0.8)
Grade 4	0	0	0	0
Grade 3 or above	31 (1.0)	8 (0.8)	189 (6.3)	8 (0.8)
Myalgia – N1	3002	993	2983	967
Any	438 (14.6)	96 (9.7)	841 (28.2)	105 (10.9)
Grade 1	315 (10.5)	73 (7.4)	426 (14.3)	75 (7.8)
Grade 2	112 (3.7)	22 (2.2)	344 (11.5)	29 (3.0)
Grade 3	11 (0.4)	1 (0.1)	71 (2.4)	1 (0.1)
Grade 4	0	0	0	0
Grade 3 or above	11 (0.4)	1 (0.1)	71 (2.4)	1 (0.1)
Arthralgia – N1	3002	993	2983	967
Any	260 (8.7)	75 (7.6)	480 (16.1)	84 (8.7)
Grade 1	213 (7.1)	65 (6.5)	307 (10.3)	71 (7.3)
Grade 2	44 (1.5)	9 (0.9)	148 (5.0)	13 (1.3)
Grade 3	3 (<0.1)	1 (0.1)	25 (0.8)	0
Grade 4	0	0	0	0
Grade 3 or above	3 (<0.1)	1 (0.1)	25 (0.8)	0
Nausea/vomiting – N1	3002	993	2983	967
Any	325 (10.8)	107 (10.8)	713 (23.9)	96 (9.9)
Grade 1	274 (9.1)	93 (9.4)	527 (17.7)	77 (8.0)
Grade 2	46 (1.5)	14 (1.4)	167 (5.6)	19 (2.0)
Grade 3	5 (0.2)	0	19 (0.6)	0
Grade 4	0	0	0	0
Grade 3 or above	5 (0.2)	0	19 (0.6)	0
Chills – N1	3002	993	2983	967
Any	309 (10.3)	67 (6.7)	904 (30.3)	74 (7.7)
Grade 1	242 (8.1)	54 (5.4)	508 (17.0)	61 (6.3)
Grade 2	64 (2.1)	13 (1.3)	377 (12.6)	13 (1.3)

Table 35: Summary of Subjects with Solicited Adverse Reactions Within 7 Days After Any Injection by Age Group and Grade, Solicited Safety Set, source: Table 14.3.1.1.3.2.1

Solicited Adverse Reaction Category Grade	Part 2 Placebo (N=995) n (%)	Part 2 mRNA-1273 50 µg (N=3007) n (%)	Part 2 Total (N=4002) n (%)	Part 1 + Part 2 mRNA-1273 50 µg (N=3387) n (%)
Solicited Systemic Adverse Reactions - N1	995	3007	4002	3387
Any Solicited Systemic Adverse Reactions	669 (67.2)	2602 (86.5)	3271 (81.7)	2916 (86.1)
95% CI	64.2, 70.1	85.3, 87.7	80.5, 82.9	84.9, 87.2
Grade 1	391 (39.3)	889 (29.6)	1280 (32.0)	1004 (29.6)
Grade 2	252 (25.3)	1312 (43.6)	1564 (39.1)	1467 (43.3)
Grade 3	25 (2.5)	401 (13.3)	426 (10.6)	445 (13.1)
Grade 4	1 (0.1)	0	1 (<0.1)	0
Grade 3 or Above	26 (2.6)	401 (13.3)	427 (10.7)	445 (13.1)
Fever - N1	995	3007	4002	3387
Any	36 (3.6)	778 (25.9)	814 (20.3)	867 (25.6)
Grade 1	24 (2.4)	409 (13.6)	433 (10.8)	454 (13.4)
Grade 2	7 (0.7)	242 (8.0)	249 (6.2)	275 (8.1)
Grade 3	4 (0.4)	127 (4.2)	131 (3.3)	138 (4.1)
Grade 4	1 (0.1)	0	1 (<0.1)	0
Grade 3 or Above	5 (0.5)	127 (4.2)	132 (3.3)	138 (4.1)
Headache - N1	994	3004	3998	3384
Any	434 (43.7)	1862 (62.0)	2296 (57.4)	2090 (61.8)
Grade 1	287 (28.9)	880 (29.3)	1167 (29.2)	989 (29.2)
Grade 2	135 (13.6)	849 (28.3)	984 (24.6)	954 (28.2)
Grade 3	12 (1.2)	133 (4.4)	145 (3.6)	147 (4.3)
Grade 4	0	0	0	0
Grade 3 or Above	12 (1.2)	133 (4.4)	145 (3.6)	147 (4.3)
Fatigue - N1	994	3004	3998	3384
Any	469 (47.2)	2194 (73.0)	2663 (66.6)	2456 (72.6)
Grade 1	274 (27.6)	896 (29.8)	1170 (29.3)	1010 (29.8)
Grade 2	180 (18.1)	1084 (36.1)	1264 (31.6)	1202 (35.5)
Grade 3	15 (1.5)	214 (7.1)	229 (5.7)	244 (7.2)
Grade 4	0	0	0	0
Grade 3 or Above	15 (1.5)	214 (7.1)	229 (5.7)	244 (7.2)
Myalgia - N1	994	3004	3998	3384
Any	172 (17.3)	1057 (35.2)	1229 (30.7)	1166 (34.5)
Grade 1	121 (12.2)	561 (18.7)	682 (17.1)	626 (18.5)
Grade 2	49 (4.9)	414 (13.8)	463 (11.6)	451 (13.3)
Grade 3	2 (0.2)	82 (2.7)	84 (2.1)	89 (2.6)
Grade 4	0	0	0	0
Grade 3 or Above	2 (0.2)	82 (2.7)	84 (2.1)	89 (2.6)
Arthralgia - N1	994	3004	3998	3384
Any	133 (13.4)	637 (21.2)	770 (19.3)	698 (20.6)
Grade 1	110 (11.1)	426 (14.2)	536 (13.4)	467 (13.8)
Grade 2	22 (2.2)	183 (6.1)	205 (5.1)	201 (5.9)
Grade 3	1 (0.1)	28 (0.9)	29 (0.7)	30 (0.9)
Grade 4	0	0	0	0
Grade 3 or Above	1 (0.1)	28 (0.9)	29 (0.7)	30 (0.9)
Nausea/Vomiting - N1	994	3004	3998	3384
Any	177 (17.8)	878 (29.2)	1055 (26.4)	978 (28.9)
Grade 1	144 (14.5)	657 (21.9)	801 (20.0)	734 (21.7)
Grade 2	33 (3.3)	197 (6.6)	230 (5.8)	218 (6.4)
Grade 3	0	24 (0.8)	24 (0.6)	26 (0.8)
Grade 4	0	0	0	0
Grade 3 or Above	0	24 (0.8)	24 (0.6)	26 (0.8)
Chills - N1	994	3004	3998	3384
Any	117 (11.8)	1038 (34.6)	1155 (28.9)	1136 (33.6)
Grade 1	94 (9.5)	596 (19.8)	690 (17.3)	648 (19.1)
Grade 2	23 (2.3)	420 (14.0)	443 (11.1)	465 (13.7)
Grade 3	0	22 (0.7)	22 (0.6)	23 (0.7)
Grade 4	0	0	0	0
Grade 3 or Above	0	22 (0.7)	22 (0.6)	23 (0.7)

Update on solicited local and systemic ARs (Cut-off date 10th November 2021)

Very minor changes in the incidence of solicited local and systemic ARs in part 1 and part 2 were noted. As described above, the minor changes are due to data clearance and additional subjects with follow-up on solicited ARs post-dose 2. The changes do not alter the benefit-risk profile of Spikevax.

Use of pain medication

In Part 1, the use of pain and/or fever medication for prevention and for treatment was notably higher in the 100 µg dose group compared with the 50 µg dose group. For both groups the use was notably higher post -dose 2 compared with post-dose 1, which is in line with the higher local and systemic reactogenicity post-dose 2. Post-dose 1 for a total of 24.9% of participants in the 50 µg dose group the use of pain/fever medication, either for prevention or for treatment was reported. In the vast majority of subjects, the medication use was for treatment (24.1%); only 1.3% of subjects in the 50 µg dose group received prophylactic pain/fever medication. In the 100 µg dose group 43.6% of participants reported the use of pain/fever medication, 6.5% for prevention and 42.3% for treatment.

In part 2, as it can be expected the use of pain/fever medication for treatment was notably higher in the mRNA-1273 vaccine group compared with the placebo group (approximately 2.7 fold higher post-dose 1 and approximately 5.7 fold higher post-dose 2). The proportion of participants with prophylactic use was comparable in the two groups post-dose 1 (2.1% in the placebo, and 2.7% in the vaccine group), but approximately 2 fold higher in the vaccine group (5.3%) compared with the placebo group (2.4%) post-dose 2. This appears to be plausible because of the blinded design and the higher reactogenicity in the vaccine group post-dose 1. The use of pain/fever medication for treatment in the placebo group was comparable post-dose 1 (8.7%) and post-dose 2 (8.1%), whereas it was in the vaccine group notably higher post-dose 2 (46.2%) compared with post-dose 1 (23.1%).

The proportion of subjects using pain medication to prevent or to treat pain and fever in the placebo and the mRNA-1273 vaccine group was not meaningful different in the 2nd update analysis. Only minimal changes, possibly due to rounding are noticed.

The proportion of subjects using medication to prevent fever or pain in the placebo group post-dose 1 was 2.1% (21) and 2.4% (23) post-dose 2. The respective proportions in the mRNA-1273 vaccine group were 2.7% (80) and 5.4% (160) post-dose 1 and post-dose 2.

The proportion of subjects using medication to treat fever or pain in the placebo group post-dose 1 was 8.7% (86) and 8.3% (80) post-dose 2. The respective proportions in the mRNA-1273 vaccine group were 23.1% (694) and 46.4% (1385) post-dose 1 and post-dose 2. No updated data were submitted for Part 1. The proportions should not differ meaningfully in the 2nd interim analysis.

Comparison of reactogenicity between Participants 6 to < 12 Years of Age in the 50 µg mRNA-1273 group of Study P204 (N=3387) and 18- to 25-year-old participants in the mRNA-1273 group (100 µg) in Part A of Study P301 (N=878)

Solicited ARs from 6- to < 12-year-old participants in the 50 µg mRNA-1273 group of Study P204 were compared with solicited ARs reported from 18- to 25-year-old participants in the mRNA-1273 group (100 µg) in Part A of Study P301, a population for which efficacy has been demonstrated. Tables comparing rates of local and systemic solicited and unsolicited AEs after were provided. The included results show AEs that occurred after any dose in children 6 to <12 years of age receiving 50 µg mRNA-1273 in study P204 (Part 1 and Part 2 combined, based on 6th October 2021 data snapshot) versus young adults 18 to 25 years of age receiving 100 µg of mRNA-1273 (study P301, based on 04 May 2021 database lock).

The proportion of subjects who reported solicited local ARs within 7 days after any dose of mRNA-1273 tended to be higher for the 50 µg dose group of participants 6 to <12 years of age in trial P204 (98.4%) compared to the 100 µg dose group participants 18-25 years of age in Study P301 (94.1%). The most frequently reported solicited local AR was injection site pain in both groups, reported by 98.2% of subjects in P204 and by 93.5% in P301. This was followed by injection site erythema (24.5% versus 9.5%), and injection site swelling (22.8% of subjects in the younger age cohort, versus 14.0% in the

older age cohort. The proportion of subjects who reported axillary or groin swelling or tenderness was comparable in both age cohorts (26.0% versus 27.9%). In participants in both studies the majority of solicited local ARs were grade 1 or 2. The incidence of grade 3 solicited local ARs was lower in P204 participants (5.5%) compared with P301 participants (11.4%). Overall, the incidence of any systemic solicited AR after any dose was comparable between subjects in P204 (86.1%) and P301 (89.1%). However, the incidence of each pre-defined solicited systemic AR except of fever was lower in subjects 6-<12 years of age compared to subjects 18-25 years of age. The most frequently reported solicited systemic ARs after any dose in both groups were fatigue (reported by 72.6% of subjects 6 to <12 years of age in P204 and by 73.0% of subjects 18-25 years and headache (61.8% versus 73.8%, respectively). This was followed by myalgia (34.5% versus 63.2%), and chills (33.6% versus 53.6%). Fever was reported by 25.6% versus 18.1% of subjects in the younger and the older age cohort, respectively. The majority of solicited systemic ARs after any dose were graded as mild or moderate in both groups. Solicited systemic grade 3 ARs were overall less frequently reported by participants 6-12 years of age in Study P204 (13.1%) compared with Study P301 participants 18-25 years of age (23.5%). The results of solicited ARs are summarised in Table 36 and Table 37 below.

Table 36: Solicited Local Adverse Reactions Occurring within 7 Days after Any Dose by Age Group (6 to <12 and 18 to 25) in Study P204 and P301

Solicited Adverse Reaction Category Grade	mRNA-1273 50 µg Study P204 Part 1 and 2 (Ages 6 to <12 years) (N = 3387) n (%)	mRNA-1273 100 µg Study P301 (Ages 18 to 25 years) (N = 878) n (%)
Solicited Local Adverse Reactions – N1	3387	878
Any Solicited Local Adverse Reactions	3334 (98.4)	826 (94.1)
95% Confidence Interval	98.0, 98.8	92.3, 95.5
Grade 1	1514 (44.7)	416 (47.4)
Grade 2	1640 (48.4)	310 (35.3)
Grade 3	180 (5.3)	100 (11.4)
Grade 4	0	0
Grade 3 or above	180 (5.3)	100 (11.4)
Pain – N1	3387	878
Any	3326 (98.2)	821 (93.5)
Grade 1	1781 (52.6)	452 (51.5)
Grade 2	1435 (42.4)	282 (32.1)
Grade 3	110 (3.2)	87 (9.9)
Grade 4	0	0
Grade 3 or above	110 (3.2)	87 (9.9)
Erythema (Redness) – N1	3387	878
Any	829 (24.5)	83 (9.5)
Grade 1	419 (12.4)	39 (4.4)
Grade 2	357 (10.5)	35 (4.0)
Grade 3	53 (1.6)	9 (1.0)
Grade 4	0	0
Grade 3 or above	53 (1.6)	9 (1.0)
Swelling (Hardness) – N1	3387	878
Any	772 (22.8)	123 (14.0)
Grade 1	470 (13.9)	66 (7.5)

Grade 2	260 (7.7)	45 (5.1)
Grade 3	42 (1.2)	12 (1.4)
Grade 4	0	0
Grade 3 or above	42 (1.2)	12 (1.4)
Axillary (or Groin) Swelling or Tenderness – N1	3387	878
Any	882 (26.0)	245 (27.9)
Grade 1	689 (20.3)	198 (22.6)
Grade 2	187 (5.5)	42 (4.8)
Grade 3	6 (0.2)	5 (0.6)
Grade 4	0	0
Grade 3 or above	6 (0.2)	5 (0.6)

Abbreviations: n/N = number

Note: Pain is injection site pain. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: Grade 1=25-50 mm; Grade 2=51-100 mm; Grade 3=>100mm; Grade 4=necrosis or exfoliative dermatitis. Toxicity grade for injection site pain and for axillary (underarm or groin) swelling or tenderness is defined as: Grade 1=no interference with activity; Grade 2=some interference with activity; Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization.

Source: Study P204 Table 14.3.1.1.3.1.2 and Study P301 Table 14.3.1.1.14.3

Table 37: Solicited Systemic Adverse Reactions Occurring within 7 Days After Any Dose by Age Group (6 to <12 and 18 to 25 Years) in Study P204 and Study P301

Solicited Adverse Reaction Category Grade	mRNA-1273 50 µg Study P204 Part 1 and 2 (Ages 6 to <12 years) (N = 3387) n (%)	mRNA-1273 100 µg Study P301 (Ages 18 to 25 years) (N = 878) n (%)
Solicited Systemic Adverse Reactions – N1	3387	878
Any Solicited Local Adverse Reactions	2916 (86.1)	782 (89.1)
95% Confidence Interval	84.9, 87.2	86.8, 91.1
Grade 1	1004 (29.6)	188 (21.4)
Grade 2	1467 (43.3)	388 (44.2)
Grade 3	445 (13.1)	206 (23.5)
Grade 4	0	0
Grade 3 or above	445 (13.1)	206 (23.5)
Fever – N1	3387	878
Any	867 (25.6)	159 (18.1)
Grade 1	454 (13.4)	90 (10.3)
Grade 2	275 (8.1)	59 (6.7)
Grade 3	138 (4.1)	10 (1.1)
Grade 4	0	0
Grade 3 or above	138 (4.1)	10 (1.1)
Headache – N1	3384	878
Any	2090 (61.8)	648 (73.8)
Grade 1	989 (29.2)	300 (34.2)
Grade 2	954 (28.2)	275 (31.3)
Grade 3	147 (4.3)	73 (8.3)
Grade 4	0	0
Grade 3 or above	147 (4.3)	73 (8.3)
Fatigue – N1	3384	878
Any	2456 (72.6)	641 (73.0)
Grade 1	1010 (29.8)	191 (21.8)
Grade 2	1202 (35.5)	347 (39.5)
Grade 3	244 (7.2)	103 (11.7)
Grade 4	0	0
Grade 3 or above	244 (7.2)	103 (11.7)
Myalgia – N1	3384	878
Any	1166 (34.5)	555 (63.2)
Grade 1	626 (18.5)	184 (21.0)
Grade 2	451 (13.3)	271 (30.9)
Grade 3	89 (2.6)	100 (11.4)
Grade 4	0	0

Grade 3 or above	89 (2.6)	100 (11.4)
Arthralgia – N1	3384	878
Any	698 (20.6)	392 (44.6)
Grade 1	467 (13.8)	146 (16.6)
Grade 2	201 (5.9)	196 (22.3)
Grade 3	30 (0.9)	50 (5.7)
Grade 4	0	0
Grade 3 or above	30 (0.9)	50 (5.7)
Nausea/Vomiting – N1	3384	878
Any	978 (28.9)	290 (33.0)
Grade 1	734 (21.7)	216 (24.6)
Grade 2	218 (6.4)	74 (8.4)
Grade 3	26 (0.8)	0
Grade 4	0	0
Grade 3 or above	26 (0.8)	0
Chills – N1	3384	878
Any	1136 (33.6)	471 (53.6)
Grade 1	648 (19.1)	198 (22.6)
Grade 2	465 (13.7)	262 (29.8)
Grade 3	23 (0.7)	11 (1.3)
Grade 4	0	0
Grade 3 or above	23 (0.7)	11 (1.3)

Abbreviations: n/N = number

Note: Toxicity grade for fever is defined as: Grade 1=38.0-38.4°C; Grade 2=38.5-38.9°C; Grade 3=39.0-40.0°C; Grade 4=>40.0°C. Toxicity grade for other solicited systemic adverse reactions is defined as: Grade 1=no interference with activity (or, for nausea/vomiting: 1-2 episodes/24 hours); Grade 2=some interference with activity (or, for nausea/vomiting: >2 episodes/24 hours); Grade 3=prevents daily activity; Grade 4=emergency room visit or hospitalization.

Source: Study P204 Table 14.3.1.1.3.2.1 and Study P301 Table 14.3.1.1.14.3

Unsolicited AEs in the two age cohorts

The incidence of unsolicited AEs experienced within 28 days after any dose was comparable in children and young adults. Any unsolicited AE during 28 days after vaccination was reported by 24.6% versus 25.9% of participants in the 2 age cohorts, respectively. 10 severe AEs were reported in 9 participants 6-<12 years of age (0.3%). 6 unsolicited grade 3 AEs were considered being vaccine related by the investigators. This included 2 severe AEs of injection site pain, 1 case each of vomiting, urticaria, and 2 cases of fatigue. The grading of the unsolicited AE of oropharyngeal pain mentioned in the clinical overview text is a bit unclear from the documents. Oropharyngeal pain was reported as grade 3 in the clinical overview, but was not included in table 14.3.1.17.2.1 that listed severe unsolicited AEs. In the p204-part2-listings, all but one AE of oropharyngeal pain were graded as mild or moderate and for one AE of oropharyngeal pain no grading and no causality assessment was provided in the listings. A summarising overview comparing and unsolicited AEs in the two age cohorts of children 6 to<12 years of age and young adults 18 to 25 years of age is given in Table 38.

Table 38: Overview of Unsolicited Adverse Events after Any Dose Occurring up to 28 Days After Any Dose by Age Group (6 to <12 and 18 to 25 Years) in Study P204 and Study P301

Unsolicited Adverse Events	mRNA-1273 50 µg Study P204 Part 1 and 2 (Ages 6 to <12 years) (N =3387) n (%)	mRNA-1273 100 µg Study P301 (Ages 18 to 25 years) (N = 878) n (%)
Unsolicited TEAE up to 28 days after any injection	832 (24.6)	227 (25.9)
Severe unsolicited adverse event up to 28 days after any injection	9 (0.3)	9 (1.0)
Related severe unsolicited adverse event	6 (0.2)	3 (0.3)
Medically attended adverse event up to 28 days after any injection	301 (8.9)	85 (9.7)
Related medically attended adverse event	35 (1.0)	15 (1.7)
Serious adverse event up to 28 days after any injection	4 (0.1)	0
Related serious adverse event	0	0
Deaths up to 28 days after any injection	0	0
Adverse event leading to discontinuation of vaccine	3 (<0.1)	3 (0.3)
Adverse event leading to discontinuation of participation in the study	0	0

Abbreviations: n/N = number; TEAE = treatment-emergent adverse event

Note: A treatment-emergent adverse event (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.

Source: Study P204 Table 14.3.1.7.1.2 and Study P301 Table 14.3.1.7.15

Additional comparison of reactogenicity to participants aged ≥ 12 to < 18 Years (n=2,485, Study P301):

The AR of fever (25.9% vs. 13.7%, grade 3: 4.2% vs. 2.2%) was the only event which was clearly more common (after any injection) in younger children (6 to <12 years), compared to adolescents (≥12 to <18 years). In contrast, lower incidences were reported for the ARs of headache (62% vs. 78.4%), myalgia (35.2% vs. 54.3%), arthralgia (21.1% vs. 34.6%), chills (34.6% vs. 49.1%), swelling (22.5% vs. 27.7%), and axillary (or groin) swelling or tenderness (26.9 % vs. 34.6%). The reporting rates were comparable for the following events: fatigue (73% vs. 75.2%), nausea/vomiting (29.2% vs. 29.3%), pain (98.4% vs. 97.2%), erythema (24.3% vs. 25.8%). The data for adolescents were extracted from the EPAR.

Solicited ARs from 6 to < 12-year-old participants in the 50 µg mRNA-1273 group of Study P204 were compared with solicited ARs reported from 18- to 25-year-old participants in the mRNA-1273 group (100 µg) in Part A of Study P301, a population for whom efficacy has been demonstrated. Tables comparing rates of local and systemic solicited and unsolicited AEs were provided. The results show AEs that occurred after any dose in children 6 to <12 years of age receiving 50 µg mRNA-1273 in study P204 (Part 1 and Part 2 combined, based on 6th October 2021 data snapshot) versus young adults 18 to 25 years of age receiving 100 µg of mRNA-1273 (study P301, based on 04 May 2021 database lock). Local reactogenicity appeared to be higher in the younger age cohort 6 to <12 years of age compared with the older age cohort 18-25 years of age. The majority of local ARs however was mild to moderate in both age cohorts and was lower in the younger ones. Grade 3 solicited local ARs were reported by 5.5% of subjects 6-<12 years of age and by 11.4% of subjects 18-25 years of age. In contrast to local reactogenicity, the systemic reactogenicity tended to be lower in the younger age cohort. The incidence of any systemic solicited AR after any dose was comparable between subjects in P204 (86.1%) and P301 (89.1%). However, the incidence of each pre-defined solicited systemic AR except of fever was lower in subjects 6-<12 years of age compared to subjects 18-25 years of age. Also solicited grade 3 systemic ARs were overall less frequently reported by participants 6-<12 years of age in Study P204 (13.1%) compared with Study P301 participants 18-25 years of age (23.5%). The incidence of unsolicited AEs up to 28 days after vaccination, including medically attended AEs, AEs leading to discontinuation from the second dose or the trial, and serious AEs were comparable. In summary, the CHMP considered that no meaningful difference

could be detected with regard to the reactogenicity in the younger paediatric population 6 to <12 years of age and young adults 18 to 25 years of age.

Unsolicited adverse events irrespective of causality Part 1 and Part 2

In both parts of the trial, unsolicited AEs after any dose were collected during the 28 days after each injection.

Part 1

In both parts of the trial, unsolicited AEs after any dose were collected during the 28 days after each injection.

Part 1

As of 6th October 2021, the incidence of unsolicited AEs irrespective of causality was slightly higher in the 50 µg mRNA-1273 vaccine group compared with the 100 µg dose group. Unsolicited AEs irrespective of causality up to 28 days after any dose were reported by 30.5% of subjects in the 50 µg and by 25.9% in the 100 µg dose group. Then incidence of medically attended adverse events (MAAEs) was comparable in the 2 dose groups (11.8% versus 12.7% of subjects in the 50 µg and the 100 µg group, respectively). One participant (in the 50 µg group) was discontinued from the study vaccine due to a TEAE of urticaria papular. The event is described and discussed in the applicable section "*Discontinuation due to adverse events*" of this AR. Serious adverse events in the time window of 28 days after each vaccination were only reported in the 50 µg dose group (by 2 subjects). These SAEs were not considered being vaccine related and included an event of palpitations and an event of foreign body ingestion. The two SAEs are described in the corresponding section "Serious adverse event/deaths/other significant events" below. The most common reported unsolicited AEs, i.e. those reported by more than 1% of subjects in the 50 µg group were injection site erythema (4.5%), upper respiratory infection (3.2%), oropharyngeal pain (3.4%), nasal congestion (2.9%), cough (2.1%), headache (1.6%), nasopharyngitis (1.3%), urinary tract infection (1.3%), rhinorrhoea (1.3%), otitis externa (1.3%), injection site lymphadenopathy (1.3%), fatigue (1.3%), and vomiting (1.1%). No severe unsolicited AEs were reported in the 50 µg dose group and only one severe unsolicited AE (injection site erythema with an onset 8 days post-dose 1) in the 100 µg dose group in part 1 of the trial.

Update 2nd IA 10th November 2021:

Nature and proportion of unsolicited AEs irrespective of causality, recorded within the first interim analyses is not different compared to the 2nd analyses with the cut-off date 10th November 2021. The most common reported unsolicited AEs up to 28 days after any dose were the same as in the 1st analysis, with only minimal changes in the incidence for some of the events (Table 14.3.1.8.1.1. topline-p1). This minimal change does not alter the benefit-risk ratio or the safety profile of Spikevax when given to children 5 to below 12 years of age. The incidence of unsolicited AEs irrespective of causality was like in the first analysis slightly higher in the 50 µg mRNA-1273 vaccine group compared with the 100 µg dose group. Unsolicited AEs irrespective of causality up to 28 days after any dose were reported by 31.3% of subjects in the 50 µg and by 27.0% in the 100 µg dose group. The incidence of medically attended adverse events (MAAEs) was almost identical as compared to the 1st interim analysis, and comparable in the 2 dose groups (11.6% versus 12.7% of subjects in the 50 µg and the 100 µg group, respectively. It should be noted, that since the last data cut (06-Oct-2021), there were no new SAEs reported in the 50 µg group. The previously reported SAE of palpitations in a 7-year old girl in the 50 µg mRNA-1273 vaccine group was subsequently downgraded to non-serious. This event was considered as not being vaccine related. Details are described in the SAE section below.

Part 2

As of 6th October 2021, the incidence of unsolicited AEs irrespective of causality was slightly higher in the mRNA-1273 vaccine group compared with the placebo group. Unsolicited AEs irrespective of causality were reported by 23.8% of subjects in the mRNA-1273 group and by 19.5% in the placebo group up to 28 days post-vaccination. The majority of AEs was due to the SOC of general disorders and administration site conditions. The most frequently unsolicited AEs in the mRNA-1273 group included the PTs injection site erythema (2.8%), upper respiratory tract infection (2.3%), headache (2.3%), oropharyngeal pain (2.0%), cough (1.8%), rhinorrhoea (1.7%), nasal congestion (1.6%), injection site lymphadenopathy (1.4%), injection site pain (1.2%), and fatigue (1.1%). In the placebo group, the most frequently reported unsolicited AEs were oropharyngeal pain (2.2%), nasal congestion (2.2%), COVID-19 (2.1%), upper respiratory tract infection (1.9%), headache (1.8%), rhinorrhoea (1.8%), cough (2.1%), and fatigue (1.2%). The comparison shows that unsolicited AEs experienced in the mRNA-1273 group do not notably differ in nature and incidence to those in the placebo group with the exception of an increase in the incidence of injection site conditions in the mRNA-1273 group. Medically-attended AEs were reported in 8.5% of participants in the mRNA-1273 group and by 10.1% in the placebo group. 2 subjects (<0.1%) were discontinued from vaccination in the mRNA-1273 vaccine group because of an AE. The events leading to discontinuation from vaccination were rash in one subject and urticaria and wheezing in the other subject. The events are discussed in this AR in the respective section ("Discontinuation due to adverse events") below. No participants in the mRNA-1273 group were discontinued from the study as a result of an unsolicited AE. 2 serious unsolicited AEs within 28 days of any dose were reported for 2 (< 0.1%) subjects in the mRNA-1273 group (appendicitis and cellulitis orbital. The two SAEs were not considered being vaccine related and are discussed in the serious adverse event section of this AR. According to table 14.3.1.17.2.1 a total of 10 severe TEAEs were reported in 9 (0.3%) participants in the mRNA-1273 vaccine group in part 2 of the trial. The unsolicited severe AEs included fatigue (2 events in 2 subjects), injection site pain (2 AEs in 2 subjects), cellulitis orbital, nasal congestion and rhinorrhoea (in 1 subject), oropharyngeal pain, vomiting, urticaria, and foot fracture. According to the P204-part2-listings overall 6 severe unsolicited AEs were considered being vaccine related. This includes 2 severe AEs of injection site pain, 2 cases of fatigue, and one case each of vomiting and urticaria were considered being vaccine related by the investigator.

Update 2nd IA 10th November 2021:

Like for Part 1, a minimal change in the incidence of AEs is noted for unsolicited AEs irrespective of causality in the 2nd interim analysis for Part 2. The difference does not alter the safety profile or the risk/ benefit of mRNA-1273 when given to the paediatric population 6-11 years of age. The incidence of unsolicited AEs up to 28 days after any dose irrespective of causality was in both groups higher than in analysis 1. The increase was comparable in both groups (approximately 6% in each group). The incidence of unsolicited AES irrespective of causality was like in analysis 1 slightly higher in the mRNA-1273 vaccine group compared with the placebo group. Unsolicited AEs irrespective of causality were reported by 29.6 % of subjects in the mRNA-1273 group and by 25.1% in the placebo group up to 28 days post-vaccination. The most frequently unsolicited AEs in the mRNA-1273 group up to 28 days after any dose were the same as in the 1st analysis with slightly different incidences (Table 14.3.1.8.1.2 topline-part2), that do not alter the benefit-risk ratio or the safety profile of Spikevax in children 6-<12 years of age. In the 2nd analysis there was also an increase in the reported MAAEs in Part 2, both in the mRNA-1273 and in the placebo group. These increases were similar in percentage in both groups (approximately 5%), reflecting a longer follow-up in the study. Medically attended AEs irrespective of causality were again comparable in the vaccine (13.4%) and the placebo group (14.2%).

The CHMP considered that the benefit-risk profile of Spikevax given to subjects 5 to below 12 years of age was not altered in the 2nd IA with regard to unsolicited AEs and medically attended AEs.

Unsolicited AEs considered being vaccine related

Part 1

As of 6th October 2021, the incidence of AEs considered being vaccine related in Part 1 was comparable between the 2 dose groups, i.e. 10.8% in the 50 µg and 11.3% in the 100 µg group. Medically attended AEs considered being vaccine related were reported in 1.1% of subjects in the 50 µg dose group and by 1.9% of subjects in the 100 µg dose group. Upon request the MAH submitted Table 14.3.1.11.1 summarising unsolicited AEs considered being vaccine related for part 1. The most frequently reported unsolicited AEs considered being vaccine related in both groups belonged to the SOC of General disorders and administration site conditions (8.4% of subjects versus 8.1% of subjects in the 50 µg and the 100 µg dose group). Leading symptom in this SOC in the 50 µg dose group was injection site erythema (4.5% versus 3.2%), followed by injection site lymphadenopathy (1.3% versus 1.1%), injection site rash (0.8% versus 1.9%), injection site induration (0.8%) versus 1.3%), and injection site pruritus (0.8% versus 0%).

Only minimal changes with regard to unsolicited AEs considered being vaccine related are seen in the 2nd analysis. The incidence of AEs considered being vaccine related in Part 1 tended to be slightly higher in both groups compared to the first analysis and is still comparable in the 2 dose groups (11.6% in the 50 µg dose group and 12.7% in the 100 µg dose group). Medically attended AEs considered being vaccine related were reported in 0.8% of subjects in the 50 µg dose group and by 1.9% of subjects in the 100 µg dose group.

The CHMP noted that overall, the vast majority of reported unsolicited AEs considered as being vaccine related belong to injection site conditions and are already covered in the SmPC. After assessment of the available clinical information, no AE considered as being vaccine related in Part 1 was identified for inclusion into section 4.8.

Part 2

The incidence of unsolicited AEs considered being vaccine related was higher in the vaccine group compared with the placebo group. As of 6th October 2021, unsolicited AEs considered being vaccine related were reported for 9.8% of subjects in the vaccine group and for 3.7% in the placebo group. Medically attended unsolicited AEs considered being vaccine related were reported for 1.0% and 0.3% of subjects respectively. The subsequently submitted table 14.3.1.11.2 summarised unsolicited AEs considered being vaccine related for part 2 (Cut-off date 6th October 2021). Like for part 1 again the most frequently reported unsolicited AEs considered being vaccine related occurred in the SOC of General disorders and administration site conditions. For this SOC the incidence was higher in the mRNA-1273 vaccine group compared with the placebo group (7.5% of subjects compared to 2.2%). The huge majority of AEs included in this SOC are injection site/vaccination site AEs already covered in the SmPC. The most frequently reported AE in the mRNA-1273 vaccine group within this SOC is injection site erythema (2.7% of subjects in the vaccine versus no subjects in the placebo group). This is followed by injection site lymphadenopathy reported by 1.4% of subjects versus 0.4%, respectively, and injection site pain, reported by a comparable proportion of subjects in the mRNA-1273 and the placebo group (1.2% versus 1.0% of subjects, respectively). Different forms of rash (11 subjects in the mRNA-1273 vaccine group and 1 subject in the placebo group) and urticaria (7 subjects versus 1 subject [0.2% versus 0.1%]), both indicative of a hypersensitivity reaction are also more frequently reported in the mRNA-1273 vaccine group compared with the placebo group. The AE "rash" is included in section 4.8 of the SmPC, and the AE "urticaria" is considered being covered by the broader term "rash". Moreover the AE of hypersensitivity is included in section 4.8. An imbalance for the treatment-related AE of "abdominal pain" was noted (5 subjects [0.2%] in the mRNA-1273 vaccine group and no subject in the placebo group).

Together with one AE of "abdominal pain upper" in the vaccine group, the proportion would be 6 versus 0 subjects. Similarly, there was also a trend for a slight imbalance for all unsolicited AEs (regardless of relatedness, Table 14.3.1.8.1.2) of the PTs abdominal pain (0.6% versus 0.4%), abdominal pain upper (0.3% versus 0.1%), and abdominal pain lower (1 subject versus 0 subject). The MAH was asked to discuss these findings. It may be warranted to include the AE of abdominal pain in section 4.8 of the SmPC. Another imbalance is observed for the AE non-cardiac-chest pain. 4 subjects in the mRNA-1273 vaccine group (0.1%) and no subject in the placebo group reported non-cardiac chest pain considered being vaccine related. In addition, one subject in the mRNA-1273 and no subject in the placebo group reported chest pain. A careful evaluation of AEs indicative of myocarditis or pericarditis has been performed by the MAH. This evaluation included the assessment of the AE chest pain and did not reveal any signal towards myo- or pericarditis. Based on the available clinical information, for none of the events of chest pain/chest discomfort, any other cardiac symptom or dyspnoea a causality could be established. More details are discussed in the section "Assessment of myocarditis and pericarditis".

Only minimal changes are noted for IA 2 with regard to vaccine related AEs/MAAEs. The incidence of unsolicited AEs considered being vaccine related was again higher in the vaccine group compared with the placebo group. Unsolicited AEs considered being vaccine related were reported for 10.6% and 5.0% of subjects in the vaccine and the placebo group, respectively. Medically attended unsolicited AEs considered being vaccine related were reported for 1.1% and 0.4% of subjects respectively.

The CHMP considered that in general, the nature of unsolicited AEs considered to be vaccine related that were provided by the MAH does not change the safety profile of the vaccine as it has been determined for the adult population and the paediatric population 12 to <18 years of age or negatively impacts the overall positive benefit-risk ratio. One imbalance was observed for the event of abdominal pain in part 2 (5 subjects [0.2%] in the mRNA-1273 vaccine group and no subject in the placebo group). Together with one AE of "abdominal pain upper" in the vaccine group, the proportion would be 6 versus 0 subjects. Similarly, there was also a trend for a slight imbalance for all unsolicited AEs (regardless of relatedness, Table 14.3.1.8.1.2) of the PTs abdominal pain (0.6% versus 0.4%), abdominal pain upper (0.3% versus 0.1%), and abdominal pain lower (1 subject versus 0 subject). The MAH was asked to discuss these findings. The MAH again summarised all AEs of abdominal pain (related and unrelated):

- **Incidence of Unsolicited Treatment-Related TEAEs**:
    - Abdominal pain was reported for 0 placebo participant and for 5 (0.2%) participants of mRNA-1273 (N=3007)
    - Abdominal pain upper was reported for 0 placebo participant and for 1 (<0.1%) participant of mRNA-1273 (N=3007).
- **Incidence of Unsolicited TEAEs**:
    - Abdominal pain was reported for 4 (0.4%) placebo participants (N= 995) and 17 (0.6%) participants of mRNA-1273 (N=3007)
    - Abdominal pain upper was reported for 1 (0.1%) placebo participant and for 9 (0.3%) participants of mRNA-1273 (N=3007)
    - Abdominal pain lower was reported for 0 placebo participant and for 1 (<0.1%) participant of mRNA-1273 (N=3007).

The MAH concluded, that the majority of the events reported in the mRNA-1273 arm were considered not related by the investigators and resolved within hours or few days after start date. Based on the analysis of the data, and given that comparison is limited given the small numbers of participants presenting the reported events and the 3:1 randomisation of the study, the MAH considers that there are no clinically meaningful differences in the proportion of reports in the placebo group vs the mRNA-1273 group. Therefore, no conclusion of an imbalance can be drawn.

The MAH finally considered that analysis of the safety data does not support inclusion of abdominal pain in the ADR table in section 4.8 of the SmPC.

The CHMP did not fully agree with this. In young children, abdominal pain is generally frequent and the abdominal region is an organ onto which discomfort from other causes is often projected. Probably, the cases of abdominal pain in the vaccine group reflects the relatively high reactogenicity of the vaccine. It is acknowledged, that the majority of abdominal pain events was considered being not related by the investigator. However, the numerical imbalance, albeit small, remains. The 3:1 ratio is taken into account when considering the proportion of subjects reporting abdominal pain 0.2% versus 0%). Therefore, the event of abdominal pain should be included into the SmPC with the corresponding frequency and a footnote, explaining that this AE is only observed in the paediatric population 6 to 11 years of age.

Serious adverse event/deaths/other significant events

Serious adverse events

Part 1

In Part 1, *throughout the study*, a total of 6 SAEs occurred, all in either the 50 µg or the 100 µg mRNA-1273 vaccine group, none in the placebo group. *Within 28 days* after vaccination two subjects in the 50 µg dose group reported one SAE each (foreign body ingestion and palpitation). Four SAEs with onset *after 28 days* were reported, 3 in the 50 µg dose group, and one in the 100 µg dose group. None of the SAEs was considered being vaccine related by the investigator. In the 50 µg dose group one participant had a grade 2 optic disc drusen, which occurred 151 days after dose 2 and was ongoing at the time of the data snapshot. In addition, 2 other participants in the 50 µg dose group experienced an SAE of grade 3 appendicitis, 97 and 72 days post-dose 2. In the 100 µg group, 1 participant had an SAE of grade 2 systemic viral infection of unknown aetiology 101 days post-dose 2.

The event of palpitations in the 50 µg dose group occurred in a 7-year-old female child with a history of palpitations. Initially report stated, that 3 days post-dose 2, the girl experienced a mild SAE of palpitations, meeting the SAE criterion of medically significant SAE of special interest. The medical history includes palpitations starting one year before. Follow-up information was received 106 days post-dose 2 (after the data snapshot on 6th October 2021), which included a downgrade of the event by the investigator to non-serious. Moreover, the event onset was confirmed as 31 days after receiving the second dose of vaccine (not as initially reported 3 days after having received the second dose of vaccine). The event onset was changed to > 28 days after dose 2. The participant was seen by a cardiologist 95 days post dose 2. Results from the electrocardiogram and echocardiogram were normal. The subject was placed on a mobile cardiac telemetry 3 lead device for 30 days for monitoring. No treatment for the event of palpitations was reported. No action was taken in regard to the IP. Electrocardiogram and echocardiogram results were normal, and the child was pending ambulatory Holter monitoring. The resolution of the event is unknown. The investigator assessed the event of palpitations to be not related to the IP. This can be agreed upon.

The event of viral infection was reported in a 9-year-old male. On Study Day 133, the participant started experiencing a red and blotchy rash on bilateral cheeks, arms, and legs and severe itching on bilateral feet which resolved the same day. He presented to the hospital with leg pain/swelling and acute abdominal pain. The participant was admitted to the hospital that day for observation. Computed tomography with contrast of the abdomen/pelvis and an ultrasound with duplex of the scrotum were performed (results not provided). On Study Day 134, the participant started experiencing neck pain. Influenza A and B, respiratory viral panel-polymerase chain reaction, and SARS-CoV-2 tests were all negative. On Study Day 135, the participant had a peripheral pulse rate of 92 beats per minute and oxygen saturation of 95%. Relevant laboratory results (reference range) included white blood cell count of 3.7 × 103/uL (4.5-13.5), haemoglobin of 12.5 g/dL (11.5-15.5), platelet count of 141 × 103/µL (150-

400), neutrophils of 50% (25%-78%), lymphocytes of 35% (35%-54%), creatinine of 0.49 mg/dL (0.72-1.25), and globulin of 2.8 g/dL (1.9-4.3). Urine culture was performed (results not provided). Treatment for the event of systemic viral infection included paracetamol and an unknown intravenous antibiotic. The event of systemic viral infection was considered to be resolved on Study Day 135.

The 2nd analysis does not alter the benefit-risk profile. Since the last data cut, there were no new SAEs reported in the 50 µg group. The previously reported SAE of palpitations in the 50 µg mRNA-1273 group was subsequently downgraded to non-serious. This SAE was reported for a 7-year-old female, with a medical history of seasonal allergies and palpitations for a year previous to receiving the 1st dose of the vaccine and is in detail described above. One new SAE of acute pancreatitis was reported in the 100 µg mRNA-1273 group. The SAE occurred in a participant with significant ongoing medical history of pancreatic insufficiency, stage 2 chronic kidney disease and haemolytic uremic syndrome, and pancreatic pseudocyst. The investigator assessed the event of pancreatitis not to be vaccine related, which can be agreed upon. The participant was continuing in the study at the time of the data cut.

A previously reported SAE of systemic viral infection was updated to constipation.

Part 2

Two SAEs (appendicitis and cellulitis orbital) both not considered being vaccine related were reported in the mRNA-1273 vaccine group. No SAEs were reported in the placebo group. The SAE of appendicitis is also an AESI. The event was reported for a 7-year-old female and occurred 25 days-post dose 1. On Study Day 27, the girl underwent an appendectomy. The event of appendicitis was considered to be resolved on Study Day 27. The SAE of cellulitis orbital happened to an 8-year old male 2 days post-dose 2. The event started on Study day 33 with headache. On Study Day 35 the boy was admitted to hospital. CT examination of the orbits with IV contrast showed right maxillary and ethmoid sinusitis with right medial orbital wall (lamina papyracea) subperiosteal abscess butting the medial rectus, associated with pre- and post-septal cellulitis. Treatment for the event of cellulitis orbital included broad-spectrum antibiotics, IV piperacillin sodium/tazobactam sodium, IV vancomycin, and oral paracetamol. The participant was discharged from the hospital Study Day 38. No action was taken in regard to the IP. The event of cellulitis orbital was considered to be resolved on Study Day 38.

The benefit-risk ratio is not altered by the 2nd analysis with regard to SAEs. Since the last data cut 5 new SAEs (in 4 participants) were reported in mRNA-1273 group and 2 new SAEs in the Placebo group. None of the 5 SAEs was considered being vaccine related. The 5 new SAEs in the 50 µg mRNA-1273 group include Type 1 diabetes mellitus (study day 63), cellulitis in the left elbow area near an insect bite (study day 45), pyelonephritis and urosepsis in one subject on study day 64, and appendicitis on study day 77. Regarding the event of Type 1 diabetes mellitus per the investigator, the participant had been experiencing increased thirst, urination, and hunger prior to screening for study entry. The 2 new SAEs in the placebo group included affective disorder and COVID-19.

The CHMP noted from the submitted documents that as of data snapshot overall 8 SAEs were reported in part 1 and part 2 together. All SAEs occurred either in the 50 µg or the 100 µg mRNA-1273 vaccine group, none in the placebo group. None of the SAEs were considered to be vaccine related by the investigator, which is agreed.

Adverse Events of Special Interest

AESI were pre-specified in the CTP and were assessed as those occurring within 28 days of any injection and across the study duration. Events of clinical interest related to hypersensitivity, potential cardiac aetiology, and myocarditis and pericarditis are discussed in a separate subsection in this AR. AESI are listed in Table 39.

Table 39: Adverse Events of Special Interest, source: table 33 Clinical overview

Adverse Event	Additional Notes
Anosmia, Ageusia	• New onset COVID associated or idiopathic events without other etiology excluding congenital etiologies or trauma
Subacute thyroiditis	• Including but not limited to events of: atrophic thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, silent thyroiditis, thyrotoxicosis and thyroiditis
Acute pancreatitis	• Including but not limited to events of: autoimmune pancreatitis, immune-mediated pancreatitis, ischemic pancreatitis, edematous pancreatitis, pancreatitis, acute pancreatitis, hemorrhagic pancreatitis, necrotizing pancreatitis, viral pancreatitis, and subacute pancreatitis • Excluding known etiologic causes of pancreatitis (alcohol, gallstones, trauma, recent invasive procedures)
Appendicitis	• Include any event of appendicitis
Rhabdomyolysis	• New onset rhabdomyolysis without known etiology such as excessive exercise or trauma
Acute respiratory distress syndrome (ARDS)	• Including but not limited to new events of ARDS and respiratory failure.
Coagulation disorders	• Including but not limited to thromboembolic and bleeding disorders, disseminated intravascular coagulation, pulmonary embolism, deep vein thrombosis
Acute cardiovascular injury	• Including but not limited to myocarditis, pericarditis, microangiopathy, coronary artery disease, arrhythmia, stress cardiomyopathy, heart failure, or acute myocardial infarction
Acute kidney injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, or iatrogenic causes such as medications or radiocontrast etc) • Include all cases that meet the following criteria o Increase in serum creatinine by ≥ 0.3 mg/dl (≥26.5 µmol/l) within 48 hours; OR o Increase in serum creatinine to ≥ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR o Urine volume ≤0.5 mL/ kg/ hour for 6 hours
Acute liver injury	• Include events with idiopathic or autoimmune etiologies • Exclude events with clear alternate etiology (trauma, infection, tumor, etc) • Include all cases that meet the following criteria o 3-fold elevation above the upper normal limit for ALT or AST OR o > 2-fold elevation above the upper normal limit for total serum bilirubin or GGT or ALP
Dermatologic findings	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme
	• Bullous rashes • Severe cutaneous adverse reactions including but not limited to: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms and fixed drug eruptions
Multisystem inflammatory disorders	• Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C) • Kawasaki's disease
Thrombocytopenia	• Platelet counts < 150 ×10^9 • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome
Acute aseptic arthritis	• New onset aseptic arthritis without clear alternate etiology (eg, gout, osteoarthritis, and trauma)
New onset of or worsening of neurologic disease	• Including but not limited to: o Guillain-Barre Syndrome o Acute disseminated encephalomyelitis o Peripheral facial nerve palsy (Bell's palsy) o Transverse myelitis o Encephalitis/Encephalomyelitis o Aseptic meningitis o Febrile seizures o Generalized seizures/convulsions o Stroke (Hemorrhagic and non-hemorrhagic) o Narcolepsy
Anaphylaxis	• Anaphylaxis as defined per protocol. • Follow reporting procedures in protocol Section 7.4.5
Other syndromes	• Fibromyalgia • Postural Orthostatic Tachycardia Syndrome • Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome) • Myasthenia gravis

Part 1

As of 6th October 2021, overall, 5 AESI were reported throughout the study in part 1, none of them considered being vaccine related. In addition to the 5 AESI, though not meeting AESI criteria, one event of palpitation was reported as an AESI. This AESI is described in the SAE section, was reported for a 7-year old girl, and was downgraded to non-serious later.5 AESI occurred beyond the time frame of 28 days after vaccination; the event of palpitation occurred within this time window. The event of palpitation fulfilled SAE criteria and occurred in a 7-year-old female in the 50 µg dose group. The event was not considered being vaccine related by the investigator. This can be agreed upon. Details are described in the SAE section in this AR. The AESI events that occurred beyond day 28 post-vaccination in the 50 µg dose group include 2 cases of appendicitis on study day 125 and study day 100, and one case of non-cardiac chest pain on day 72 post-dose 2. The event of non-cardiac chest pain was considered being vaccine related by the investigator. The narrative has been submitted but does not contain any further clinical information. Taking the time to onset into account, a relationship is considered unlikely. No AESI occurring within 28 days after vaccination were reported in the 100 µg dose group. Beyond 28 days after any dose, 2 AESIs were reported, both not considered being vaccine related, which can be agreed upon based on time to onset. One mild event of bullous impetigo was reported in a 6-year-old male 48 days post-dose 2 and one event of ageusia reported in a 11-year-old female 28 days post-dose 2. The event of mild ageusia was accompanied by pyrexia, cough, nasal congestion, and oropharyngeal pain. No information on COVID-19 diagnostic is available in the submitted narrative.

As of 10th November 2021, one new AESI of acute pancreatitis, which is described in the SAE section of this AR was reported in the Part 1 100 µg mRNA-1273 group. This event was not considered being vaccine related by the investigator, which can be agreed upon.

Part 2

In part 2 of the study, 1 AESI was reported by one subject in the vaccine group and 2 AESI by one subject in the placebo group. None of the events was considered being vaccine related. The AESI in the vaccine group was an event of appendicitis occurring 25 days post-dose 1 in a 7-year-old female. The 2 AESI in the placebo group were COVID-19 associated ageusia and anosmia reported in a 11-year old male. All 3 events were considered to be resolved.

No relevant new AESIS were reported for the 2nd analysis, that might alter the benefit-risk profile. A total of 4 new AESIs was reported in Part 2, 3 in the 50 µg mRNA-1273 group and 1 in the placebo group. The new events in the 50 µg mRNA-1273 group include appendicitis (described in the SAE section above), loss of taste, and loss of smell and taste in another subject. For the AESI of isolated loss of taste no information of underlying COVID-19 is reported in the narrative. For the subject with combined loss of smell and taste, it was reported that the participant had these events without having a positive COVID-19 test result. Associated events were nasal congestion, rhinorrhoea, and oropharyngeal pain. One new AESI in the placebo group was loss of taste, associated with COVID-19. None of the new AESIs were assessed as being vaccine related, which can be agreed upon.

No event of MIS-C was reported throughout the study until the 2nd IA data cut-off.

The CHMP noted that a total of 9 AESI in 8 subjects were reported throughout the study in part 1 and part 2 together. Based on the submitted information, none of the events are considered to be vaccine related. Although palpitations were not considered AESI based on definitions above, an investigator reported an event of palpitations as an AESI. It should be noted that 2 more AEs of palpitation were reported in 2 subjects in the 100 µg dose group. The events are discussed in the Cardiomyopathy SMQ section below.

Events of clinical interest based on the narrow and the narrow and broad hypersensitivity standard Medical Dictionary for Regulatory Activities queries (SMQs) of Hypersensitivity

All unsolicited AEs within the narrow and the narrow and broad hypersensitivity standard Medical Dictionary for Regulatory Activities queries (SMQs), Version 23 were summarised for Part 1 and Part 2 of the study.

Part 1

As of 6th October 2021, no cases of anaphylaxis or severe hypersensitivity reaction were reported in part 1. Hypersensitivity reactions were slightly more frequent reported in the 100 µg dose group compared with the 50 µg dose group. Overall, 23 subjects (6.1%) in the 50 µg mRNA-1273 group and 31 (8.4%) in the 100 µg group experienced events indicative of hypersensitivity reaction. The most commonly reported events by PT in the 50 µg dose group were seasonal allergy (6 [1.6%] participants), injection site rash (3 [0.8%] participants), urticaria (3 [0.8%] participants)/urticaria papular (1 [0.3%], vaccination site rash (2 [0.5%] participants), and sneezing. In the 100 µg group in Part 1, the most commonly reported events were injection site rash (7 [1.9%] participants), seasonal allergy (5 [1.3%] participants), and sneezing (5 [1.3%] participants). 2 events were reported on the day of or day after dose administration. These events were seasonal allergies (not considered being vaccine related) and urticaria. The event of urticaria occurred in an 8-year-old female in the 50 µg dose group and started the day after the second dose. The event was reported as mild, related and reported as resolved the next day

Beyond 48 hours of any dose, 2 events were reported with PTs of bronchial hyperreactivity and wheezing. The event of bronchial hyperreactivity was reported in the 50 µg dose group in a 11-year-old male participant with history of reactive airways, 45 days after the second dose. The event was considered related by the investigator, the late onset however makes the event rather unlikely being vaccine related. The event of wheezing in the 50 µg dose group was reported in a 11-year-old male with past medical history of mild intermittent asthma, 28 days after the second dose and reported as moderate and not related. The event resolved 4 days after it started. Moreover, one event of urticaria papular in the 50 µg dose group occurred in a 11-year-old female with history of seasonal allergies and facial maculopapular rash. The event started on Day 9 post-dose 1 and was considered being vaccine related by the investigator. The girl had 50-mm redness at vaccine site and small sporadic papular lesions on hands, elbows and feet. No additional symptoms were reported with the rash. The participant had previously reported a facial rash prior to the delayed skin reaction that was thought to be related to her seasonal allergies. The second dose was withdrawn due to the event of urticaria papular. The girl continued participation in the trial. Additional 2 participants with 3 events indicative of hypersensitivity were reported in the 50 µg group of Part 1. In the 100 µg group, there were 5 additional participants reporting a total of 6 events indicative of hypersensitivity.

The CHMP noted that in part 1, no case indicative of anaphylaxis or severe hypersensitivity reaction has been reported. The reported AEs indicative of hypersensitivity were mild or moderate and resolved. One subject has been withdrawn from dose 2 due to urticaria popular occurring on day 9 post-dose 1. The following AEs indicating hypersensitivity were considered being vaccine related in the 50 µg dose group: injection site rash (3 subjects), vaccination site rash (2 subjects), urticaria (1 subject)/urticarial popular (1 subject). In the 100 µg dose group injection site rash (7 subjects), vaccination site rash (2 subjects), and pruritus, dermatitis, rash, rash macular, and rash pruritic (1 subject each) were considered being vaccine related. Currently in the SmPC all forms of hypersensitivity reaction except of rash, which is mentioned separately, are covered under the PT hypersensitivity. 2 events in the 50 µg dose group were reported on the day of or day after dose administration, seasonal allergies and urticaria. The event of urticaria occurred in an 8-year-old female and started 1 day post-dose 2. The event was reported as related, mild and as resolved the next day. It is agreed that relatedness is possible. One event of bronchial hyperreactivity was reported in a 11-year-old male participant with history of reactive airways, 45 days after the second dose. The event was considered related, mild and reported as resolved 2 days after it started. The late onset makes the event rather unlikely related. One event of non-serious moderate urticaria papular occurred in a 11-year-old female with history of seasonal allergies and facial

maculopapular rash. The event started on Day 9 post-dose 1 and was reported as related. The participant had 50-mm redness at vaccine site and small sporadic papular lesions on hands, elbows and feet. No additional symptoms were reported with the rash. The participant had previously reported a facial rash prior to the delayed skin reaction that was thought to be related to her seasonal allergies. The girl recovered within 6 days of the onset of the event. The second dose was not given due to the event of urticaria papular. Due to the predisposition for allergies and sporadic papular lesions causality cannot be excluded. Although symptom onset of delayed hypersensitivity reactions can occur up to 2 to 3 weeks after trigger event, delayed-type reactions occur commonly within hours or days after exposure.

Part 2

No cases of anaphylaxis or severe hypersensitivity reaction were reported in part 2. Hypersensitivity reactions were more frequent reported in the 50 µg mRNA-1273 vaccine group compared with the placebo group. Overall, 98 subjects (3.3%) in the 50 µg mRNA-1273 group and only 14 (1.4%) in the placebo group experienced events indicative of hypersensitivity reaction. 58 subjects (1.9%) versus only 2 subjects (0.2%) in the 2 groups reported hypersensitivity reactions considered being vaccine related. Of the related events, the most frequent PTs were injections site reaction (injection site rash, injection site hypersensitivity, injection site urticaria and vaccination site rash). The most frequently reported PT indicative of hypersensitivity, not associated with injection site reaction, was urticaria.

Two participants were withdrawn from vaccine dose 2 due to AEs indicative of hypersensitivity. One participant, a 9-year-old male with history of seasonal allergies, was discontinued from study vaccine due to non-serious events of moderate urticaria on day 24 post-dose 1 and mild wheezing starting on day 29 post-dose 1. The participant recovered from the wheezing 3 days after the onset of the event. The event of urticaria was still resolving and the participant was continuing in the study at the time of the data snapshot. The event of wheezing was not considered being vaccine related. Results of the causality assessment for the event of urticaria has not yet been reported. The other participant, a 10-year-old male with history of chronic kidney disease, experienced a non-serious, mild AE of rash on Day 10 following dose 1, which led to withdrawal of the study IP. The participant was continuing follow-up in the study at the time of data snapshot. The event was considered to be resolved on Day 18.

None of the urticaria AEs started on the day of vaccination, but one event of urticaria considered being vaccine related occurred in a 6-year old female (hives on body with the exception of face) and started on day 2 (i.e. 1 day post-dose 2). The event resolved the day after. A causality cannot be excluded. A total of 13 events were reported in the mRNA-1273 group on the day of or day after vaccination. The following are described in more detail here:

An episode of asthma occurred the same day of the second dose and was reported as not related. This episode occurred in a child with history of asthma and multiple allergies who was already on albuterol. One event of flushing occurred within 15 minutes of dosing and lasted less than 30 min. It was reported as mild and considered being vaccine related. Without further information it is not possible to distinguish between a vaccine or a procedural related AE. One participant had more than one event indicative of hypersensitivity reported the same day or the day after any dose. An event of bronchospasm was reported in a 11-year-old male with history of asthma 8 days after the second dose. It was reported as related, moderate, and resolved the same day. The late onset however makes a causal relationship unlikely. An event of periorbital swelling was reported in a 9-year-old male 2 days after receiving the first dose, and one event of eye swelling in an eight year old female 6 days post-dose 1. Both events were considered being vaccine related. Causality for the case of periorbital swelling cannot be finally assessed based on the limited information. Eye swelling starting on day 6 is rather unlikely to be vaccine related. Both events were non-serious and resolved.

In the combined 50 µg dose group (Part 1+Part 2, n=3,387), 121 subjects (3.6%) reported 136 potential hypersensitivity AES. The most commonly occurring PTs were injections site reaction (injection site rash,

injection site hypersensitivity, injection site urticaria or vaccination site rash) and seasonal allergies. Of note, the incidence differed between subjects in Part 1, 6.1% of participants receiving 50 µg reported such events compared to 3.3% in the 50 µg group in Part 2. In the vaccine group, approximately 50% of events were considered as related to IP, while only two events in the placebo group were considered as related. No event of anaphylaxis occurred during the study until cut-off.

The number of subjects reporting PTs in the broad scope SMQ Angioedema were 3 (0.3%) in the placebo group and 16 (0.5%) in the vaccine group in Part 2, versus 5 (1.3%) subjects in the 50 µg group and 2 (0.5%) in the 100 µg group of Part 1, driven by the PT of urticaria. These rates are higher than those observed in children 12-<18, who reported such events at a rate of 0.3% in both the placebo and the vaccine arm. In conclusion, the incidence of adverse events associated with hypersensitivity appears to be slightly higher in the younger children, but are mainly driven by cutaneous reactions and seasonal allergies. As of 10th November 2021, there were an additional 42 participants reporting 43 events indicative of hypersensitivity in the mRNA-1273 group. In the placebo group, there was an increase of 9 participants reporting 11 events.

The CHMP noted that no cases of anaphylaxis or severe hypersensitivity reactions were reported in either parts of the study. The most frequently reported AE indicative of hypersensitivity and not associated with local reaction is the AE of urticaria. Urticaria is currently not included as AE in section 4.8 but could be considered as being covered by the broader term rash. Two participants in the mRNA-1273 vaccine group of part 2 however have been withdrawn from dose 2 due to AEs indicative of hypersensitivity. One AE of urticaria started on day 24 and was ongoing at the time of data snapshot. The other event was rash that started on day 10 and resolved on day 18. Both events were non-serious. Although symptom onset of delayed hypersensitivity reactions can occur up to 2 to 3 weeks after trigger event, delayed-type hypersensitivity reactions occur commonly within hours or days after exposure. Both AEs were non-serious. Causality for the AE of periorbital swelling 2 days post-dose 2 in the 50 µg dose group in part 2 cannot finally be established based on the available clinical information.

Assessment of myocarditis and pericarditis

On July 09, 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. On Dec 03, 2021, after a review of two large European epidemiological studies (Epi-phare, FR and Nordic registry data, DK, SE, NO, FI) the PRAC confirmed that the risk for both of these conditions is overall "very rare", meaning that up to one in 10,000 vaccinated people may be affected. Additionally, the data show that the increased risk of myocarditis after vaccination is highest in younger males.

To perform an enhanced surveillance on the events of myocarditis and pericarditis the CTP has been updated. Two overlapping approaches were used to interrogate all TEAEs. This included:

1. narrow and broad cardiomyopathy standard Medical Dictionary for Regulatory Activities queries (MedDRA SMQs)
2. an algorithm generated using MedDRA terms from Version V.23.0 implemented in the CDC working case definitions for acute myocarditis and acute pericarditis (Gargano et al. 2021)

Sites were instructed to ask the caregiver the following question: "Has your child experienced any of the following symptoms since we last spoke? Chest pain, pressure or discomfort; Shortness of breath, fast breathing at rest, or any pain with breathing; Fast-beating, fluttering or pounding heart."

Cases of Clinical Interest Based on Medical Dictionary for Regulatory Activities (MedDRA) Cardiomyopathy SMQs

Part 1

The events recorded within the enhance surveillance for myocarditis/pericarditis based on cardiomyopathy SMQ for part 1 are summarised in Table 40.

Table 40: Summary of PTs within the MedDRA Cardiomyopathy SMQs – Narrow and Broad Scope (Part 1 – Safety Set), source: Table 36 clinical overview

Preferred Term	mRNA-1273 50 µg (N=380) n (%)	mRNA-1273 100 µg (N=371) n (%)
Number of Events	3	5
Number of Subjects Reporting Events	3 (0.8)	5 (1.3)
Dyspnoea	2 (0.5)	2 (0.5)
Palpitations	1 (0.3)	2 (0.5)
Chest pain	0	1 (0.3)

Source: Study P204 Table 14.3.1.22.3.15.2.1

During the 1st analysis with cut-off 6th October 2021, no cases of myocarditis or pericarditis were reported in part 1 of the study. Three events with PTs included in the narrow and broad scope cardiomyopathy SMQs were reported in 3 (0.8%) participants in the 50 µg group and 5 events were reported in 5 (1.3%) participants in the 100 µg group, respectively. The 3 events in the 50 µg dose group included 2 cases of dyspnoea, and one case of palpitation. One case of dyspnoea occurred in an 11-year-old male together with symptoms indicative of upper respiratory tract infection (non-serious, mild chest discomfort and musculoskeletal discomfort (back pain). The other event of dyspnoea occurred in an 11-year-old female with a medical history of asthma 23 days post-dose 1. The event of dyspnoea occurred together with the non-serious moderate AE of wheezing, chills, nasal congestion, and oropharyngeal pain. Other relevant non-serious AEs reported by the participant included: otitis externa, cough and fatigue, all prior to the event of dyspnoea. The third event (palpitation) occurred in a 7-year-old female with a medical history of palpitation 31 days post-dose 2 and was not considered being vaccine related by the investigator. Details are described in the SAE section of this AR. None of the AEs matching with PTs defined for enhance surveillance for myocarditis/pericarditis was considered being vaccine related by the investigators, which can be agreed.

In the 100 µg group there were 5 events of interest reported by 5 subjects within the cardiomyopathy SMQ. 2 events of dyspnoea, 2 events of palpitations, and 1 event of chest pain. Both cases of dyspnoea were not considered being vaccine related by the investigators. One case of mild dyspnoea was reported for an 8-year-old male, starting 92 days post-dose 2. The dyspnoea was accompanied by events of headache, cough, nasal congestion, oropharyngeal pain and rhinorrhoea. The other event of non-serious mild dyspnoea occurred in a 9-year-old participant starting 2 days post-dose 2 together with non-serious, mild chest discomfort and musculoskeletal discomfort (back pain), all of which resolved within 'a few hours' according to the parents. The child had a relevant history of asthma for which he was receiving albuterol and budesonide. The first event of palpitation occurred on the day of receiving dose 2, was reported for an 11-year-old female and was considered being vaccine related by the investigator. The event was associated with an anxiety reaction. According to the parents the child felt like she could not catch her breath upon returning home and felt her heart skipped a few beats for a brief time. O2 sat and pulse was normal at home; per the parent. No other cardiac symptoms like chest pain, syncope or near syncope, or chest wall pain were reported. Concomitant medication included paracetamol and ibuprofen (due to chills and elevated temperature, according to the MAH). Symptoms resolved the same day. In contrast to the investigator, the MAH did not assess the event of palpitation as being vaccine related, which is supported. There is Causality cannot be finally demonstrated, it is also possible, that the event of palpitation is an anxiety-related reaction. The second AE of palpitation in part 2 was also considered being vaccine related by the investigator and was reported for a 10-year-old female, who reported palpitation on exertion 6 days after dose 2. Concomitant medication ongoing at the time of the event of palpitations

included ibuprofen given because of pain at injection site, and headache. Palpitation resolved on the same day. The MAH did not agree with the investigator`s conclusion, which is supported. Causality cannot be finally demonstrated, because the event happened upon exertion. One event of chest pain (moderate) was reported in a 9-year-old male occurring 17 days after dose 2 and resolving the same day. The child had a history of attention deficit hyperactivity disorder (ADHD) for which he received the concomitant medication of Methylphenidate hydrochloride, which could also be a cause for chest pain/chest discomfort. The chest pain occurred while exercising. ECG and a chest x-ray were performed, both of which were unremarkable. The investigator considered the event related, which is not supported by the investigator. It is agreed that causality to the vaccine cannot be established, due to concomitant medication and exertion. The results of unremarkable cardiac evaluation together with an onset of 17 days and resolution the same day do not indicate myocarditis or pericarditis.

The CHMP noted that no case of myocarditis or pericarditis was reported in part A of the study. A total of 8 AEs in 8 subjects were reported within the cardiomyopathy MedDRA SMQ. The events included dyspnoea, palpitation, and chest pain. The CHMP considered that these events are not indicative of myocarditis or pericarditis. 2 events of palpitation and 1 event of chest pain in the 100 µg dose group were considered being vaccine related by the investigator, but not by the MAH. The MAH's assessment of the events is supported based on the submitted clinical information. In summary, none of the events reported within MedDRA cardiomyopathy SMQ is indicative of myocarditis or pericarditis and none of the events is considered being vaccine related.

Part 2

All events reported within the MedDRA cardiomyopathy SMQ are summarised in Table 41.

Table 41: Summary of PTs Reported by Subjects within the MedDRA Cardiomyopathy SMQs (Part 2 – Safety Set)

Preferred Term	mRNA-1273 50 µg (N=3007) n (%)	Placebo (N=995) n (%)
Number of Events	10	1
Number of Subjects Reporting Events	8 (0.3)	1 (0.1)
Dyspnoea	5 (0.2)	1 (0.1)
Chest pain	3 (< 0.1)	0
Syncope	1 (< 0.1)	0

Source: Study P204 Table 14.3.1.22.3.15.2.2

Three events of chest pain occurred in 3 subjects, one that occurred together with dyspnoea was considered being vaccine related by the investigator.

One report of chest pain in an 8-year-old female with a medical history of asthma for which her medication included albuterol. It should be noted that β2-sympathomimetic medication can result in tachycardia, chest pain, and palpitation. The event occurred 7 days post-dose 1 and was resolved 3 days later. The event was not considered being vaccine related by the investigator. The girl received dose 2 of mRNA-1273 with no additional AEs reported. A second report of chest pain happened to an 11-year-old male 2 days post-dose 2 was described as 2 brief discrete episodes of chest pain, occurring a couple of days apart with each episode lasting only seconds in duration. This child had a medical history of seasonal allergies, asthma and anxiety and was described as clearly anxious on examination; otherwise, physical examination and ECG were reported as unremarkable. The Investigator assessed this event as not being vaccine related. A third report of chest pain was reported for a 7-year-old male and occurred 2 days post-dose 2, resolving within 4 days. The chest pain was described as mild and intermittent. The event was

accompanied by mild dyspnoea starting also 2 days post-dose 2 and resolved on the same day. The child had no relevant medical history. Per the investigator the participant was evaluated in the emergency department where he was considered to be in good health with no respiratory or cardiac issues identified. Electrocardiogram and echocardiogram were performed and excluded cardiac origin for the chest pain and dyspnoea. Concomitant medication at the time of the events of dyspnoea and chest pain included: children's ibuprofen (headache, muscle aches), children's paracetamol (body aches in neck region), and paracetamol (shortness of breath and intermittent chest pain).The event was considered to be related to the IP by the investigator, which was agreed by the MAH.

6 events of dyspnoea were reported in 5 subjects in the mRNA-1273 vaccine group. One of these events of dyspnoea was considered being vaccine related by the investigator and occurred in the 7-year-old male described above, together with intermittent chest pain. The 5 remaining events (in 4 subjects) are described here in detail.

A 6-year-old female with a medical history of seasonal allergies experienced difficulty breathing due to seasonal allergies occurring 6 days post-dose 1 which resolved the same day. Concomitant medications included albuterol and loratadine. The events were considered not related by the investigator. A 9-year-old male with a medical history of seasonal allergies and ADHD reported 2 events of dyspnoea both occurring 13 days post-dose 1, together with fatigue, oropharyngeal pain and cough. The events were reported as "difficulty breathing" (moderate) and once as "shortness of breath" (mild), and both occurred and both resolved on the same day. Concomitant medications included diphenhydramine (seasonal allergies), fluticasone (seasonal allergies), risperidone (attention deficit hyperactivity disorder, combined), atomoxetine (attention deficit hyperactivity disorder, combined), paracetamol (minor aches/pains related to childhood injuries/conditions), paracetamol (headache), and cetirizine(seasonal allergies). The events were considered not related by the investigator, compatible with possible respiratory tract infection as the cause of the dyspnoea given the fatigue, oropharyngeal pain and cough. A 9-year-old female with no relevant medical history, reported dyspnoea one day post-dose 2 which resolved the next day. Concurrent symptoms included headache and a urinary tract infection. The event was not considered being vaccine related by the investigator. The concurrent occurrence of headache and urinary tract infection may have resulted in feeling of malaise, which could increase the perception of subjective symptoms such as dyspnoea. A 9-year-old female with unknown medical history, reported dyspnoea 21 days post-dose 1 which resolved in 3 days. The participant also experienced concurrent rhinorrhoea and cough. The constellation of dyspnoea, rhinorrhoea and cough are more compatible with possible respiratory tract infection than potential myocarditis or pericarditis. The event was considered not related to the vaccine by the investigator.

The last event is an event of syncope reported in a 10-year-old female with medical history of asthma, who experienced syncope on the day of dose 1 and which resolved the same day. No other information was provided. The event was considered not related to the vaccine by the investigator.

The CHMP noted that in part 2 of the study 8 events within the MedDRA SMQ occurred in 10 subjects. This included 3 events of chest pain, 6 events of dyspnoea (one dyspnoea together with chest pain in one subject, 2 events of dyspnoea in one subject), and one event of syncope occurred. Except for the event of chest pain together with dyspnoea occurring in one subject (a 7-year-old boy) none of the events were considered being vaccine related. The event of dyspnoea and chest pain occurred 2 days post-dose 2, resolving on the same day (dyspnoea) and within 4 days (chest pain). The chest pain was described as intermittent. The child had no relevant medical history. Per the investigator the participant was evaluated in the emergency department where he was considered to be in good health with no respiratory or cardiac issues identified. Electrocardiogram and echocardiogram were performed and excluded cardiac origin for the chest pain and dyspnoea. Concomitant medication at the time of the events of dyspnoea and chest pain included: children's Motrin/Ibuprofen (headache, muscle aches), children's Tylenol/paracetamol (body aches in neck region), and Tylenol (shortness of breath and intermittent chest

pain). The provided information, particularly the unremarkable cardiac investigations (ECG and cardiac echo), do not indicate myocarditis or pericarditis. Vaccine relatedness cannot be excluded, but on the other hand not finally be confirmed. The CHMP agrees not to include dyspnoea and chest pain into section 4.8 solely based on these solicited events.

Additional Analysis of Myocarditis and Pericarditis

Part 1

In this additional analysis (algorithm generated using MedDRA terms from Version V.23.0 implemented in the CDC working case definitions for acute myocarditis and acute pericarditis) only one additional relevant PT was identified in part 1 of the study. This event was report for a 10- year-old male in the 50 µg mRNA-1273 dose group, with medical history of obstructive sleep-related breathing disorders. The participant received the first dose on Study Day 1 and the second dose on Study Day 30. Sixty days after the 2nd dose of the vaccine, on Study Day 90, the participant experienced a non-serious mild AE of musculoskeletal chest pain (musculoskeletal chest pain). Other relevant non-serious AEs reported by the participant included: viral infection (viral like illness; prior to the event of musculoskeletal chest pain) and arthropod bite (insect bites on chest and legs; prior to the event of musculoskeletal chest pain). No action was taken in regard to the IP. The event of musculoskeletal chest pain was considered to be resolved on Study Day 119. The investigator assessed the event of musculoskeletal chest pain to be not related to the IP. The participant was continuing in the study at the time of the data cut.

Part 2:

In Part 2, this additional analysis identified 5 participants with relevant PTs, all in the mRNA-1273 group, 1 with angina pectoris, 2 with chest discomfort and 2 with musculoskeletal chest pain. Angina pectoris was reported for a 10-year-old male in the mRNA-1273 group, occurring one day post-dose 1 and resolving on the same day. His parents reported him feeling squeezing around the heart. The next morning, the participant reported the same squeezing feeling approximately 10-12 times and it resolved after eating breakfast. The participant was brought into the clinic for cardiac evaluation. A Troponin level was drawn, ECG 12 Lead and Pediatric Transthoracic Echo complete with Doppler/CF were performed. All three tests were within normal limits and Myocarditis was ruled out. The event was considered being vaccine related by the investigator, and the second dose of the vaccine was given as planned without additional AEs.

Two events of chest discomfort in the mRNA-1273 vaccine group, both not considered being vaccine related by the investigator were identified within this search according to the MAH. One event of chest discomfort occurred in a 9-year-old male with a history of anxiety reported on the day of administration of dose 1. No other non-serious AEs were reported by the participant. No action was taken in regard to the IP. The event of chest discomfort was considered to be resolved on Study Day 3. A diagnosis of non-cardiac chest pressure related to worsening anxiety was made. The participant received dose 2 of the vaccine as planned with no other reported events. The second event of chest discomfort in the 50 µg mRNA-1273 vaccine group occurred in a 10-years old female with no medical history reported. The event occurred four days after dose 2, on Study day 27 and was described as non-serious mild AE of chest discomfort (chest tightness). According to her guardian the chest discomfort lasted for less than 24 hours and symptoms resolved without any treatment. Concomitant medication or concomitant procedures ongoing at the time of the event of chest discomfort included: Tylenol (i.e. paracetamol, for chest tightness). No action was taken in regard to the IP. The investigator assessed the event of chest discomfort to be not related to the IP. The participant was continuing in the study at the time of the data cut. The listing revealed a third case of chest discomfort in the mRNA-1273 vaccine group in part 2, reported by a 9-year-old male. The narrative was subsequently submitted by the MAH. The event started

and ended on the day of administration of dose 1 and was considered being vaccine related by the investigator. The event was reported as chest tightness, that lasted 25 minutes, with no wheezing, not worsening with deep breath, vital signs were stable, and chest tightness was gone after reassurance. The event resolved the same day. No other adverse events were reported at that time. Based on the available information the event is not indicative of myo-or pericarditis. The MAH evaluated the event as "immunisation stress-related response (ISRR)" which describes a range of symptoms and signs that may arise around immunisation that are related to "anxiety" and not to the vaccine product. These reactions are described as AEFI arising from anxiety about immunisation and include vasovagal-mediated reactions, hyperventilation-mediated reactions and stress-related psychiatric reactions or disorders. It is agreed that an anxiety related reaction is possible and a vaccine relatedness cannot be finally concluded on.

In addition, there were 2 reports of musculoskeletal chest pain identified in 2 participants, both in the mRNA-1273 group and both not considered being vaccine related. An 8-year-old male with concurrent medical history of URTI, fever and concomitant medications of azithromycin, diphenhydramine and guaifenesin, reported musculoskeletal chest pain occurring 13 days post-dose 2 which resolved the following day. The participant was evaluated by the paediatrician who determined that the event was unlikely to be due to cardiac origin. It can be agreed, that the event is likely due to the concurrent URTI. A second report was a 7-year-old male with medical history of chronic lung disease, retinopathy of prematurity and asthma, who reported musculoskeletal chest pain 22 days post-dose 2. This event is ongoing. No further medical details are provided. One event of non-cardiac chest pain was reported in a 11-year-old male 2 days post-dose 2 in part 2. This child had a medical history of seasonal allergies, asthma and anxiety and was described as clearly anxious on examination. No associated diaphoresis, dyspnoea, radiation or pallor were described. Myocarditis or pericarditis were excluded by physical examination and ECG, both was reported as unremarkable. The Investigator assessed this event as 'possibly musculoskeletal in origin (e.g., costochondritis) and more likely related to a hypervigilant state secondary to anxiety. The event resolved and was considered mild and non-serious, and not being vaccine related by the study investigator, which can be agreed upon.

The CHMP noted the MAH summary of the clinical information available for all 3 participants (one case considered to be vaccine related by the investigator, and the other two cases being considered not to be vaccine related). The MAH assessed all 3 events as cases of "immunization anxiety-related reaction" or how they are now described "immunization stress-related response (ISRR)" which describe a range of symptoms and signs that may arise around immunisation that are related to "anxiety" and not to the vaccine product. These reactions are described as AEFI arising from anxiety about immunisation and include vasovagal-mediated reactions, hyperventilation-mediated reactions and stress-related psychiatric reactions or disorders, and cover the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom, anxiety. Chest pain and or chest discomfort as the only manifestation or adverse event, are part of the range of symptoms that can be present during an ISRR event. The MAH assessment can be agreed upon. Based on the available clinical information a relatedness to the mRNA-1273 cannot be concluded on. The CHMP agreed not to include the AE of chest pain or chest comfort into the SmPC. None of the events is indicative of myo-or pericarditis, based on the submitted clinical information.

Summarising evaluation of the Assessment of myocarditis and pericarditis

Following the identified safety signal of events of myocarditis and pericarditis following vaccination with mRNA based COVID-19 vaccines the MAH amended the CTP to implement an enhanced surveillance on the events of myocarditis and pericarditis. A careful analysis based on two overlapping approaches used to interrogate all AEs indicative of myocarditis or pericarditis has been performed. This included:

1. narrow and broad cardiomyopathy standard Medical Dictionary for Regulatory Activities queries (MedDRA SMQs) and
2. an algorithm generated using MedDRA terms from Version V.23.0 implemented in the CDC working case definitions for acute myocarditis and acute pericarditis (Gargano et al. 2021)

AEs detected within this search included cases of chest pain, chest discomfort, angina, dyspnoea, syncope, palpitations, and musculoskeletal chest pain. Overall, only 2 participants in the mRNA-1273 vaccine group (both in part 2, i.e. they received the 50 µg dose) reported more than one PT indicative of myocarditis or pericarditis concurrently. Both narratives have been provided. The available clinical information does not indicate that the events are indicative of myocarditis or pericarditis.

One is a 7-year-old male who experienced mild intermittent chest pain on day 2 post-dose 2. The event was accompanied by mild dyspnoea starting also 2 days post-dose 2 and resolving on the same day. The child had no relevant medical history. Per the investigator the participant was evaluated in the emergency department where he was considered to be in good health with no respiratory or cardiac issues identified. Electrocardiogram and echocardiogram were performed and excluded cardiac origin for the chest pain and dyspnoea. Concomitant medication at the time of the events of dyspnoea and chest pain included: children's ibuprofen (headache, muscle aches), children's paracetamol (body aches in neck region), and paracetamol (shortness of breath and intermittent chest pain). The event was considered to be related to the IP by the investigator, which was agreed by the MAH.

The other one is a 9-year-old male with a medical history of seasonal allergies and ADHD reported 2 events of dyspnoea both occurring 13 days post-dose 1, together with fatigue, oropharyngeal pain and cough. The events were reported as "difficulty breathing" (moderate) and once as "shortness of breath" (mild), and both occurred, and both resolved on the same day. Concomitant medications included diphenhydramine (seasonal allergies), fluticasone (seasonal allergies), risperidone (attention deficit hyperactivity disorder, combined), atomoxetine (attention deficit hyperactivity disorder, combined), paracetamol (minor aches/pains related to childhood injuries/conditions), paracetamol (headache), and cetirizine (seasonal allergies). The events were considered not related by the investigator, compatible with possible respiratory tract infection as the cause of the dyspnoea given the fatigue, oropharyngeal pain and cough.

No other participant reported more than one PT indicative of myo-or pericarditis.

Neither in Part 1 nor in Part 2 a case of myo-or pericarditis has been reported. In addition, the careful enhanced analysis of relevant PTs does not suggest any case of myo-or pericarditis. In summary, the submitted clinical data do not reveal any case of myo-or pericarditis up to the data snapshot. The sample size however is too small to finally assess the safety signal of myo-and pericarditis.

Update on myocarditis/pericarditis (Cut-off date 10th November 2021)

Part 1

There have not been any repots of myocarditis or pericarditis as of 10th November 2021 in Part 1. Moreover, there were no new events identified in Part 1 under the MedDRA Cardiomyopathy SMQs.

Part 2

As of 10th November 2021, there were 5 new events of clinical interest included in the MedDRA Cardiomyopathy SMQs, 4 in the mRNA-1273 vaccine group and 1 in the placebo group (3:1 randomisation). Narratives were provided. None of the events was indicative of myo-or pericarditis or considered being vaccine related.

Subsequently in one subject with 2 reported episodes of dyspnoea on the same day, the events were updated to fever and streptococcal infection. An additional event of dyspnoea was updated to a non-serious mild AE of respiratory disorder (upper respiratory illness, aetiology unknown).

In summary the evaluation of cardiomyopathy SMQ and additional analysis of myocarditis and pericarditis performed within the 2nd analysis did not reveal a case of myo-or pericarditis, neither in part 1 nor in part 2 of trial P204.

Laboratory findings

No scheduled laboratory assessments for safety were implemented in the study.

Safety in special populations

The incidence of unsolicited adverse events is comparable for males and females, both with regard to those AEs considered related to IP and to AEs irrespective of relationship.

Similarly, for seropositive vs. seronegative trial participants, the incidences of unsolicited AEs are overall comparable, with the caveat that the size of the seropositive group was fairly small.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not evaluated in this trial.

Discontinuation due to adverse events

Part 1

One 11-year-old female in the 50 µg dose group with history of seasonal allergies and facial maculopapular rash did not receive the second dose of mRNA-1273 because of a non-serious, moderate AE of urticaria papular. The event started on study day 9 and was considered being vaccine related by the investigator. The girl had 50-mm redness at vaccine site and small sporadic papular lesions on hands, elbows and feet. No additional symptoms were reported with the rash. The participant had previously reported a facial rash prior to the delayed skin reaction that was thought to be related to her seasonal allergies. The second dose was withdrawn due to the event of urticaria papular. The girl continued participation in the trial. As of 10th November 2021, no additional participants have been withdrawn due to AEs in Part 1.

Part 2

Two participants in the mRNA-1273 vaccine group were discontinued from the second vaccine dose, but continued participation in the study. One participant (generalised rash all over body), a 9-year-old male with history of seasonal allergies, was discontinued from study vaccine due to non-serious events of moderate urticaria on study day 24 and mild wheezing starting on study day 29. The participant recovered from the wheezing 3 days after the onset of the event. The AE of wheezing was not considered being vaccine related by the investigator. The event of urticaria was still resolving and results from the causality assessment were not reported. The participant was continuing in the study at the time of the data snapshot. The other participant, a 10-year-old male with history of chronic kidney disease, experienced a non-serious, mild AE of rash on study Day 10. The participant was continuing follow-up in the study at the time of data snapshot. The event was considered to be resolved on Day 18. Causality assessment for this event has not been reported.

One 8-year-old male participant in the 50 µg dose group in Part 2 was discontinued from the trial 20 days post-dose 2 because of an event of inflammatory bowel disease. The boy had received the first dose of 50 µg mRNA-1273 on Study Day 1 and the second vaccine dose on Study Day 30. 20 days post-dose 1 (study day 50), he experienced a moderate treatment-emergent adverse event of inflammatory bowel disease. The boy had a past medical history of seizure disorder treated with the anticonvulsant levetiracetam, headaches treated with ibuprofen, and occasional abdominal pain. According to the mother he had occasional abdominal pain for many years, but has never been worked up for diagnosis until that date. The participant was withdrawn from the study because of the mother`s decision. 63 days post-dose 1additional information was received from the investigator's site noting that an endoscopy failed to indicate IBD, but did identify granulomas. Additional immunology and genetics testing revealed that the child had no immune response to previous routine vaccinations. The new possible diagnosis is Common Variable Immunodeficiency (CVID).

As of 10th November 2021, there were 3 new AEs that led to withdrawal from vaccination and/or from the study; 1 in the 50 µg mRNA-1273 group (Rash) and 2 in the Placebo group (asymptomatic COVID-19; and symptomatic COVID-19).

The CHMP noted that no cases of anaphylaxis or severe or serious AE indicative of hypersensitivity occurred up to data snapshot. 3 participants in the 50 µg mRNA-1273 vaccine group (one in part 1 and 2 in part 2) however were withdrawn from dose 2 due to AEs indicative of hypersensitivity (urticaria papular, urticaria, and rash). Two of the 3 subjects had predisposing factors (history of seasonal allergy). None of the events was serious or severe. All AEs had a rather delayed onset (study day 9, day 24, and day 10). Although symptom onset of delayed hypersensitivity reactions can occur up to 2 to 3 weeks after trigger event, delayed-type reactions occur commonly within hours or days after exposure. The 50-mm redness at vaccine site on study day 9 reported for a girl is consistent with a delayed skin reaction, but was also accompanied by sporadic papular lesions on hands, elbows and feet, indicative of a delayed hypersensitivity. The onset of study day 24 in the 9-year-old boy with a history of seasonal allergy and generalised rash all over body is rather late to finally establish vaccine relatedness. Urticaria are not currently listed as an adverse reaction separately, only hypersensitivity and rash are listed. The CHMP agreed to summarise different hypersensitivity reaction under the term of hypersensitivity. The term urticaria could also be covered under the broad term rash, which is listed separately.

Post-marketing experience

Very rare cases of myocarditis and pericarditis have occurred post-marketing, mainly in male young adults and adolescents who received COVID-19 vaccines. EMA's safety committee (PRAC) recommended listing myocarditis and pericarditis as new side effects in the product information for these vaccines, together with a warning to raise awareness among healthcare professionals and people taking these vaccines. The Committee concluded that the cases primarily occurred within 14 days after vaccination, more often after the second dose and in younger adult men. In five cases that occurred in the EEA, people died. They were either of advanced age or had concomitant diseases. Available data suggest that the course of myocarditis and pericarditis following vaccination is similar to the typical course of these conditions, usually improving with rest or treatment.

2.5.1. Discussion on clinical safety

Safety data base and follow-up

The safety data base comprises safety and reactogenicity data from subjects in the unblinded dose finding part 1 and the placebo-controlled part 2. In the dose finding part 1 subjects received either a dose of 100 µg of mRNA-1273 or a dose of 50 µg. On 29th October 2021, a competitor's COVID-19 vaccine

became available for the age group 5 –below 12 years of age via EUA by the FDA. If a child became eligible for a COVID-19 vaccine outside of the study, it became eligible to unblind and, if having received placebo, also eligible to receive comparator vaccine or to cross-over to receive 2 doses of mRNA-1273. Unblinding and cross-over vaccinations for the 6 to <12-year-old age group in Part 2 started on 1 November 2021, 9 days before the data cut-off date for the pre-specified IA, marking the ending of the blinded follow-up for this age group. Data collected after participant unblinding are not included in the blinded phase analyses. Only 80 /1000 placebo participants have left the trial to date to seek an alternative vaccine. The vast majority of placebo recipients have crossed over to mRNA-1273 and contribute to additional safety follow-up, albeit unblinded.

The final selected dose for the paediatric population 6-<12 years of age is 50 µg. This dose could be justified by the reactogenicity and immunogenicity data submitted within this procedure. The data base however is insufficient to detect rare events like immune disorders or the confirmed AE of pericarditis. Due to these potential risks it is nonetheless desirable to have clinical data evaluating lower doses in this age group in the future. The MAH added a Part 3 to the protocol where one additional cohort of approximately 300 participants 6 to < 12 years of age will receive 2 doses of 25 µg of mRNA-1273 followed by a pre-planned booster dose 6 months after the second dose, to assess the reactogenicity profile and immunogenicity of a lower dose in this age group. As stated in the response to the request for supplementary information, results from this part 3 are not expected to be available before the second half of 2022.

A pooled analysis for all subjects who received the final selected dose of 50 µg mRNA-1273 has not been performed.

The first data snapshot supporting the extension of indication to the paediatric population from 6-<12 years of age is 6th October 2021. The safety sets include data from 4753 participant (data snapshot 6th October 2021), including 3758 participants who received at least 1 dose of either 50 µg or 100 µg mRNA-1273 and from 995 participants who received at least 1 dose of placebo. Overall, 3387 participants had received at least one dose of 50 µg mRNA-1273, which is the final selected dose for the paediatric population 6-<12 years of age. Follow-up time is rather short. A safety follow-up of at least 28 days after dose 2 was performed for 853 participants who had received at least one dose of 50 µg mRNA-1273. Safety follow-up for 3 months post-dose 2 was provided for 749 subjects who had received at least one dose of either 50 µg or 100 µg mRNA-1273 (in Part 1). The MAH was asked to submit safety data for a later time point. The MAH proposed to conduct another interim analysis (IA) based on a 10th November 2021 data cut-off, meeting per protocol IA specification (all participants 6 to <12 years in Part 2 reach Day 57 or had discontinued the study). This 2nd IA with data cut-off 10th November 2021 was submitted subsequently, but still not all participants have reached day 56 post-dose 2. In the 10th November 2021 IA safety analysis, a median follow-up of 56 days post-dose 2 is provided for a total of 3387 participants exposed to 50 µg mRNA-1273 across study Parts 1 and 2 from the blinded and open label phases. From Part 2, median follow-up of 55 days post-dose 2 is provided for 4002 participants (3007 exposed to 50 µg, and 995 placebo).

Taking blinded phase and open-label phase of part 2 together, there are 2984 (99.2 %) participants in the mRNA-1273 group and 967 (97.2 %) participants in the placebo group who have been followed for 28 days or more after dose 2. 1498 (49.8%) participants in the mRNA-1273 group and 456 (45.8%) participants in the placebo group have been followed for 56 days or more after dose 2.

Exposure to vaccine

The dropout rate was low in both parts of the trial. In part 1 one subject (in the 50 µg dose group) discontinued study vaccination due to an adverse event of urticaria papular on Day 9 following dose 1. One subject in the 100 µg dose group withdraw from the study because of lost to follow-up. 3 subjects (0.4%), 1 in the 50 µg dose group and 2 in the 100 µg dose group withdraw consent. In part 2, 20 subjects (0.5%) withdraw from the study, 9 participants (0.3%) in the mRNA-1273 group and 11 (1.1%) in the placebo group.

In Part 1, at the time of the 2nd IA, 380 participants in the 50 µg group and 371 participants in the 100 µg group received dose 1 and 379 participants in the 50 µg group and 371 participants in the 100 µg group received dose 2. As of 10th November 2021, no additional participants have been withdrawn due to TEAE in Part 1.

In Part 2, a total of 4002 participants had received dose 1 (3007 in mRNA1273 group and 995 in placebo group) and a total of 3961 participants had received dose 2 (2988 in the mRNA-1273 group and 973 in placebo group. The proportion of subjects who discontinued through 10th November 2021 was comparable to the first interim analyses.

The sample size in this trial is too low to detect rare events.

Demography and baseline characteristics

Demographics and baseline characteristics were balanced between the two dose groups in Part 1 and between the mRNA-1273 and the placebo group in Part 2. Part 1 and Part 2 were also comparable with regards to Demographics and baseline characteristics. The majority of participants in both parts of the study were SARS-CoV-2 seronegative at baseline (86.4% in Part 1 and 89.2% in Part 2). The proportion of obese and non-obese children was comparable between the placebo and the vaccine group in part 2 of the trial. In the placebo group 19 children (1.9%) were obese and in the vaccine group 20.2% (607 children). The proportion of obese/non-obese children overall in the 50 µg vaccine group (part 1 and part 2 together) was 20.5% obese versus 79.5% non-obese and was comparable in the placebo and the vaccine group. At least one medical history was reported by 53.5% of subjects in the placebo and by 55.8% of subjects in the 50 µg mRNA-1273 vaccine group (taking part 1 and part 2 together). Less data with regards to risk factors for severe COVID-19 outcome are available for the paediatric population compared to the adult population. Limited data suggest an increased risk of severe or critical disease in children less than one year of age and those with certain underlying medical conditions like e.g. congenital heart disease, and chronic pulmonary disease. The trial enrolled only individuals who are in a good health. Children with stable chronic underlying disease were however allowed to be enrolled into the trial. At least one medical history was reported by 53.5% of subjects in the placebo and by 55.8% of subjects in the 50 µg mRNA-1273 vaccine group (taking part 1 and part 2 together).

Local and systemic reactogenicity

The incidence of solicited local and more notable of systemic ARs was lower in the 50 µg dose group compared with the 100 µg dose group in Part 1. This well justifies the selection of the 50 µg dose for the paediatric population 6-<12 years of age. A lower dose of mRNA-1273 (25 µg) has not been tested in this population. In Part 2, solicited local and systemic ARs occurred in a higher incidence in the mRNA-1273 group compared with the placebo group, as it can be expected. The incidence of solicited local and more notable of solicited systemic ARs in the mRNA-1273 group was, as previously observed in Part 1 and in other mRNA-1273 clinical trials higher post-dose 2 compared with post-dose 1. In part 2, the most often reported solicited local AR in the mRNA-1273 group after any dose was pain reported by 98.4% of subjects in the mRNA-1273 versus 64.1% in the placebo group. The majority of solicited local ARs was reported as mild to moderate in both groups. Again, the incidence of severe ARs was higher in the mRNA-1273 compared with the placebo group. The most frequently reported grade 3 local solicited AR after any dose in the mRNA-1273 group was pain, reported by 3.3% of subjects. Grade 3 erythema was reported by 1.6%, and grade 3 injection site swelling by 1.3% of subjects. Grade 3 axillary (or groin) swelling or tenderness was reported for only 0.2% of subjects. No grade 4 solicited local ARs was reported in the mRNA-1273 vaccine group. The majority of the solicited local ARs in the mRNA-1273 group in Part 2 occurred within Day 1 (94.8%) to day 2 (3.6%) after any dose and persisted for a median of 3 days. Any solicited local AR persisting beyond 7 days after any injection was reported by 4.6% of subjects in the vaccine and by 2.4% of subjects in the placebo group. The most frequently reported solicited local AR persisting beyond 7 days after any injection in the mRNA-1273 group was axillary (or groin) swelling or

tenderness reported by 2.2% of subjects. Late onset solicited local ARs starting after day 7 in the mRNA-1273 group were reported by 2.7% of subjects in the mRNA-1273 vaccine group post-dose 1, but only by < 0.1% of participants post-dose 2. Late onset ARs reported after any dose were injection site swelling (0.7%) participants, injection site pain (0.5%), erythema (2.1%), and axillary (or groin) swelling or tenderness (< 0.1%). Very minor changes in the incidence of solicited local and systemic ARs in part 1 and part 2 were noted. The minor changes are due to data clearance and additional subjects with follow-up on solicited ARs post-dose 2. The changes do not alter the benefit-risk profile of Spikevax.

Solicited ARs from 6-<12-year-old participants in the 50 µg mRNA-1273 group of Study P204 were compared with solicited ARs reported from 18- to 25-year-old participants in the mRNA-1273 group (100 µg) in Part A of Study P301, a population for whom efficacy has been demonstrated. Local reactogenicity appeared to be higher in the younger age cohort 6 to <12 years of age compared with the older age cohort 18-25 years of age. Of note, the majority of local ARs was mild to moderate in both age cohorts and the incidence of severe local solicited ARs was lower in the P204 population of 6-<12 years of age compared to the older age cohort. Grade 3 solicited local ARs were reported by 5.5% of subjects 6-<12 years of age and by 11.4% of subjects 18-25 years of age. In contrast to local reactogenicity, the systemic reactogenicity tended to be lower in the younger age cohort. Fever was the only systemic solicited AR with a higher incidence in subjects 6-<12 years of age. Any fever after any dose was reported by 25.6% of subjects in P204 and by 18.1% in P301). Except for fever, solicited grade 3 systemic ARs were overall less frequent reported by participants 6-<12 years of age in Study P204 (13.1%) compared with Study P301 participants 18-25 years of age (23.5%). The incidence of unsolicited AEs up to 28 days after vaccination, including medically attended AEs, AEs leading to discontinuation from the second dose or the trial, and serious AEs were comparable. In summary, no meaningful difference could be detected with regard to the reactogenicity in the younger paediatric population 6 -<12 years of age and young adults 18 to 25 years of age.

Use of pain medication

In Part 1, the use of pain and/or fever medication for prevention and for treatment was notably higher in the 100 µg dose group compared with the 50 µg dose group. In part 2, as it can be expected, the use of pain/fever medication for treatment was notably higher in the mRNA-1273 vaccine group compared with the placebo group (approximately 2.7 fold higher post-dose 1 and approximately 5.7 fold higher post-dose 2). The proportion of participants with prophylactic use was comparable in the two groups post-dose 1 (2.1% in the placebo, and 2.7% in the vaccine group), but approximately 2 fold higher in the vaccine group (5.3%) compared with the placebo group (2.4%) post-dose 2. This appears to be plausible because of the blinded design and the higher reactogenicity in the mRNA-1273 group post-dose 1. The use of pain/fever medication for treatment in the placebo group was comparable post-dose 1 (8.7%) and post-dose 2 (8.1%), whereas it was in the vaccine group notably higher post-dose 2 (46.2%) compared with post-dose 1 (23.1%), which is explained by the higher reactogenicity of the vaccine post-dose 2.

The proportion of subjects using pain medication to prevent or to treat pain and fever in the placebo and the mRNA-1273 vaccine group was only minimal different in the 2nd IA.

Unsolicited AEs

The incidence of unsolicited AEs irrespective of causality was slightly higher in the 50 µg mRNA-1273 vaccine group compared with the 100 µg dose group. Unsolicited AEs irrespective of causality up to 28 days after any dose were reported by 30.5% of subjects in the 50 µg and by 25.9% in the 100 µg dose group. Then incidence of medically attended adverse events (MAAEs) was comparable in the 2 dose groups (11.8% versus 12.7% of subjects in the 50 µg and the 100 µg group, respectively).

In part 2, the incidence of unsolicited AEs irrespective of causality was slightly higher in the mRNA-1273 vaccine group compared with the placebo group. Unsolicited AEs irrespective of causality were reported

by 23.8% of subjects in the mRNA-1273 group and by 19.5% in the placebo group up to 28 days post-vaccination. The majority of AEs is due to the SOC of general disorders and administration site conditions. The most frequently unsolicited AEs in the mRNA-1273 group included the PTs injection site erythema (2.8%), upper respiratory tract infection (2.3%), headache (2.3%), oropharyngeal pain (2.0%), cough (1.8%), rhinorrhoea (1.7%), nasal congestion (1.6%), injection site lymphadenopathy (1.4%), injection site pain (1.2%), and fatigue (1.1%). In the placebo group, the most frequently reported unsolicited AEs were oropharyngeal pain (2.2%), nasal congestion (2.2%), COVID-19 (2.1%), upper respiratory tract infection (1.9%), headache (1.8%), rhinorrhoea (1.8%), cough (2.1%), and fatigue (1.2%). The comparison shows that unsolicited AEs experienced in the mRNA-1273 group do not notably differ in nature and incidence as those in the placebo group with the exception of an increase in the incidence of injection site conditions in the mRNA-1273 group. Medically-attended AEs were reported in 8.5% of participants in the mRNA-1273 group and by 10.1% in the placebo group

Unsolicited AEs considered being vaccine related

The vast majority of reported unsolicited AEs considered being vaccine related belong to injection site conditions and are already covered in the SmPC. After assessment of the available clinical information, No AE considered being vaccine related in part 1 is considered for inclusion into section 4.8 of the SmPC. The nature of unsolicited AEs considered being vaccine related that were provided by the MAH for part 2 does not change the safety profile of the vaccine as it has been determined for the adult population and the paediatric population 12 to <18 years of age or negatively affects the overall positive benefit-risk ratio. An imbalance was observed for the event of abdominal pain in part 2 (5 subjects [0.2%] in the mRNA-1273 vaccine group and no subject in the placebo group). Together with one AE of "abdominal pain upper" in the vaccine group, the proportion would be 6 versus 0 subjects. Similarly, there was also a trend for a slight imbalance for all unsolicited AEs (regardless of relatedness) of the PTs abdominal pain (0.6% versus 0.4%), abdominal pain upper (0.3% versus 0.1%), and abdominal pain lower (1 subject versus 0 subject). In young children, abdominal pain is generally frequent and the abdominal region is an organ onto which discomfort from other causes is often projected. Probably, the cases of abdominal pain in the vaccine group reflect the relatively high reactogenicity of the vaccine. It is acknowledged, that the majority of abdominal pain events was considered being not related by the investigator. However, the numerical imbalance, albeit small, remains. The 3:1 ratio is taken into account when considering the proportion of subjects reporting abdominal pain (0.2% versus 0%). Therefore, the event of abdominal pain should be included into the SmPC with the corresponding frequency and a footnote, explaining that this AE is only observed in the paediatric population 6-<12 years of age.
The incidence of unsolicited adverse events is comparable for males and females, both with regard to those AEs considered related to IP and to AEs irrespective of relationship.
Similarly, for seropositive vs. seronegative trial participants, the incidences of unsolicited AEs are overall comparable, with the caveat that the size of the seropositive group was fairly small.
Only minimal changes in the incidence of unsolicited AES are observed for the 2nd IA. The nature of unsolicited AEs was identical. The minor changes with regard to the incidence do not alter the benefit-risk profile of Spikevax.

Serious adverse events
As of data snapshot overall 8 SAEs were reported in part 1 and part 2 together. All SAEs occurred either in the 50 µg or the 100 µg mRNA-1273 vaccine group, none in the placebo group. None of the SAEs was considered being vaccine related by the investigator, which could be agreed upon. No events indicative of autoimmune disease, Multisystem Inflammatory Syndrome in Children, or immune thrombocytopenia were observed. Neither in Part 1 nor in Part 2 a case of myo-or pericarditis has been reported. In addition, the careful enhanced analysis of relevant PTs does not suggest any case of myo-or pericarditis. Of note, the sample size is not sufficiently large to detect rare or very rare AEs.
One 8-year-old male participant in the 50 µg dose group in Part 2 was discontinued from the trial 20 days post-dose 2 because of an event of inflammatory bowel disease (the event was moderate and did not fulfil SAE criteria). 20 days post-dose 1, he experienced a moderate treatment-emergent adverse event of inflammatory bowel disease. The boy had a past medical history of seizure disorder, headaches and occasional abdominal pain. According to the mother, he had occasional abdominal pain for many years,

but has never been worked up for diagnosis until that date. 63 days post-dose 1 additional information was received from the investigator's site noting that an endoscopy failed to indicate IBD, but did identify granulomas. Additional immunology and genetics testing revealed that the child had no immune response to previous routine vaccinations. The new possible diagnosis is Common Variable Immunodeficiency (CVID).

The number of subjects reporting PTs in the broad scope SMQ Angioedema were 3 (0.3%) in the placebo group and 16 (0.5%) in the vaccine group in Part 2, versus 5 (1.3%) subjects in the 50 µg group and 2 (0.5%) in the 100 µg group of Part 1, driven by the PT of urticaria. These rates are higher than those observed in children 12-<18, who reported such events at a rate of 0.3% in both the placebo and the vaccine arm. In conclusion, the incidence of adverse events associated with hypersensitivity appears to be slightly higher in the younger children, but are mainly driven by cutaneous reactions and seasonal allergies.

In both parts, no vaccine related SAEs or AESIs were reported in the 2nd IA.

Evaluation of myo-and pericarditis

To perform an enhanced surveillance on the events of myocarditis and pericarditis the CTP has been updated. Two overlapping approaches were used to interrogate all TEAEs. This included:

1. narrow and broad cardiomyopathy standard Medical Dictionary for Regulatory Activities queries (MedDRA SMQs)
2. an algorithm generated using MedDRA terms from Version V.23.0 implemented in the CDC working case definitions for acute myocarditis and acute pericarditis (Gargano et al. 2021)

Sites were instructed to ask the caregiver the following question: "Has your child experienced any of the following symptoms since we last spoke? Chest pain, pressure or discomfort; Shortness of breath, fast breathing at rest, or any pain with breathing; Fast-beating, fluttering or pounding heart."

Neither in Part 1 nor in Part 2 a case of myo-or pericarditis has been reported. In addition, the careful enhanced analysis of relevant PTs does not suggest any case of myo-or pericarditis. In summary, the submitted clinical data do not reveal any case of myo-or pericarditis up to the data snapshot. The sample size however is too small to finally assess the safety signal of myo-and pericarditis. The evaluation of cardiomyopathy SMQ and additional analysis of myocarditis and pericarditis performed within the 2nd analysis did not reveal a case of myo-or pericarditis in part 1 and part 2. It must be stated, that the sample size of the trial in general is still too low to detect this rare event. Myocarditis and pericarditis is a confirmed signal which cannot be excluded for this age group. Myocarditis and pericarditis is reflected in the SmPC and concerns all individuals of the indicated target population irrespective of age.

2.5.2. Conclusions on clinical safety

This type II variation aims to include children aged 6 to <12 years of age to the label of Spikevax. The database for evaluation of the safety profile of mRNA-1273 in the paediatric population 6 to <12 years of age derives from study P204. This is an ongoing Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age. The study population includes 3 age groups (6 years to < 12 years, 2 years to < 6 years, and 6 months to < 2 years). This submission focus as mentioned above on children 6 years to < 12 years of age. The open-label dose selection Part 1 is evaluating up to 3 dose levels (25, 50, and 100 µg) of mRNA-1273 in each age group. It should be noted, that the 25 µg dose was not tested in the age group 6 to < 12 years of age. The selection of the 50 µg dose of mRNA-1273 is justified by the lower local and systemic reactogenicity compared to 100 µg mRNA-1273. But still, also the 50 µg dose is reactogenic. This is reflected not only in the incidence of solicited ARs but also in the use of pain/fever medication.

The comparison of reactogenicity between 6 to < 12-year-old participants in the 50 µg mRNA-1273 group of Study P204 with 18- to 25-year-old participants in the mRNA-1273 group (100 µg) in Part A of Study P301, a population for whom efficacy was demonstrated, showed a slightly higher local reactogenicity, with a lower incidence of grade 3 local ARs. Systemic reactogenicity tended not to be higher in the younger population except for fever that was reported with a clearly higher incidence in the younger population. Unsolicited AEs irrespective of causality experienced in the mRNA-1273 group do not notably differ in nature and incidence as those in the placebo group with the exception of an increase in the incidence of injection site conditions in the mRNA-1273 group. The comparison indicates, that the reactogenicity in the population 6-<12 years of age is not clinically meaningful higher compared to young adults, when a lower dose is given, but with a different pattern of solicited AEs, e.g. more events of fever, and a slightly higher incidence of adverse events associated with hypersensitivity.

Literature indicates an increased risk of severe or critical COVID-19 disease in children less than one year of age and those with certain underlying medical conditions like e.g. congenital heart disease, and chronic pulmonary disease. The trial enrolled only individuals who are in a good health. Children with stable chronic underlying disease were allowed to be enrolled into the trial, but no conclusion on the safety profile in individuals with severe comorbidities or who are immunocompromised can be drawn.

Another imbalance was seen in the SOC of Gastrointestinal disorders (vaccine: 2.2% vs. placebo 1.6%). For the AE of abdominal pain, there was an imbalance for events considered related to vaccination and regardless of relationship. The 3:1 ratio in the 2 groups is hereby is taken into account. Therefore, an amendment with regard to section 4.8 is considered necessary. The event of abdominal pain should be included into the SmPC with the corresponding frequency and a footnote, explaining that this AE is only observed in the paediatric population 6 to 11 years of age. No events indicative of autoimmune disease, Multisystem Inflammatory Syndrome in Children, or immune thrombocytopenia were observed. Neither in Part 1 nor in Part 2 a case of myo-or pericarditis has been reported. In addition, the careful enhanced analysis of relevant PTs does not suggest any case of myo-or pericarditis. Of note, the sample size is not sufficiently large to detect rare or very rare AEs.

In summary:

Reactogenicity was in principle comparable to that seen in older children or young adults, but with a different pattern of solicited AEs, e.g. more events of fever but less events of myalgia, arthralgia or chills. With regard to unsolicited AEs, a difference in incidence (between vaccine and placebo) was noted, which was primarily driven by events in the SOC of General disorders and administration site conditions, mainly consisting of injection site reactions that persisted beyond 7 days after injection (e.g., erythema, lymphadenopathy, rash, induration or swelling at the injection site). Further, a higher incidence of hypersensitivity and cutaneous events was observed, not only vs. placebo but also compared to older children.

The data collected in the 2nd IA with data cut-off 10th November 2021 do not alter the benefit-risk profile of Spikevax when given to individuals 5 to below 12 years of age.

As this part of Study P204 is not a stand-alone MAA, but bridges to the already authorised populations, including children 12 to <18 years of age, the safety profile observed in these older age cohorts can be extrapolated to this younger age group.

This dose of 50 µg could be justified by the reactogenicity and immunogenicity data submitted within this procedure. The data base however is insufficient to detect rare events like immune disorders or the confirmed AE of pericarditis. Due to these potential risks it is nonetheless desirable to have clinical data evaluating lower doses in this age group in the future. Such analysis is planned to be conducted by the MAH. Results will not be available before the second half of 2022.

Literature reference

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID- 19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021a. MMWR Morb Mortal Wkly Rep 2021;70(27):977–982.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity Grading SSale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials. Sep 2007 [cited 2021 Oct 13]. Available from: https://www.fda.gov/media/73679/download

Law B. Safety Platform for Emergency vACcines -SO2-D2.3 Priority List of Adverse Events of Special Interest: COVID-19: Quarterly Update December 2020. 2020 December 23. [cited 2021 Oct 22]. Available from: https://brightoncollaboration.us/wpcontent/ uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020- review_final.pdf

Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. Jul 9 2021b;70(27):977- 82. doi:10.15585/mmwr.mm7027e2

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 was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

> The PRAC considered that the risk management plan version 3.0 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

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

No changes in the list of safety concerns was introduced in the updated RMP.

Pharmacovigilance plan

Study Number, Title, and Categories **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances				
Study mRNA-1273-P301 Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older Study Status: Ongoing	Evaluate long-term safety data and durability of vaccine effectiveness (VE)	Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Anaphylaxis Myocarditis Pericarditis Long-term safety	Interim CSR	15 Oct 2021
			Final CSR	31 Dec 2022
Study mRNA-1273-P203 A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age Study Status: Ongoing	Evaluate the safety, reactogenicity, and effectiveness of the vaccine	Anaphylaxis Myocarditis Pericarditis Long-term safety	Final CSR	30 Sep 2022
Study mRNA-1273-P204 Phase 2/3, two-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of mRNA-1273 administered as 2 doses 28 days apart in healthy children 6 months to less than 12 years of age	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-	Study start	15 Mar 2021
			Final CSR	31 Mar 2024

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children 6 months to less than 12 years of age Study status: Ongoing		associated enhanced respiratory disease (VAERD) Long-term safety		
Category 3 – Required pharmacovigilance activities				
Study 20-0003 Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults Study status: Ongoing	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels. IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses.	Anaphylaxis Myocarditis Pericarditis Long-term safety	Interim CSR	01 May 2021
			Final CSR (Main Study)	01 Nov 2022
Study mRNA-1273-P201 Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Confirmation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults ≥ 18 Years Study status: Ongoing	Safety and reactogenicity and immunogenicity of 2 dose levels 50 and 100 µg administered as 2 doses 28 days apart. Follow up period extended by 6 months for a total of over 12 months in those that receive vaccine/booster	Anaphylaxis Myocarditis Pericarditis	Interim CSR	01 Mar 2021
			Final CSR	Mid-Apr 2022
Study mRNA-1273-P304 A Phase 3b, Open-Label, Safety and Immunogenicity Study of SARS-CoV-2 mRNA-1273 Vaccine in Adult Solid Organ Transplant Recipients and Healthy Controls	Safety and reactogenicity and adverse events for 12 months after receiving 2 or 3 doses of SARS-CoV-2 mRNA-1273 vaccine. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.	Anaphylaxis Myocarditis Pericarditis Use in immunocompromised subjects AESI	Protocol submission	05 Feb 2021
			Interim report	31 Mar 2023
			Final CSR	31 Jan 2024

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study status: Ongoing				
Study mRNA-1273-P903 Post-Authorisation Safety of SARS-CoV-2 mRNA-1273 Vaccine in the US: Active Surveillance, Signal Refinement and Self-Controlled Risk Interval (SCRI) Signal Evaluation in HealthVerity Study status: Ongoing	Enhanced pharmacovigilance study to provide additional evaluation of AESI (including myocarditis and pericarditis) and emerging validated safety signals. The study has 3 core objectives: -Estimation of background rates for AESI and other outcomes in the cohort -Assessment of observed versus expected rates -Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety AESI and emerging validated safety signals	Protocol submission	31 Jan 2021
			Interim updates	30 Apr 2021, 31 Jul 2021, 31 Oct 2021, 31 Jan 2022, 30 Apr 2022, 31 Jul 2022, 31 Oct 2022, 31 Dec 2022
			Final study report	30 Jun 2023
Study mRNA-1273-P904 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Study status: Ongoing	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: - To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group. Secondary objective: - To assess whether vaccination with Spikevax is associated with	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety Interaction with other vaccines Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary	Protocol submission	30 Jun 2021
			Interim Updates	30 Sep 2021, 31 Mar 2022, 30 Sep 2022 31 Mar 2023,
			Final study report	31 Dec 2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	increased rates of the AESI compared with the expected rates in subpopulations of interest: women of childbearing age, patients who are immunocompromised, patients previously diagnosed with COVID-19 infection, patients with unstable health conditions and comorbidities, and patients with autoimmune or inflammatory disorders	disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders		
Study mRNA-1273-P905 Monitoring safety of COVID-19 Vaccine Moderna in pregnancy: an observational study using routinely collected health data in five European countries Study status: Planned	The overarching research question is: is there a greater risk or prevalence of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes following pregnancies exposed to Spikevax compared with pregnancies unexposed to Spikevax? Primary objectives: - To determine whether exposure to the Moderna COVID-19 vaccine during pregnancy is associated with an increased risk of: a. Pregnancy complications b. Adverse pregnancy outcomes c. Major congenital malformations in the offspring (overall and organ-specific if feasible) d. Adverse neonatal outcomes Secondary objectives: - To describe utilization of COVID-19 Vaccine Moderna in pregnancy	Use in pregnancy	Protocol submission	30 Jun 2021
			Interim updates	31 Mar 2022, 30 Sep 2022 31 Mar 2023
			Final study report	31 Dec 2023
Study mRNA-1273-P902 Moderna mRNA-1273 Observational pregnancy outcome study	Evaluate outcomes of pregnancies and birth in females exposed to mRNA-1273 vaccine during pregnancy. Evaluate infant outcomes.	Use in pregnancy and while breast-feeding	Protocol submission	31 Jan 2021
			Interim updates	31 Jul 2021, 31 Jan 2022, 31 Jul 2022, 31 Jan 2023, 31 Jul 2023, 31 Jan 2024

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study status: Ongoing			Final study report	30 Jun 2024
Study mRNA-1273-P901 Real-world study to evaluate mRNA-1273 effectiveness and long-term effectiveness in the U.S. Study Status: Ongoing	Primary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease Secondary Objectives 1. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by age and by sex 2. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis by race/ethnicity groups 3. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals with chronic diseases (e.g., chronic kidney disease, lung disease including chronic obstructive pulmonary disease [COPD] and asthma, diabetes) 4. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in individuals who are immunocompromised (e.g., HIV, cancer, transplant, immunosuppressive medications) 5. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in	Use in immunocompromised subjects Interaction with other vaccines, as possible Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders	Protocol submission	01 Mar 2021
			Interim updates	14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 14 Dec 2022; 14 Jun 2023; 14 Dec 2023
			Final study report	14 Apr 2025 Study milestones were updated due to a refinement of the initial assessment conducted during the start of the study. Interim updates were delayed by 6 weeks, and the final report was brought forward by 2 months.

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	individuals with autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus) 6. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in frail individuals 7. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis in pregnant women 8. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis among individuals with a history of COVID-19 diagnosis 9. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis when given concomitantly with another vaccine 10. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing asymptomatic COVID-19 11. To evaluate the effectiveness of 2 doses of Moderna COVID-19 vaccine in preventing symptomatic COVID-19 12. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 13. To evaluate the durability of 2 doses of Moderna COVID-19 vaccine in preventing severe COVID-19 disease			

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	14. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing COVID-19 diagnosis 15. To evaluate the effectiveness of 1 dose of Moderna COVID-19 vaccine in preventing severe COVID-19 disease.			
mRNA-1273-P910 Natural history and clinical outcomes of vaccine associated myocarditis Study status: Planned	Characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults	Myocarditis	Protocol submission	28 February 2022
			Interim report	30 Aug 2022 28 Feb 2023 30 Aug 2023 28 Feb 2024 30 Aug 2024
			Final study report	28 February 2025

Study mRNA-1273-P204 was added in the RMP as a category 2 study. This study will address the following safety concerns: Anaphylaxis, Myocarditis, Pericarditis, Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) and Long-term safety

Risk minimisation measures

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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis	Routine risk minimisation measures: SmPC Sections 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects PL Section 2 and 4 Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire to collect structured clinical details of myocarditis or myopericarditis in individuals who have received Spikevax. Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P903 (final CSR: 30 Jun 2023) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023) • Study mRNA-1273-P204 (final CSR; 31 Mar 2024) • Study mRNA-1273-P301 (final CSR: 31 Dec 2022) • Study 20-0003 (final CSR [Main Study]: 01 Nov 2022; • Study mRNA-1273-P304 (final CSR: 31 Jan 2024) • Study mRNA-1273-P203 (final CSR: 30 Sep 2022) • Study mRNA-1273-P201 (final CSR: Mid-Apr 2022) • Study mRNA-1273-P910 (final CSR: 28 February 2025)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Pericarditis	Routine risk minimisation measures: SmPC Sections 4.4 Special Warnings and Precautions for Use; 4.8 Undesirable effects; PL Section 2 and 4. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire to collect structured clinical details of pericarditis in individuals who have received Spikevax. Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P903 (final CSR: 30 Jun 2023) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023) • Study mRNA-1273-P204 (final CSR; 31 Mar 2024) • Study mRNA-1273-P301 (final CSR: 31 Dec 2022) • Study 20-0003 (final CSR [Main Study]: 01 Nov 2022; • Study mRNA-1273-P304 (final CSR: 31 Jan 2024) • Study mRNA-1273-P203 (final CSR: 30 Sep 2022) • Study mRNA-1273-P201 (final CSR: Mid-Apr 2022)
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire to collect structured clinical details of COVID-19 disease in individuals who have received Spikevax. The intent is to provide insight into potential cases of vaccine lack of effect or VAED. Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P903 (final CSR: 30 Jun 2023) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023) • Study mRNA-1273-P204 (final CSR; 31 Mar 2024) • Study mRNA-1273-P301 (final CSR: 31 Dec 2022)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnancy and while breast-feeding	Routine risk minimisation measures: SmPC Sections 4.6 Fertility, pregnancy and lactation; 5.3 Preclinical safety data; PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P905 (final CSR: 31 Dec 2023) • Study mRNA-1273-P902 (final CSR: 30 Jun 2024)
Long-term safety	Routine risk minimisation measures: None. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P903 (final CSR: 30 Jun 2023) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023) • Study mRNA-1273-P204 (final CSR; 31 Mar 2024) • Study mRNA-1273-P301 (final CSR: 31 Dec 2022) • Study 20-0003 (final CSR [Main Study]: 01 Nov 2022; Study mRNA-1273-P203 (final CSR: 30 Sep 2022)
Use in immunocompromised subjects	Routine risk minimisation measures: SmPC Section 4.4 Special Warnings and Precautions for Use; PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P901 (final CSR: 14 Apr 2025) • Study mRNA-1273-P304 (final CSR: 31 Jan 2024)
Interaction with other vaccines	Routine risk minimisation measures: SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction; PL Section 2. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities (final CSR due date): • Study mRNA-1273-P901 (final CSR: 14 Apr 2025) • Study mRNA-1273-P904 (final CSR: 31 Dec 2023)

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

No changes to the Risk minimisation measures are proposed within the updated RMP.

In addition, the MAH took the opportunity to merge editorially the version submitted in this procedure with the latest approved RMP version.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC 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 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 children above 6 years of age, SARS-CoV-2 infections cause mostly asymptomatic or mild disease. Therefore, any conclusions on the incidence of COVID-19 i.e. symptomatic infection in children have considerable uncertainty. However, severe COVID-19 cases including cases of death do occur but are mostly described in children with underlying diseases such as congenital cardiovascular disease, pulmonary disease, malignancy and hereditary syndromes. Currently there is an incomplete understanding of the burden of severe COVID-19 in the paediatric population and knowledge is evolving.

A complication of SARS-CoV-2 infection in children which is distinct from COVID-19 and likely not related to underlying disease is the so-called "paediatric inflammatory multisystem syndrome (PIM-S, also referred to as multisystem inflammatory syndrome in children, MIS-C) which has some resemblance to the Kawasaki Syndrome. PIM-S is characterised by generalised inflammatory state also involving internal organs including the heart and kidney leading to shock and organ failure. The exact incidence is currently unknown. Even though intensive care treatment is necessary in a substantial fraction of patients most patients survive the acute phase with appropriate treatment. The long-term sequelae are currently unknown.

The information of post-COVID-19 syndrome ("long COVID") in children is currently sparse.

The MAH is seeking an extension of the indication for Spikevax to children ≥6-<12 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 children aged 5 years or older 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 children. Study P204 is an ongoing Phase 2/3, 2-part, open-label, dose escalation, age de-escalation and subsequent randomized (3:1), observer-blind, placebo-controlled expansion study that evaluates the safety, reactogenicity, immunogenicity and efficacy of Spikevax in children aged ≥ 6 months to < 12 years. With this submission interim data on the ≥ 6 to <12 years age group were provided.

Vaccine efficacy is inferred based on demonstrating non-inferiority of the geometric mean value of serum Ab and the seroresponse rate from children aged ≥ 6 to <12 years 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 children ≥6 to <12 years of age without previous SARS-CoV-2 infection compared

to young adults ≥18 to <25 years. Based on these immunobridging results (GMT, GMR and seroresponse rates) efficacy can be inferred for children.

3.3. Uncertainties and limitations about favourable effects

Due to the difference seen in nAb responses in the dose selection and expanded immunogenicity set in part 1 of the study the true difference in antibody responses between children and young adults remains uncertain. The observed large discrepancy in nAb GMTs (PsVNA ID50) between 'dose-selection' and 'pivotal' cohorts casts doubt on the comparability of assay readouts between different cohorts used for dose selection and immunogenicity analysis for immunobridging and assay variability does not explain these effects alone. Further potential sources for the observed differences in nAb GMT, which likely contribute to this observation are the small sample size and lack of random selection of the serum samples.

The study plans remain rather vague and together with the observed deviations are not up to the usual standard of a confirmatory trial (e.g. the timing and sample size of key analyses, the definition of analysis sets used for the confirmation of immune bridging concerning the combination/separation of parts and age groups as well as the lack of pre-specification of the immunogenicity subset). It cannot be fully excluded that decision were made in the light of the accrued data from the open-label Part 1.

Upon request, further immunogenicity data on a larger cohort from the blinded part 2 of the study were provided by the MAH. These data support the immunogenicity results initially provided and the immunobridging results although the root cause for the divergent results could not conclusively be determined.

No data are available from children with a risk of more severe disease. Unless there is clear immunocompromise associated with the underlying disease it is expected that the vaccine protects these individuals to a similar degree.

No information is available in patients with immune suppressive therapy. A study in immunocompromised children is included in the PIP.

It is currently unknown how long protection will last in children and adults and, if vaccination provides protection against newly emerging variants. However, it is expected that the duration of protection from symptomatic disease follows the trajectory observed in adults. As the results of the requested analyses on a larger subset of children randomised in study part 2 (n=319) indicate a lower GM than initially observed it is not possible to predict whether a longer duration of protection is likely.

The impact on transmission is currently unknown.

No (immune) correlate of protection has been identified to date.

Due to the short median follow-up period of 51 days post-dose 2 and the very low number of COVID-19 cases observed no reliable vaccine efficacy data are available for the time being.

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

3.4. Unfavourable effects

Spikevax is reactogenic. The incidence of solicited local ARs (pain, axillary swelling, erythema, injection site swelling) in the Spikevax group was, as previously observed in other Spikevax clinical trials, higher post-dose 2 compared with post-dose 1. Almost all of participants in the 50 µg mRNA-1273 group of the blinded part 2 reported solicited local ARs (98.6% of subjects in the mRNA-1273 group versus 65.2% in the placebo group). The incidence of severe ARs was higher in the mRNA-1273 compared with the

placebo group. The most frequently reported grade 3 local solicited AR after any dose in the mRNA-1273 group was pain, reported by 3.3% of subjects. Grade 3 erythema was reported by 1.6%, and grade 3 injection site swelling by 1.3% of subjects. Grade 3 axillary (or groin) swelling or tenderness was reported for only 0.2% of subjects. No grade 4 solicited local ARs was reported in the mRNA-1273 vaccine group.

The most frequently reported solicited local AR persisting beyond 7 days after any injection in the mRNA-1273 group was axillary (or groin) swelling or tenderness reported by 2.2% of subjects, followed by injection site pain and injection site erythema reported by 1.4% of subjects each in the vaccine group. Persisting injection site swelling was reported by 0.9% of subjects in the vaccine group. Late onset solicited local ARs starting after day 7 in the mRNA-1273 group occurred and were reported by 2.7% of subjects in the mRNA-1273 vaccine group post-dose 1, but only by < 0.1% of participants post-dose 2. The late onset ARs reported after any dose were injection site swelling (0.7%) participants, injection site pain (0.5%), erythema (2.1%), and axillary (or groin) swelling or tenderness (< 0.1%) of participants.

Also, the incidence of solicited systemic ARs in the mRNA-1273 group was notably higher post-dose 2 compared with post-dose 1, which is in line with previous Spikevax trials. The most often reported solicited systemic AR in the mRNA-1273 group after any dose was fatigue reported by 73.0% of subjects in the mRNA-1273 versus 47.2% in the placebo group. This was followed by headache (62.0% versus 43.7%), myalgia (35.2% versus 17.3%), chills (34.6% versus 11.8), nausea (29.2% versus 17.8%), fever (25.9% versus 3.6%), and arthralgia (21.2% versus 13.4%). The most frequently reported grade 3 systemic solicited AR after any dose in the mRNA-1273 group was fatigue, reported by 7.1% of subjects. Grade 3 headache was reported by 4.4%, and grade 3 fever by 4.2%. Grade 3 myalgia was reported by 2.7% of subjects. All other solicited systemic ARs were reported by not more than 0.9% of subjects in the mRNA-1273 group after any dose. The use of pain/fever medication for treatment was notably higher in the mRNA-1273 vaccine group compared with the placebo group (approximately 2.7 fold higher post-dose 1 and approximately 5.7 fold higher post-dose 2). The use of pain/fever medication for treatment in the placebo group was comparable post-dose 1 (8.7%) and post-dose 2 (8.1%), whereas it was in the vaccine group notably higher post-dose 2 (46.2%) compared with post-dose 1 (23.1%), which is explained by the higher reactogenicity of the vaccine post-dose2.

Only very minor changes with regard to solicited systemic and local AR incidence were noted in the second interim analysis compared to the first. Upon request, the MAH confirmed that the root cause for these changes is that additional subjects having completed ≥ 7 days since second injection. Moreover, with the ongoing nature of the study additional queries were closed, and further activities regarding data cleaning were conducted, which may contribute. The minor changes in the incidence of solicited ARs do not impact the benefit-risk balance of Spikevax. The effects table (Table 42) has been updated accordingly.

Comparison of reactogenicity to participants Aged ≥ 12 to < 18 Years (n=2,485, Study P301): The AR of fever (25.9% vs. 13.7%, grade 3: 4.2% vs. 2.2%) was the only event which was clearly more common (after any injection) in younger children (6 to <12 years), compared to adolescents (≥12 to <18 years). In contrast, lower incidences were reported for the ARs of headache (62% vs. 78.4%), myalgia (35.2% vs. 54.3%), arthralgia (21.1% vs. 34.6%), chills (34.6% vs. 49.1%), swelling (22.5% vs. 27.7%), and axillary (or groin) swelling or tenderness (26.9 % vs. 34.6%). The reporting rates were comparable for the following events: fatigue (73% vs. 75.2%), nausea/vomiting (29.2% vs. 29.3%), pain (98.4% vs. 97.2%), erythema (24.3% vs. 25.8%). The data for adolescents were extracted from the EPAR.

Comparison of reactogenicity to participants Aged ≥ 18 to 25 Years (n=878, Study P301): Participants between 6-11 years had higher reporting rates for the local ARs of pain (98.2% vs. 93.5%), erythema (24.5% vs. 9.5%), swelling (22.8% vs. 14.0%), and the systemic AR of fever (25.6% vs. 18.1%, grade 3: 4.1% vs. 1.1%). In contrast, lower incidences were noted for the systemic ARs of headache (61.8%

vs. 73.8%), myalgia (34.5% vs. 63.2%), arthralgia (20.6% vs. 44.6%), nausea/vomiting (28.9% vs. 33.0%) and chills (33.6% vs. 53.6%). The incidences of fatigue (72.6% vs. 73.0%) and axillary (or groin) swelling or tenderness (26% vs. 27.9%) were very similar.

The number of subjects reporting unsolicited AEs up to 28 Days after any vaccination was higher in the mRNA-1273 group (23.8%), compared to placebo (19.5%). This difference was primarily driven by events in the SOC of General disorders and administration site conditions (vaccine: 9.0%; placebo: 3.5%), mainly consisting of injection site reactions that persisted beyond 7 days after injection (e.g., erythema, lymphadenopathy, rash, induration or swelling at the injection site).

The subject incidence of unsolicited treatment-related AEs was also higher in the mRNA-1273 group (9.8%; placebo: 3.7%). The difference was again mainly caused by injection site reactions persisting beyond day 7 after vaccination (vaccine: 7.5% vs. placebo: 2.2%). The injection site reactions are already adequately reflected in the SmPC.

Study Part 1 (dose finding): The decision to go for the lower dose is supported due to the overall milder profile of ARs, also regarding the incidence of severe ARs (see discussion of Part 1 for detailed data). However, even with the lower dose, the reactogenicity caused by the vaccine was still very pronounced. Investigating the additional (optional) 25 µg dose in study P204 would have been desirable from a safety perspective.

3.5. Uncertainties and limitations about unfavourable effects

Spikevax has been administered to a large number of adults and adolescents and the safety profile is to a large extent described by the data from the controlled trials. No meaningful difference could be detected with regard to the reactogenicity of the lower dose in the younger paediatric population 6 to <12 years of age and young adults 18 to 25 years of age.

Not unexpectedly, rare ADRs have occurred in the post-authorisation phase. The rare ADR of myocarditis and pericarditis have been described mostly in young men. The cause of myo/pericarditis remains unknown at the present point in time. The age pattern for myo/pericarditis following vaccination indicates a specific vulnerability in young males. The data on myo/pericarditis in adolescents are currently still inconclusive so it is unknown whether the vulnerable age extends to children. However, myocarditis in children is an extremely rare event and the peak observed in young adults (and potentially adolescents) may indicate a specific vulnerable phase in life for this specific condition. Neither in Part 1 nor in Part 2 a case of myo-or pericarditis has been reported. In addition, the careful enhanced analysis of relevant PTs does not suggest any case of myo-or pericarditis. Of note, the sample size is not sufficiently large to detect rare or very rare AEs.

No events indicative of autoimmune disease were observed.

The trial enrolled only individuals who were in good health. Children with stable chronic underlying disease were allowed to be enrolled into the trial, but no conclusion on the safety profile in individuals with severe comorbidities or who are immunocompromised can be drawn. It is not expected that a worse safety profile will be observed in patients with underlying disease that predisposes to severe COVID-19.

The safety database submitted within the initial submission was limited as regards follow-up time of the majority of children following the second dose, especially in Part 2 of the study. A meaningful short term follow-up (4 weeks post-dose 2) was only available for a minority of subjects, i.e. 18.8%, n=474 in this part of the trial. Therefore, the MAH was asked to provide a further safety analyses when all participants 6 to <12 years in Part 2 reach Day 57 or had discontinued the study. Upon request the MAH requested safety data for a pre-specified second interim analysis with data cut-off 10th November 2021. It should be noted, that due to EUA of a COVID-19 vaccine for this age group, unblinding and cross-over vaccinations

in part 2 of the trial started 1 November 2021, i.e. 9 days before the data cut-off date for the pre-specified second analysis. Almost all subjects had their 28 day follow-up post-dose 2 in part 1 and part 2. Less participants in part 2 have had their follow-up of 56 days post-dose 2. 1,066 (35.5%) participants in the mRNA-1273 group and 218 (21.9%) participants in the placebo group have been followed for 56 days or more after dose 2. The safety data collected in the second analysis do not alter the benefit-risk profile of Spikevax when given to individuals 6-<12 years of age.

3.6. Effects Table

Table 42 - Effects Table for Spikevax (50 µg) indicated in children 6 through 11 years of age (data cut-off: 11th November 2021)

Effect	Short Description		Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Immunogenicity			**6-<12y N=319**	**18-25y N=296**		
	GMR (nAb) (95% CI)	**1.239** (1.072, 1.432)			Non-inferiority demonstrated	
	Difference in nAb Seroresponse rate at day 57 (95% CI)	**0.1** (-1.9, 2.1)			Non-inferiority demonstrated	
Unfavourable Effects						
			50 µg	Placebo		
Any solicited local AR Grade 3 or above after dose 1	Part 2		54/3004 (1.8%)	3/993 (0.3%)	AR grade 3 and above generally of lower frequency when compared to adults receiving 100 µg	Table 14.3.1.1.1.2.1
Any solicited local AR Grade 3 or above after dose 2	Part 2		122/2988 (4.1%)	5/969 (0.5%)		Table 14.3.1.1.2.2.1
Any solicited systemic AR Grade 3 or above after dose 1	Part 2		53/3004 (1.8%)	13/993 (1.3%)		Table 14.3.1.1.1.2.1

Effect	Short Description		Treatment	Control	Uncertainties/ Strength of evidence	References
Any solicited systemic AR Grade 3 or above after dose 2	Part 2		364/2988 (12.2%) Fever Grade 3 113/2988 Headache Grade 3 119/2988	14 (1.4%)		Table 14.3.1.1.2.2.1
Unsolicited AR	Imbalance in reported abdominal pain		17/3007 (0.6%)	4/995 (0.4%)	Small difference, not observed in adults, "typical" paediatric symptom Follow-up overall still limited: 474/3007 (part 2) with >21 days follow-up after 2nd dose; 0/3007 with >56 days follow-up after 2nd dose	
Serious AE	Part 1 and 2 (50 and 100 µg)		8	0	Data cut-off 06 Oct 2021: 4 cases appendicitis, 1 orbital cellulitis, 1 foreign body, 1 palpitation, 1 viral infection (unknown virus). All SAE considered not related, no deaths reported. Data cut-off 11 Nov 2021: 5 new SAEs (in 4 participants) in the mRNA-1273 group: Type I diabetes mellitus, cellulitis left elbow, pyelonephritis, appendicitis. None of the 5 SAEs was considered being vaccine related.	

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, severe disease that has been demonstrated for Spikevax in the pivotal trials that were submitted for marketing authorisation as well as in subsequent effectiveness studies. A similar degree of the benefit of Spikevax in children aged ≥6 to <12 years can be inferred by successful immunobridging. This relates to the degree of protection, the duration of protection as well as the protection from disease caused by variants of concern where cross-neutralisation is expected (such as the Delta variant). A non-inferior immune response with respect to neutralising antibody levels and seroresponse rates is suggested by the presented data although discrepant results between the dose finding and confirmatory cohorts were observed. The root cause of the discrepant results was not conclusively identified. However, further data from a larger

number of subjects randomised in the blinded part of the study were presented that support the immunobridging approach.

Whether vaccination can prevent PIM-S is currently unknown as the pathogenesis is not understood.

The safety database overall could be sufficient. The known unfavourable effects are acceptable - even though Spikevax is reactogenic, the ADRs are only of short-term duration. The safety profile is comparable to what has been observed in adolescents and adults and no new ADR were observed. No cases of myocarditis were observed. As outlined above, myocarditis may be a phenomenon restricted to a certain age range only and therefore no reliable predictions can be made. Current data indicated that the cases of myocarditis are of short duration without sequelae.

3.7.2. Balance of benefits and risks

Even though the course of COVID-19 in children is generally milder than in the older population, there are individuals that suffer from direct consequences of the infection. The average reactogenicity profile balances well vs. average natural course; rare (more severe) AEs should be outweighed by assuming protection against the reasonably more frequent hospital and ICU admissions and severe complications to an important degree. The benefits of preventing COVID-19 with potential irreversible and long-lasting consequences could outweigh the identified risks of vaccination, especially in children at risk of severe COVID-19.

3.7.3. Additional considerations on the benefit-risk balance

Spikevax is currently authorised as a conditional marketing authorisation.

The new paediatric indication is also intended to prevent COVID-19, in response to a public health threat duly recognised by the World Health Organisation and EU.

The CHMP considers that this new indication also fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- 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.
- It is likely that the MAH will be able to provide comprehensive data.
- The MAH will continue the ongoing paediatric study mRNA-1273-P204 in order to confirm the efficacy and safety of Spikevax in this paediatric population. The MAH is therefore requested to submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P204, to confirm the efficacy of Spikevax, designated a specific obligation (**SOB**).
- Based on the presented data for this new indication, the benefits to public health of the immediate availability is considered to outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit-risk of Spikevax is positive for use in individuals aged 6 to 11 years of age.

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 children 6-11 years of age for Spikevax, based on data from study mRNA-1273-P204, an ongoing Phase 2/3, 2-part, open-label, dose-escalation, age de-escalation and subsequent randomized, observer-blind, placebo-controlled expansion study to evaluate the safety, tolerability, reactogenicity, and effectiveness of mRNA-1273 in healthy children; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. Annex II and the Package Leaflet are updated in accordance.

The CHMP adopted an updated RMP version 3.0.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex 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.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to complete the characterisation of the active substance and finished product manufacturing processes, the MAH should provide additional data.	July 2021
In order to confirm the consistency of the active substance and finished product manufacturing process (Initial and final scales), the MAH should provide additional comparability and validation data.	July 2021 Interim reports will be provided monthly

Description	Due date
	prior to this date.
In order to ensure consistent product quality, the MAH should provide additional information on stability of the active substance and finished product and review the active substance and finished product specifications following further manufacturing experience.	July 2021
In order to confirm the efficacy and safety of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P301.	December 2022
In order to confirm the efficacy and safety of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P203, including the full bioanalytical report.	30 September 2022
In order to confirm the efficacy of Spikevax, the MAH should submit the final Clinical Study Report for the randomised, placebo-controlled, observer-blind study mRNA-1273-P204.	31 March 2024

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/0041'