EMA/895850/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Spikevax

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

Procedure No. EMEA/H/C/005791/II/0067

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.

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

Table of contents

List of abbreviations

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
GMC	Geometric mean concentration
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 29 April 2022 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 immunisation of paediatric individuals from 6 months through 5 years of age based on results from the study P204 (KidCove); this is a phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomised, 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. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. The MAH also took the opportunity to implement minor editorial changes in the product information. The submission includes a revised RMP version 4.1.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet, and to the Risk Management Plan (RMP).

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

Timetable	Actual dates
Submission date	29 April 2022
Start of procedure	23 May 2022
CHMP Rapporteur Assessment Report	10 June 2022
PRAC Rapporteur Assessment Report	25 May 2022
PRAC members comments	31 May 2022
Updated PRAC Rapporteur Assessment Report	2 June 2022
PRAC Outcome	10 June 2022
CHMP members comments	11 June 2022
Updated CHMP Rapporteur Assessment Report	15 June 2022
Request for supplementary information	23 June 2022
CHMP Rapporteur Assessment Report	14 September 2022
PRAC Rapporteur Assessment Report	16 September 2022
PRAC members comments	21 September 2022
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	29 September 2022
CHMP members comments	3 October 2022
Updated CHMP Rapporteur Assessment Report	7 October 2022
Request for supplementary information	13 October 2022
Submission of responses	14 October 2022
CHMP Opinion	19 October 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

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

March 2020 a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak. According to ECDC, histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

State the claimed the therapeutic indication

The proposed indication and dosing administration for Spikevax 25 µg are:

- **Proposed indication:** Spikevax is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 months to 5 years of age.
- **Dosing administration:** Spikevax is administered as a primary series course of 2 (two) 25 microgram doses (0.1 mg/mL, 0.25 mL per dose), 1 month apart, to children 6 months to 5 years of age.

For children 6 months to 5 years of age who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, a third primary series dose at least 1 month following the second dose is recommended, aligned with similar recommendations in older age groups.

Epidemiology and risk factors, screening tools/prevention

From the start of the pandemic to March 2022, over 7.7 million cases of COVID-19 have been reported among children 0 to 4 years of age and approximately 11.4 million cases of COVID-19 have been reported among children 5 to 9 years of age in 104 countries (UNICEF 2022). The true number of cases is almost certainly much larger, as testing is not widely available in many countries. According to the Coronavirus Disease 2019 Associated Hospitalization Surveillance Network (COVID-NET 2022b), a population-based surveillance system in the US that collects data on laboratory-confirmed COVID-19-associated hospitalisations among children and adults through a network of over 250 acute-care hospitals in 14 states (COVID-NET 2022a), there were 3,606 hospitalised children between 0 to 4 years of age through 16 April 2022, with an estimated 24.1% of these children requiring ICU interventions, and with 21 related in-hospital deaths reported observed (CDC 2022a). Additionally, approximately 6% of these children required mechanical ventilation (COVID-NET 2022b).

Generally, national US data regarding children between 0 and 4 years are aligned with those identified from the COVID-NET surveillance system. Overall, in the US in the 0-to-4-year age group, there have been over 2.2 million cases of COVID-19 reported and over 465 deaths (COVID-19 Data Tracker 2022) reported to the CDC. An evaluation of COVID-19 incidence over time indicates marked increases in the 0-to-4-year age group occurring with the Delta and Omicron variant waves. The cumulative incidence of COVID-19–associated hospitalisations was 49.7 per 100,000 children and adolescents from 01 Mar 2020 through 14 Aug 2021 (Delahoy et al 2021). Prior to the Delta wave, in June 2021, there were 14.1 incidence case of COVID-19 per 100,000 population among ages 0 to 4 years. Peak incidence among 0 to 4 years was 187.0 incident cases per 100,000 population in Aug 2021 during the Delta wave, increasing to 894.6 cases per 100,000 population during the Omicron wave in Jan 2022 (COVID-19 Data Tracker 2022b).

Initial data suggest that the demographics of hospitalised patients with COVID-19 shifted to younger age groups after the onset of the Omicron wave (Goga et al 2021; United Kingdom Health Security Agency 2021; Abdullah et al 2022). During the Omicron wave, hospitalisations among those aged 0 to 17 years

rose to 46.2% when comparing the week of 01 to 07 January 2022 to the last week in December 2021. Children aged 0-4 had a dramatic three-fold increase from 4.9 to 15.6 per 100,000 children. The 7-day proportion of emergency room visits increased from 18.4% at the peak of the Delta wave to a current 7-day proportion of 31.3% among those 17 years and younger in relation to older age groups (CDC 2022d). During the Omicron variant wave, peak hospitalisations were nearly four times (7.1 per 100,000 children and adolescents) that observed during the Delta variant wave (1.8 per 100,000 children and adolescents). Hospitalisation rates among children aged 0 to 4 years were approximately five times higher during the Omicron-predominant peak period (15.6) compared with the -Delta predominant period (2.9) (response rate [RR] = 5.4; 95% confidence interval [CI] = 4.0, 7.2). Since March 2020, approximately 1 in 4 hospitalised children and adolescents with COVID-19 has required intensive care. While rates of severe disease have not increased since the start of the pandemic, the increase in absolute numbers of cases has added substantial burden overall, including the number of children requiring ICU admissions. In addition, children with underlying conditions and/or immune deficiency or immunocompromised status, as well as infants (i.e., <1 year of age), may be at higher risk for severe disease due to SARS-CoV-2 infection (Shen et al 2020; Marks et al 2022b).

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, hospitalisation 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

A distinctive manifestation of SARS-Co-V-2 in children and adolescents is development of a life-threatening hyperinflammatory state 4 to 6 weeks after infection with primary COVID-19, called multisystem inflammatory syndrome in children (MIS-C) (Vogel et al 2021). MIS-C often presents with persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock (CDC 2021d). There is also evidence of chronic sequelae known as "long-COVID-19" in children even after mild infection; this includes fatigue, muscle and joint pain, insomnia, respiratory problems, and palpitations that may be seen up to 6 months after infection (Dembiński et al 2021).

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. Neutralising antibodies are directed against it and hence it is considered a relevant target antigen for vaccine development.

Spikevax is currently indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older.

Spikevax is administered as a course of two 100 microgram doses to individuals 12 years of age and older and to children 6 through 11 years of age as a course of two 50 microgram doses, which is half of the primary dose for individuals 12 years and older. A third dose of Spikevax may be given at least 28 days after the second dose to individuals 12 years of age and older (100 micrograms) and children 6 through 11 years (50 micrograms) who are severely immunocompromised.

A booster dose of Spikevax (50µg) given at least 3 months after completion of the primary series has currently been approved for adults 18 years of age and older.

In addition, a 50 µg booster dose of Spikevax to adolescents (12 to < 18 years) at a dosing interval of at least 3 months after completion of the primary series with Spikevax (homologous boost) to prevent COVID-19 has been approved, mostly based on the extrapolation of safety, immunogenicity and efficacy data from young adults (18 to 25 years of age) to the adolescent target age group.

Within the present submission the MAH requests the use of Spikevax 25 µg for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 6 months to 5 years of age administered as a primary series of two 25 microgram doses (0.1 mg/mL, 0.25 mL per dose), 1 month apart.

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

According to the MAH, the study P204 protocol development, the paediatric study plan, and the paediatric investigation plan were extensively discussed with EMA, Health Canada, and other agencies as part of the authorisation pathway developed to expedite regulatory approval in each country. Clinical protocol and study design elements were developed in collaboration with the US National Institutes of Health.

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

Table 1: Listing of Clinical Studies: Primary vaccination with Spikevax in children aged 6 months to 5 years

Type of Study	Study Identifier (CT Identifier)/ Study Status	Primary Objective(s) of Study	Study Design	Dose, Test Product(s) Regimen Route of Administration	Number of Participants Exposed	Study Population	Type of Report Location of Study Reports
Phase 2/3							
Immunogenicity Efficacy Safety	mRNA-1273-P204 (NCT04796896)/ Ongoing	Primary Safety 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 Primary Efficacy 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	**Part 1 (6 months to <12 YOA cohort)**				
			Open-label, dose ranging, age de-escalation	100 µg of mRNA-1273 or 50 µg of mRNA 1273; 2 doses, 28 days apart; IM	6-12y: Total (n=751) 100 µg (n=371) 50 µg (n=380) 2-5y: Total (n=224) 50 µg (n=155) 25 µg (n=69) 6-24m: Total (n=150) 25 µg (n=150)	Children (male and female) 6 months to 12 years of age	• No report, data snapshot analysis included in M2.5
			Part 2 (6 months to <12 YOA cohort)				
			Randomized, observer-blind, placebo controlled	50 µg of mRNA 1273 or placebo 2 doses, 28 days apart; IM	6-12y: Total (n=4002) Placebo (n=995) 50 µg (n=3007) 2-5y: Total (n=4038) Placebo (n=1007) 25 µg (n=3031) 6-24m: Total (n=2350) Placebo (n=589) 50 µg (n=1761)	Children (male and female) 6 months to 12 years of age	• No report, data snapshot analysis included in M2.5

Clinical Trial Exposure

Seven clinical trials of mRNA-1273 are ongoing and reported below. Two of the seven studies are sponsored by DMID of NIAID and include a dose-ranging Phase 1 safety and immunogenicity study 20-0003 (Phase 1 mRNA-1273-P101) and 21-0002 to evaluate safety and immunogenicity of a SARS-CoV-2 variant mRNA1273.351 in naive and previously vaccinated adults. The remaining five studies are a dose-confirming Phase 2a safety and immunogenicity study (mRNA-1273-P201); a Phase 2/3 safety, reactogenicity, and efficacy study in healthy adolescents ages 12 to < 18 years (mRNA-1273-P203); 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 (mRNA-1273-P204); 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 (mRNA-1273-P304) and a pivotal Phase 3 efficacy, safety, and immunogenicity study (mRNA-1273-P301).

Summary of vaccination groups by dose (µg) in the ongoing studies Phase 1 (P101) 20-0003, P201 (Part A), P301 (Part A), P203, P204 (Part 1 and Part 2)

Study	Dose				
	25 µg	50 µg	100 µg	250 µg	Total
20-0003 (Phase 1 P101)	35	35	35	15	120
P201 Part A (Phase 2a)	0	200	200	0	400
P301 Part A (Phase 3)	0	0	15184	0	15184
P203 (Phase 2/3)	0	0	2486	0	2486
P204 Part 1 (Phase 2/3)[1]	219	535	371	0	1125
P204 Part 2 (Phase 2/3)[1]	4792	3007	0	0	7799

Note: Does not include DMID NIAID sponsored phase 1 study 21-0002 a Phase 1 open label study to evaluate safety and immunogenicity of prototypes and modified SARS-CoV-2 vaccines in naïve and previously vaccinated adults and mRNA-1273-P204
[1]Includes children 6 months to < 12 years of age
Source: Tables 2A-2C in Safety Summary Report Protocol 20-0003: Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults 26 October 2020; mRNA-1273-P201 (Part A) study Table 14.1.6.1 (Data extraction date: 11 June 2021); mRNA-1273-P203 study Table 1.4 (08 May 2021); mRNA-1273-P301 (Part A) study Table 14.1.6.2.1 (Data extraction date: 04 May 2021); mRNA-1273-P204 study Part 1 Table 14.1.5.1 and Part 2 Table 14.1.5.2 (Data extraction dates: 10 November 2021 and 21 February 2022).

Summary of Vaccination groups by dose (µg) in the ongoing open label studies

Study	Dose		
	50 µg	100 µg	Total
P201 Part B	173	171	344
P301 Part B	0	27832	27832
P304	0	10	10

Note: Does not include P201 Part C.
Source: mRNA-1273-P201 (Part B) study Table 14.1.1.1 Day 29 Interim Analysis (Data extraction date 11 June 2021); mRNA-1273-P304 study Data from ongoing trial as of 13 May 2021; mRNA-1273-P301 (Part B) study Table 14.1.3.2.2.2 (Data extraction date: 04 May 2021).

2.4. Clinical efficacy

2.4.1. Main study

Study mRNA-1273-P204 (hereafter Study P204) is an ongoing Phase 2/3, 3-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 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).

	Part 1			Part 2		Part 3
Age Group	mRNA-1273 25 µg	mRNA-1273 50 µg	mRNA-1273 100 µg	Selected Dose Level of mRNA-1273 From Part 1	Placebo	mRNA-1273 25 µg 2 doses of primary series +a third dose (0, 1, 5[1] months)
6 years 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)	Study Arm 14 (n = approximately 300)
2 years 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)	

Abbreviations: mRNA = messenger RNA

1. Four months post-Dose 2 ± 28 days (at least 3 months post-Dose 2)

Study mRNA-1273-P204 Design for Children 6 Months to < 6 Years

Age Group	Part 1		Part 2	
	mRNA-1273 25 µg	mRNA-1273 50 µg	Selected Dose Level of mRNA-1273 from Part 1	Placebo
2 years to < 6 years	n = 75 Enrollment completed	n = 150 Enrollment completed	n = up to 3000 Enrollment completed	n = up to 1000 Enrollment completed
6 months to < 2 years	n = 150 Enrollment completed	Not enrolled	n = up to 3000 Enrollment ongoing	n = up to 1000 Enrollment ongoing

Completed and planned enrollment numbers shown.

Vaccine effectiveness is inferred based on demonstrating noninferiority of the neutralising antibody responses compared with those obtained from young adults (≥18 to <25 years of age) enrolled in the ongoing adult study P301. Immunogenicity data from the comparator group of young adults in study P301 are based on results from the Duke University Medical Center (Part 1) and PPD Vaccine Laboratories (Part 2) performed on samples from study P301.

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 (eg, 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 (eg, 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 nonchildbearing potential may be enrolled in the study. Nonchildbearing 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) and the third dose in Part 3 (Day 149/BD-Day 1).
- 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 nonmelanoma 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).

- 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.

Treatments

In Part 1, doses of mRNA-1273 were evaluated in an open-label fashion, leading to the selection of one dose for evaluation in the larger, blinded, placebo-controlled Part 2. The older children 2 to < 6 years were enrolled to Part 1 first in order to evaluate dose levels of 25 µg and 50 µg mRNA-1273 administered as a two-dose schedule one month apart. Dose-escalation to 100-µg dose was not performed. The youngest children of 6 months to < 2 years received 25 µg of mRNA-1273 in Part 1 while no children were enrolled in the 50-µg mRNA-1273 study arm in this age group. For each of the two paediatric age groups, the selection of 25 µg was agreed for Part 2. In Part 2, participants received either 25 µg of Spikevax 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 2.

Table 2

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 (SRR) 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 noninferiority for each age group (6 years to < 12 years, 2 years 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 SRR. — For Part 3, the GM value of serum antibody level and SRR from Study P204 vaccine recipients at Day 57 compared with those from adult (≥ 18 years of age) vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301) • Seroresponse is defined as a titer change from baseline (pre-Dose 1) below the LLOQ to ≥ 4 × LLOQ, or at least a 4-fold rise if baseline is ≥ LLOQ
• To evaluate the safety of mRNA-1273 booster or third dose	• Solicited local and systemic ARs through 7 days after booster or third dose • Unsolicited AEs through 28 days after booster or third dose injection • MAAEs through the entire study period • SAEs through the entire study period • AESIs through the entire study period • AEs leading to discontinuation from study participation post-booster or post-third dose through the last day of study participation
• To infer effectiveness of the mRNA- 1273 booster or third dose by establishing noninferiority of Ab response after the booster dose or third dose compared to primary series from adult recipients of mRNA-1273 in the clinical endpoint efficacy trial (Study P301)	• GM value of post-booster (post-third dose) Ab in Study P204 as compared to post-primary series (post-Dose 2) in adults (18 to 25 years) in Study P301 • Seroresponse rate of post-booster (post-third dose) from baseline (pre-Dose 1) as compared to post-Dose 2 from baseline (pre-Dose 1) in the adults (18 to 25 years) in Study P301, using 4-fold rise definition — Seroresponse is defined as a titer change from baseline (pre Dose 1) below the LLOQ to ≥ 4 × LLOQ, or at least a 4 fold rise if baseline is ≥ LLOQ • For Part 3, the GM value and SRR of post-third dose Ab in Study P204 compared to primary series (post-Dose 2) from adults (≥ 18 years of age) in Study P301
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response to mRNA-1273 vaccine (25, 50, and 100 µg)	• 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), Day 394 (1 year after Dose 2), BD-Day 1 (at least 3 months or 6 months after Dose 2), BD-Day 29 (1 month after booster dose or third dose), BD-Day 181 (6 months after booster dose or third dose), and BD-Day 366 (1 year after booster dose or third dose)

	• 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), Day 394 (1 year after Dose 2), BD-Day 1 (at least 3 months or 6 months after Dose 2), BD-Day 29 (1 month after booster dose or third dose), BDDay 181 (6 months after booster dose or third dose), and BD-Day 366 (1 year after booster dose or third dose)
• 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) postbaseline • 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) postbaseline, OR — Positive RT-PCR postbaseline
• 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) postbaseline 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 postbaseline, 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 characterize 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)
• To evaluate immune response elicited by the primary series or booster dose or third dose of mRNA-1273 against variant(s) of interest	• GM, SRR, and GMFR of Ab against variant(s) of concern or interest

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; BD = booster dose; CDC = Center for Disease Control; COVID-19 = coronavirus disease 2019; GM = geometric mean; GMFR = geometric mean fold-rise; IgG = immunoglobin G; LLOQ = lower limit of quantification; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; mRNA = messenger RNA; nAb = neutralizing antibody; RT-PCR = reverse transcriptase polymerase

chain reaction; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate.

[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 rhinorrhea, new loss of taste or smell, sore throat, abdominal pain, diarrhea, 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 were analysed for:

- Serum nAb titer against SARS-CoV-2 as measured by pseudotyped virus neutralising assay (PsVNA).
- 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. Swabs were also collected on Day 43 from a subset of children (Cohort E).

The assays used for the immunogenicity analyses are based on both the D614G form (neutralisation) and the Wuhan-Hu-1 strain (binding).

The primary efficacy/immunogenicity objectives and endpoints are endorsed.

All serological assays are considered acceptably validated for use in the assessment of clinical samples. Of note, testing of nAb levels (PsVNA against the prototype (D614G) virus strain) was transferred from Duke University Medical Center (Part 1) to PPD Vaccine Laboratories for Part 2 (after concordance between the two PsVNAs was established), according to MAH due in part to capacity restrictions at the Duke Laboratory. The Study P301 comparator subset was retested at PPD Vaccine Laboratories to enable comparisons for analysis of Part 2. Technicians performing all PsVNAs were blinded to the associated study visits of samples at both Duke University Medical Center and PPD Vaccine Laboratories. Although the change of the test centre was not optimal, comparability is thus considered to be given. The MAH was asked to clarify whether the analysis of P204 samples and P301 samples were conducted contemporaneously at PPD or not. The MAH has confirmed that P204 and P301 samples were tested contemporaneously at PPD.

Several exploratory objectives and corresponding endpoints were defined in the protocol, and it is noted that information on VoCs causing breakthrough infections, T-cell responses and Omicron neutralisation data will only become available by Q2 2023 and will be included in the P204 interim CSR. As these data are considered as supportive, no impact on the overall conclusion is foreseen.

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.

Table 3: Case Definitions in Study mRNA-1273-P204

Endpoint	Definition
COVID-19 "CDC case definition"	At least 1 symptom from a prespecified 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. • Absence 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; COVID-19 = coronavirus disease 19; PCR = polymerase chain reaction; RT-PCR = reverse transcriptasepolymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

Source: Study P204 protocol amendment 7 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 (eg, 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 (Figure 1) 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.

Study objectives and endpoints correspond well and both are endorsed. The endpoint based on COVID-19 'P301 case definition' was not specified in protocol P304 (amendment 5).

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

Sample size

Sample size considerations for booster doses and a three dose regimen in children above 6 years of age are not covered in this section as they are not relevant to this procedure.

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 the 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 sero-response 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 sero-response rate of 85% in young adults of 18 to 25 years of age from Study P301, true sero-response 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 sero-response rate difference.

In the 1273-P203 interim analysis (data snapshot on 08 May 2021), the observed sero-response 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 to 17 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 sero-response 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 sero-response rate in children compared with 18 to 25 years of age in Study P301, at a 2-sided alpha of 0.05.

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 3:1 randomisation of subjects in Part 2 is considered acceptable. For children 6-12 years of age the MAH stated upon request 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. It is assumed that also for these age cohorts all available samples were used. The sampling itself was however not randomly done. Overall, the immunogenicity subset is not considered as fully "pre-specified".

Part 1 and Part 2 populations were independent.

Immunogenicity comparisons (primary efficacy) are essentially addressed by a single-arm trial (with comparator arm 18-24 yoa from study P301) randomisation is of secondary relevance in this regard. However, in terms of secondary/ exploratory efficacy and safety outcomes (comparison with placebo), randomisation of individuals according to pre-generated randomisation schedules to the treatment groups is considered adequate.

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

The following display of statistical methods does not cover methods for Part 3 (3-dose regimen with 25µg per dose for 6 to 12 year old children) introduced with Protocol Amendment 6 and the additional option for booster doses which was introduced with Amendment 7.

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.

Methods for analyses were defined dependent on the availability of a threshold of protection against COVID-19. As this was not the case the following display is restricted to the other case.

If no accepted serum antibody threshold of protection against COVID-19 was 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 were to be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) was to be estimated by the ratio of GLSM from the model. 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 hierarchical 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. The primary series immunogenicity co-primary endpoint hypotheses for the oldest age group (6 years to < 12 years of age) was to be tested first at alpha level of 0.05 *in Part 1 expansion*. If the testing in the oldest age group is statistically significant (meeting the non-inferiority success criteria of the co-primary endpoints), the alpha level of 0.05 will be passed to the testing of the primary series co-primary endpoint hypotheses in the middle age group (2 years to < 6 years of age) *in Part 2*. If the testing in the middle age group is statistically

significant at alpha level of 0.05, then the alpha 0.05 is preserved for testing the primary series co-primary endpoint hypotheses in the youngest age group (6 months to < 2 years of age) *in Part 2*.

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 was 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 analysis 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.

Results

Conduct of the study

The study was amended 7 times (original protocol 24 Feb 2021, amendments: 30 Apr 2021, 17 Jun 2021, 23 Jul 2021, 25 Aug 2021, 29 Sept 2021, 07 Jan 2022, 18 Feb 2022).

Timing of the Application

This submission represents a data snapshot of 21 Feb 2022. It was triggered by:

- the availability of data from Part 1 and Part 2 of Study P204
- at least 2 months post-dose 2 follow-up from over 1000 participants per age group from Part 2 who received mRNA-1273 (2180 subjects in the 2 to <6 years and 1138 subjects in the 6 months to < 2 years cohort).

Availability of the CSR is expected by Q4 2022.

Baseline data

Demographics and Baseline Characteristics (2 to < 6 Years)

Part 1: Participant demographics and baseline characteristics in the Part 1 Safety Set are shown in Table 4.

Table 4: Participant Demographics and Baseline Characteristics by Dose Level in Part 1 (Safety Set) (2 to < 6 Years)

	mRNA-1273 25 µg N = 69	mRNA-1273 50 µg N = 155	Total N = 224
Age, years			
Mean (SD)	3.6 (1.04)	3.8 (1.10)	3.7 (1.08)
Median	4.0	4.0	4.0
Min, max	2, 5	2, 5	2, 5
Age group, n (%)			
≥ 2 years and < 4 years	32 (46.4)	65 (41.9)	97 (43.3)
≥ 4 years and < 6 years	37 (53.6)	90 (58.1)	127 (56.7)
≥ 2 years and ≤ 36 months	9 (13.0)	26 (16.8)	35 (15.6)
> 36 months and < 6 years	60 (87.0)	129 (83.2)	189 (84.4)
Age (years), n (%)			
2	11 (15.9)	25 (16.1)	36 (16.1)
3	21 (30.4)	40 (25.8)	61 (27.2)
4	19 (27.5)	35 (22.6)	54 (24.1)
5	18 (26.1)	55 (35.5)	73 (32.6)
Sex, n (%)			
Male	36 (52.2)	80 (51.6)	116 (51.8)
Female	33 (47.8)	75 (48.4)	108 (48.2)
Race, n (%)			
White	49 (71.0)	133 (85.8)	182 (81.3)
Black	3 (4.3)	7 (4.5)	10 (4.5)
Asian	8 (11.6)	3 (1.9)	11 (4.9)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	3 (4.3)	10 (6.5)	13 (5.8)
Other	6 (8.7)	2 (1.3)	8 (3.6)
Not reported	0	0	0
Unknown	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	18 (26.1)	23 (14.8)	41 (18.3)
Not Hispanic or Latino	51 (73.9)	129 (83.2)	180 (80.4)
Not reported	0	3 (1.9)	3 (1.3)
Unknown	0	0	0
Race and ethnicity group[a], n (%)			
White non-Hispanic	36 (52.2)	113 (72.9)	149 (66.5)
Communities of Color	33 (47.8)	42 (27.1)	75 (33.5)
Weight, kg			
Mean (SD)	17.96 (4.574)	18.22 (4.218)	18.14 (4.322)
Median	17.14	17.60	17.19

Min, max	11.3, 38.6	10.5, 39.7	10.5, 39.7
Baseline SARS-CoV-2 status[b], n (%)			
Negative	64 (92.8)	147 (94.8)	211 (94.2)
Positive	5 (7.2)	6 (3.9)	11 (4.9)
Missing	0	2 (1.3)	2 (0.9)

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 Part 1 Safety Set.

[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 (2 to < 6 years): Study P204 Table 14.1.3.1.1

Part 2: Participant demographics and baseline characteristics in the mRNA-1273 group and placebo group in the Safety Set are presented in Table 5.

Table 5: Participant Demographics and Baseline Characteristics in Part 2 (Safety Set) (2 to < 6 Years)

	Placebo N = 1007	**mRNA-1273 25 µg N = 3031**	**Total N = 4038**
Age, years			
Mean (SD)	3.0 (0.89)	3.0 (0.88)	3.0 (0.88)
Median	3.0	3.0	3.0
Min, max[a]	1, 5	1, 5	1, 5
Age group, n (%)			
< 2 years[a]	12 (1.2)	24 (0.8)	36 (0.9)
≥ 2 years and < 4 years	655 (65.0)	2057 (67.9)	2712 (67.2)
≥ 4 years and < 6 years	340 (33.8)	950 (31.3)	1290 (31.9)
≥ 2 years and ≤ 36 months	345 (34.3)	999 (33.0)	1344 (33.3)
> 36 months and < 6 years	662 (65.7)	2032 (67.0)	2694 (66.7)
Age (years), n (%)			
< 2[a]	12 (1.2)	24 (0.8)	36 (0.9)
2	315 (31.3)	933 (30.8)	1248 (30.9)
3	340 (33.8)	1124 (37.1)	1464 (36.3)
4	308 (30.6)	833 (27.5)	1141 (28.3)
5	32 (3.2)	117 (3.9)	149 (3.7)
Sex, n (%)			
Male	510 (50.6)	1543 (50.9)	2053 (50.8)
Female	497 (49.4)	1488 (49.1)	1985 (49.2)
Race, n (%)			
White	792 (78.6)	2297 (75.8)	3089 (76.5)
Black	38 (3.8)	142 (4.7)	180 (4.5)
Asian	51 (5.1)	191 (6.3)	242 (6.0)
American Indian or Alaska Native	3 (0.3)	12 (0.4)	15 (0.4)
Native Hawaiian or other Pacific Islander	4 (0.4)	7 (0.2)	11 (0.3)
Multiracial	99 (9.8)	322 (10.6)	421 (10.4)
Other	16 (1.6)	43 (1.4)	59 (1.5)
Not reported	4 (0.4)	13 (0.4)	17 (0.4)
Unknown	0	4 (0.1)	4 (0.1)
Ethnicity, n (%)			
Hispanic or Latino	142 (14.1)	433 (14.3)	575 (14.2)
Not Hispanic or Latino	856 (85.0)	2579 (85.1)	3435 (85.1)

Not reported	8 (0.8)	14 (0.5)	22 (0.5)
Unknown	1 (0.1)	5 (0.2)	6 (0.1)
Race and ethnicity group[b], n (%)			
White non-Hispanic	678 (67.3)	1975 (65.2)	2653 (65.7)
Communities of Color	327 (32.5)	1054 (34.8)	1381 (34.2)
Missing	2 (0.2)	2 (< 0.1)	4 (0.1)
Weight, kg			
Mean (SD)	16.02 (2.974)	16.13 (3.201)	16.10 (3.146)
Median	15.64	15.73	15.70
Min, max	9.6, 44.4	7.0, 56.9	7.0, 56.9
Baseline SARS-CoV-2 Status[c], n (%)			
Negative	898 (89.2)	2695 (88.9)	3593 (89.0)
Positive	82 (8.1)	266 (8.8)	348 (8.6)
Missing	27 (2.7)	70 (2.3)	97 (2.4)

Abbreviations: COVID-19 = coronavirus disease 2019; IRT = interactive response technology; 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 Part 2 Safety Set. a Some participants < 2 years were included in the ≥ 2 to 6 year subgroup, likely because of coincident enrollment of both age groups, entry errors at the time of randomization and other limitations of the IRT system. 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 (2 to < 6 years): Study P204 Table 14.1.3.2

Participant demographics and baseline characteristics in the mRNA-1273 group in the Part 2 PP Immunogenicity Subset are shown in Table 6.

Table 6: Participant Demographics and Baseline Characteristics in Part 2 (Per Protocol Immunogenicity Subset) (2 to < 6 Years)

	mRNA-1273 25 µg (N = 264)
Age, years	
Mean (SD)	3.3 (0.95)
Median	3.0
Min, max	2, 5
Age group, n (%)	
< 2 years	0
≥ 2 years and < 4 years	158 (59.8)
≥ 4 years and < 6 years	106 (40.2)
≥ 2 years and ≤ 36 months	69 (26.1)
> 36 months and < 6 years	195 (73.9)
Age (years), n (%)	
< 2	0
2	64 (24.2)
3	94 (35.6)
4	77 (29.2)
5	29 (11.0)
Sex, n (%)	
Male	141 (53.4)
Female	123 (46.6)
Race, n (%)	
White	188 (71.2)
Black	20 (7.6)
Asian	16 (6.1)
American Indian or Alaska Native	1 (0.4)
Native Hawaiian or other Pacific Islander	0
Multiracial	34 (12.9)
Other	2 (0.8)
Not reported	2 (0.8)
Missing	1 (0.4)
Ethnicity, n (%)	
Hispanic or Latino	47 (17.8)
Not Hispanic or Latino	217 (82.2)
Race and ethnicity group[a], n (%)	
White non-Hispanic	152 (57.6)
Communities of Color	112 (42.4)
Weight, kg	
Mean (SD)	16.50 (3.096)
Median	16.09
Min, max	10.7, 34.8

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Part 1 Per Protocol Immunogenicity Subset.
[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.
Source (2 to < 6 years): Study P204 Table 14.1.3.3.2

Demographics and Baseline Characteristics (6 Months to < 2 Years)

Participant demographics and baseline characteristics in the Part 1 Safety Set are presented in Table 7.

Table 7: Participant Demographics and Baseline Characteristics by Dose Level in Part 1 (Safety Set) (6 Months to < 2 Years)

	mRNA-1273 25 µg N = 150
Age, years	
Mean (SD)	0.9 (0.13)
Median	1.0
Min, max	1, 1
Age group, n (%)	
≥ 6 months and < 1 year	37 (24.7)
≥ 1 year and < 2 years	113 (75.3)
Sex, n (%)	
Male	83 (55.3)
Female	67 (44.7)
Race, n (%)	
White	125 (83.3)
Black	3 (2.0)
Asian	7 (4.7)
American Indian or Alaska Native	1 (0.7)
Native Hawaiian or other Pacific Islander	0
Multiracial	10 (6.7)
Other	3 (2.0)
Not reported	0
Unknown	1 (0.7)
Ethnicity, n (%)	
Hispanic or Latino	15 (10.0)
Not Hispanic or Latino	134 (89.3)
Not reported	0
Unknown	1 (0.7)
Race and ethnicity group[a], n (%)	
White non-Hispanic	112 (74.7)
Communities of Color	37 (24.7)
Missing	1 (0.7)
Weight, kg	
Mean (SD)	10.78 (1.996)
Median	10.76
Min, max	6.6, 19.5
Baseline SARS-CoV-2 status[b], n (%)	
Negative	141 (94.0)
Positive	7 (4.7)
Missing	2 (1.3)

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 Part 1 Safety Set.

[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 (6 months to < 2 years): Study P204 Table 14.1.3.1.1

Participant demographics and baseline characteristics in the mRNA-1273 group and placebo group in the Part 2 Safety Set are shown in Table 8.

Table 8: Participant Demographics and Baseline Characteristics in Part 2 (Safety Set) (6 Months to < 2 Years)

	Placebo N = 589	mRNA-1273 25 µg N = 1761	Total N = 2350
Age, years			
Mean (SD)	0.9 (0.16)	0.9 (0.20)	0.9 (0.19)
Median	1.0	1.0	1.0
Min, max[a]	1, 2	1, 4	1, 4
Age group, n (%)			
≥ 6 months and < 1 year	124 (21.1)	375 (21.3)	499 (21.2)
≥ 1 year and < 2 years	462 (78.4)	1373 (78.0)	1835 (78.1)
≥ 2 years[a]	3 (0.5)	13 (0.7)	16 (0.7)
Sex, n (%)			
Male	290 (49.2)	910 (51.7)	1200 (51.1)
Female	299 (50.8)	851 (48.3)	1150 (48.9)
Race, n (%)			
White	466 (79.1)	1390 (78.9)	1856 (79.0)
Black	16 (2.7)	57 (3.2)	73 (3.1)
Asian	35 (5.9)	79 (4.5)	114 (4.9)
American Indian or Alaska Native	0	4 (0.2)	4 (0.2)
Native Hawaiian or other Pacific Islander	0	0	0
Multiracial	64 (10.9)	186 (10.6)	250 (10.6)
Other	5 (0.8)	31 (1.8)	36 (1.5)
Not reported	2 (0.3)	9 (0.5)	11 (0.5)
Unknown	1 (0.2)	5 (0.3)	6 (0.3)
Ethnicity, n (%)			
Hispanic or Latino	84 (14.3)	227 (12.9)	311 (13.2)
Not Hispanic or Latino	498 (84.6)	1517 (86.1)	2015 (85.7)
Not reported	6 (1.0)	15 (0.9)	21 (0.9)
Unknown	1 (0.2)	2 (0.1)	3 (0.1)
Race and ethnicity group[b], n (%)			
White non-Hispanic	393 (66.7)	1221 (69.3)	1614 (68.7)
Communities of Color	194 (32.9)	538 (30.6)	732 (31.1)
Missing	2 (0.3)	2 (0.1)	4 (0.2)
Weight, kg			
Mean (SD)	10.88 (2.089)	10.88 (2.053)	10.88 (2.062)
Median	10.80	10.80	10.80
Min, max	1.1, 27.4	5.0, 29.3	1.1, 29.3
Baseline SARS-CoV-2 status[c], n (%)			
Negative	530 (90.0)	1575 (89.4)	2105 (89.6)
Positive	38 (6.5)	106 (6.0)	144 (6.1)
Missing	21 (3.6)	80 (4.5)	101 (4.3)

Abbreviations: COVID-19 = coronavirus disease 2019; IRT = interactive response technology; 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 Part 2 Safety Set.

[a] Some participants ≥ 2 years were included in the 6 months to < 2-year subgroup, likely because of coincident enrollment of both age groups, entry errors at the time of randomization and other limitations of the IRT system.

[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 (6 months to < 2 years): Study P204 Table 14.1.3.2

Participant demographics and baseline characteristics in the mRNA-1273 group in the Part 2 PP Immunogenicity Subset are presented in Table 9.

Table 9: Participant Demographics and Baseline Characteristics in Part 2 (Per Protocol Immunogenicity Subset) (6 Months to < 2 Years)

	mRNA-1273 25 µg N = 230
Age, years	
Mean (SD)	11.5 (1.31)
Median	12.0
Min, max	6, 12
Age group, n (%)	
≥ 6 months and < 1 year	42 (18.3)
≥ 1 year and < 2 years	188 (81.7)
≥ 2 years[a]	0
Sex, n (%)	
Male	110 (47.8)
Female	120 (52.2)
Race, n (%)	
White	173 (75.2)
Black	12 (5.2)
Asian	12 (5.2)
American Indian or Alaska Native	1 (0.4)
Native Hawaiian or other Pacific Islander	0
Multiracial	24 (10.4)
Other	8 (3.5)
Not reported	0
Missing	0
Ethnicity, n (%)	
Hispanic or Latino	39 (17.0)
Not Hispanic or Latino	189 (82.2)
Not reported	2 (0.9)
Unknown	0
Race and ethnicity group[a], n (%)	
White non-Hispanic	143 (62.2)
Communities of Color	87 (37.8)
Weight, kg	
Mean (SD)	11.20 (2.522)
Median	11.00
Min, max	7.0, 29.3

Abbreviations: max = maximum; min = minimum; SD = standard deviation.
Percentages are based on the number of participants in the Part 1 Per Protocol Immunogenicity Subset.
[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.
Source (6 months to < 2 years): Study P204 Table 14.1.3.3.2

Numbers analysed

Study Populations (2 to < 6 Years)

The number of participants in each analysis set for Part 1 and reasons for exclusions from the Part 1 PP Immunogenicity Subset are presented in Table 10.

Table 10: Number of Participants in Each Analysis Set by Dose Level in Part 1 (FAS) (2 to < 6 Years)

	mRNA-1273 25 µg	mRNA-1273 50 µg
Part 1 FAS[a], n	75	149
Part 1 Immunogenicity Subset[b], n	53	70
Part 1 PP Immunogenicity Subset[b], n (%)	50 (94.3)	69 (98.6)
Excluded from Part 1 PP Immunogenicity Subset	3 (5.7)	1 (1.4)
Reason for exclusion[c], n (%)		
Positive baseline SARS-CoV-2 status	3 (5.7)	1 (1.4)
Part 1 Safety Set[d], n	69	155
Part 1 Solicited Safety Set[d], n (%)	69 (100)	154 (99.4)
Part 1 First Injection Solicited Safety Set	69 (100)	152 (98.1)
Part 1 Second Injection Solicited Safety Set	69 (100)	154 (99.4)

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 Part 1 Immunogenicity Subset.

[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 (2 to < 6 years): Study P204 Table 14.1.2.1.1.1 and Study P204 Table 14.1.2.3.1

The number of participants in each analysis set for Part 2 and reasons for exclusion are provided in Table 11. Part 2 Immunogenicity Subset represents a subset of Part 2 full analysis set participants (n=302 mRNA-1273 recipients; Part 2 Immunogenicity Subset). Of the 302 participants in the Immunogenicity Subset, 264 (87.4%) met the criteria to be included in the Part 2 PP Immunogenicity Subset.

Table 11: Number of Participants in Each Analysis Set by Treatment Group in Part 2 (Randomisation Set) (2 to < 6 Years)

	Placebo	mRNA-1273 25 µg
Part 2 Randomization Set[a], n	1008	3040
Part 2 FAS[a], n (%)	1007 (99.9)	3031 (99.7)
Part 2 Immunogenicity Subset[a], n	NA[d]	302
Part 2 PP Immunogenicity Subset[a], n (%)	NA[d]	264 (87.4)
Excluded from Part 2 PP Immunogenicity Subset, n (%)		38 (12.6)
Reason for exclusion[b], n (%)		
Positive baseline SARS-CoV-2 status		21 (7.0)
Did not receive dose 2 per schedule		1 (0.3)
Received dose 2 out of window		2 (0.7)
Had no immunogenicity data at Day 57		13 (4.3)
Age outside the randomized age group		1 (0.3)
Part 2 PP Set for Efficacy[a], n (%)	858 (85.1)	2594 (85.3)
Excluded from PP Set for Efficacy, n (%)	150 (14.9)	446 (14.7)
Reason for exclusion[b], n (%)		
Randomized but not dosed	1 (0.1)	9 (0.3)
Baseline SARS-CoV-2 status positive or missing	109 (10.8)	336 (11.1)
Discontinued study treatment or participation without receiving dose 2	17 (1.7)	16 (0.5)
Did not receive dose 2 and passed window	10 (1.0)	37 (1.2)
Received incorrect vaccination	0	1 (< 0.1)
Received dose 2 out of window	13 (1.3)	47 (1.5)
Had other major protocol deviations	0	0
Part 2 mITT[a], n (%)	898 (89.1)	2695 (88.7)
Part 2 mITT1[a], n (%)	898 (89.1)	2693 (88.6)
Part 2 Safety Set[c], n	1007	3031
Part 2 Solicited Safety Set[c], n (%)	997 (99.0)	3016 (99.5)
Part 2 First Injection Solicited Safety Set	970 (96.3)	2957 (97.6)
Part 2 Second Injection Solicited Safety Set	959 (95.2)	2938 (96.9)

Abbreviations: FAS = full analysis set; mITT = modified intent-to-treat; NA = not applicable; 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.

[d] Placebo samples were not tested.

Source (2 to < 6 years): Study P204 Table 14.1.2.1.2.1, Study P204 Table 14.1.2.3.2, and Study P204 Table 14.1.2.5

Study Populations (6 Months to < 2 Years)

The number of participants in each analysis set for Part 1 referenced in this document and reasons for exclusions from the Part 1 PP Immunogenicity Subset are presented in Table 12.

Table 12: Number of Participants in Each Analysis Set by Dose Level in Part 1 (FAS) (6 Months to < 2 Years)

	mRNA-1273 25 µg
Part 1 FAS[a], n	150
Part 1 Immunogenicity Subset[b], n	102
Part 1 PP Immunogenicity Subset[b], n (%)	98 (96.1)
Excluded from Part 1 PP Immunogenicity Subset, n (%)	4 (3.9)
Reason for exclusion[c], n (%)	
Positive baseline SARS-CoV-2 status	4 (3.9)
Part 1 Safety Set[d], n	150
Part 1 Solicited Safety Set[d], n (%)	150 (100)
Part 1 First Injection Solicited Safety Set	149 (99.3)
Part 1 Second Injection Solicited Safety Set	150 (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 Part 1 Immunogenicity Subset.

[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 (6 months to < 2 years): Study P204 Table 14.1.2.1.1.1 and Study P204 Table 14.1.2.3.1

The number of participants in each analysis set for Part 2 and reasons for exclusion are provided in Table 13. A subset of Part 2 full analysis set participants (Part 2 Immunogenicity Subset) was selected for measuring immunogenicity data. Among the participants enrolled in Part 2 with immunogenicity samples selected for the Part 2 Immunogenicity Subset, 274 participants were in the mRNA-1273 arm. Of the 274 participants, 230 (83.9%) met the criteria to be included in the Part 2 PP Immunogenicity Subset.

Table 13: Number of Participants in Each Analysis Set by Treatment Group in Part 2 (Randomisation Set) (6 Months to < 2 Years)

	Placebo	mRNA-1273 25 µg
Part 2 Randomization Set[a], n	593	1762
Part 2 FAS[a], n (%)	590 (99.5)	1760 (99.9)
Part 2 Immunogenicity Subset[a], n	NA[d]	274
Part 2 PP Immunogenicity Subset[a]	NA[d]	230 (83.9)
Excluded from Part 2 PP Immunogenicity Subset, n (%)		44 (16.1)
Reason for exclusion[b], n (%)		
Positive baseline SARS-CoV-2 status		15 (5.5)
Received dose 2 out of window		2 (0.7)
Had no immunogenicity data at Day 57		25 (9.1)
Age outside of the randomized age group		2 (0.7)
Part 2 PP Set for Efficacy[a], n (%)	513 (86.5)	1511 (85.8)
Excluded from PP Set for Efficacy, n (%)	80 (13.5)	251 (14.2)
Reason for exclusion[b], n (%)		
Randomized but not dosed	3 (0.5)	2 (0.1)
Baseline SARS-CoV-2 status positive or missing	59 (9.9)	186 (10.6)
Discontinued study treatment or participation without receiving dose 2	5 (0.8)	4 (0.2)
Did not receive dose 2 and passed window	7 (1.2)	21 (1.2)
Received incorrect vaccination	1 (0.2)	0
Received dose 2 out of window	5 (0.8)	37 (2.1)
Had other major protocol deviations	0	1 (< 0.1)
Part 2 mITT[a], n (%)	531 (89.5)	1574 (89.3)
Part 2 mITT1[a], n (%)	530 (89.4)	1574 (89.3)
Part 2 Safety Set[c], n	589	1761
Part 2 Solicited Safety Set[c], n (%)	585 (99.3)	1758 (99.8)
Part 2 First Injection Solicited Safety Set	582 (98.8)	1746 (99.1)
Part 2 Second Injection Solicited Safety Set	526 (89.3)	1596 (90.6)

Abbreviations: FAS = full analysis set; mITT = modified intent-to-treat; NA = not applicable; 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.

[d] Placebo samples were not tested.

Source (6 months to < 2 years): Study P204 Table 14.1.2.1.2.1, Study P204 Table 14.1.2.3.2, and Study P204 Table 14.1.2.5

Outcomes and estimation

Immunogenicity

Study mRNA-1273-P204 Design for Children 6 Months to <6 years

The MAH submitted data showing the evaluation of children 6 months to < 2 years and 2 to < 6 years of age (snapshot data on 21 Feb 2022).

For each of the 2 younger age groups, children were enrolled first to Part 1 for dose selection and subsequently to Part 2. Part 1 evaluated dosages of mRNA-1273 in an open-label fashion and led to the selection of a dosage for evaluation in the larger, blinded, placebo-controlled Part 2. As the study followed a pattern of age de-escalation, the older children (2 to < 6 years) were enrolled to Part 1 (to evaluate dose levels of 25 µg and 50 µg administered as a two-dose schedule one month apart) prior to younger children (6 months to < 2 years).

Assessment of the 50-µg dose (n=150 enrolled) in the 2 to < 6-year group indicated a rate of fever similar to that after the 100-µg dose in the older age group (6 to < 12 years). Accordingly, a lower dose

(25 µg) was evaluated in a group of 2 to < 6-year-old children in Part 1, a dose that proved less reactogenic than 2 injections of 50 µg of mRNA-1273.
The youngest children (6 months to < 2 years) received 25 µg of mRNA-1273 in Part 1. No children were enrolled in the 50-µg mRNA-1273 study arm in children 6 months to < 2 years of age.

For the submission for extension of the indication to children (6 months to <6 years), mRNA-1273 effectiveness is inferred based on meeting pre-specified non-inferiority criteria for immunobridging to young adults (18 to 25 years) in the pivotal P301 study, which established the clinical efficacy of mRNA-1273.

Vaccine Immunogenicity

Immunogenicity data from Study P204 are described, first for children 2 to <6 years and then for infants 6 months to <2 years. Where applicable, data are presented first for Part 1 and then for Part 2 for each age group.
The immunogenicity analysis from Part 2 serves as the basis for the demonstration of vaccine effectiveness in support of EUA. Results of neutralising antibody (nAb; measured by PsVNA) are provided by the MAH.

The protocol stated that the primary immunogenicity objective of Study P204 is to infer the effectiveness of mRNA-1273 based on the primary endpoint as follows:

- If an acceptable threshold of protection has been established, the proportion of participants with a serum Ab level at Day 57 that is greater than or equal to Ab threshold of protection
- If an acceptable threshold of protection has not been established, the geometric mean (GM) value of serum Ab 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)

Day 57 (1 month after the second dose) was chosen for the timepoint of immunogenicity analysis because Abs tend to peak approximately 28 days after vaccination. This timepoint was used for immunogenicity in the pivotal adult study (Study P301) in which the VE has been established. This timepoint was also used for immunobridging in the adolescent and older paediatric populations (Study P203).

At the time of analysis for this submission, a serum antibody threshold of vaccine protection against COVID-19 had not been established. Therefore, the primary objective to infer the effectiveness of mRNA-1273 was evaluated by comparing the GM value of serum antibody level and seroresponse rates from Study P204 vaccine recipients at Day 57 to those obtained from young adult (18 to 25 years of age) vaccine recipients (Day 57) in the pivotal study (Study P301), which established the efficacy of mRNA-1273.

Part 1 PP Immunogenicity Subset (2 to < 6 Years)

The immunogenicity results from the Part 1 PP Immunogenicity Subset for the 25-µg (n=50) and the 50-µg (n=69) groups in children 2 to < 6 years of age are presented.

Day 57 (28 days post-dose 2) nAb results for children 2 to < 6 years were compared with previously generated results from the PP Immunogenicity Subset of 18- to 25-year-old participants in Study P301.

Part 1 recipients of 25 µg (n=50) had a nAb GMT of 1013.766 (Table 16) with 100% achieving seroresponse. Comparison of this GMT to that of young adults in Study P301 (18 to 25 years; n = 295) yielded a GMR of 0.78 (95% CI 0.61, 1.00) and a difference in seroresponse rates (SRR) of 1.0% (95% CI: -6.1%, 3.0%).

Part 1 recipients of 50 µg (n=69) had a nAb GMT of 1844.127 (Table 16) with 100% achieving seroresponse. Comparison of this GMT to that of the P301 young adults yielded a GMR of 1.42 (95% CI 1.14, 1.77) and a difference in SRR of 1.0% (95% CI: -4.3%, 3.0%).

Part 1 Analysis of Day 57 nAb Level and Seroresponse Rate by Pseudovirus Neutralization Assay (ID_{50}) (Part 1 PP Immunogenicity Subset) (2 to < 6 Years)

	Study P204 2 to < 6 Years mRNA-1273 25 µg N = 50	Study P204 2 to < 6 Years mRNA-1273 50 µg N = 69	Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N = 295
Baseline GMT	9.250	9.250	9.285
GMT observed at Day 57	1013.766	1844.127	1299.855
GMFR (95% CI)[a] at Day 57 from baseline	109.596 (91.479, 131.301)	199.365 (173.226, 229.449)	139.990 (126.103, 155.405)
GMT (model based) (95% CI) at Day 57	1013.766 (803.087, 1279.714)	1844.127 (1512.393, 2248.625)	1299.855 (1180.977, 1430.698)
GMR (P204 vs P301; model based) (95% CI)[b]	0.780 (0.606, 1.003)	1.419 (1.138, 1.768)	NA
Participants achieving seroresponse, n (%)[c] at Day 57	50/50 (100)	69/69 (100)	292/295 (99.0)
95% CI[d]	(92.9, 100.0)	(94.8, 100.0)	(97.1, 99.8)
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	1.0 (-6.1, 3.0)	1.0 (-4.3, 3.0)	NA

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMFR = geometric mean fold rise; 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.

Based on PsVNA by Duke University Medical Center Laboratory.

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 to 25 years of age).

[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 analyzed 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 (2 to < 6 years): Study P204 Table 14.2.1.1.3.1.1, Study P204 Table 14.2.1.2.3.1.1, and Study P204 Table 14.2.3.1.1.1

Part 2 PP Immunogenicity Subset (2 to < 6 Years)

The Part 2 PP Immunogenicity Subset was the pre-specified cohort for the assessment of the primary immunogenicity objective.
Table 13 summarises the analysis of Day 57 serum nAb levels (measured by PsVNA ID50 assay) for children 2 to < 6 years of age in the Part 2 PP Immunogenicity Subset, which are also depicted in *Figure 1* and the comparison with those from young adults (18 to 25 years of age) in Study P301.
In the Part 2 PP Immunogenicity Subset (n = 264; 25 µg) baseline nAb GMC was below the LLOQ; Day 57 GMC was 1410.0 (95% CI: 1272.02, 1562.98) and 98.9% achieved sero-response. Sero-response 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. The geometric mean fold rise (GMFR) from baseline to Day 57 was 183.3 (95% CI: 164.03, 204.91).

The pre-specified success criteria for the primary immunogenicity objective were met thus enabling the inference of vaccine effectiveness from Study P301.

The GMR of Day 57 nAb concentration from children 2 to < 6 years of age in Part 2 PP Immunogenicity Subset compared to Study P301 young adults 18 to 25 years was 1.014 (95% CI: 0.881, 1.167), meeting the non-inferiority success criterion (ie, lower bound of the 95% CI for GMR ≥ 0.67); the GMR point estimate criterion (≥ 0.8) was also met. The difference in sero-response rates (SRR) between the 2 immunobridging groups was -0.4% (95% CI: -2.7%, 1.5%), also meeting the non-inferiority success criterion (lower bound of the 95% CI of the SRR difference > -10%). Therefore, the pre-specified success criteria for the primary immunogenicity objective were met.

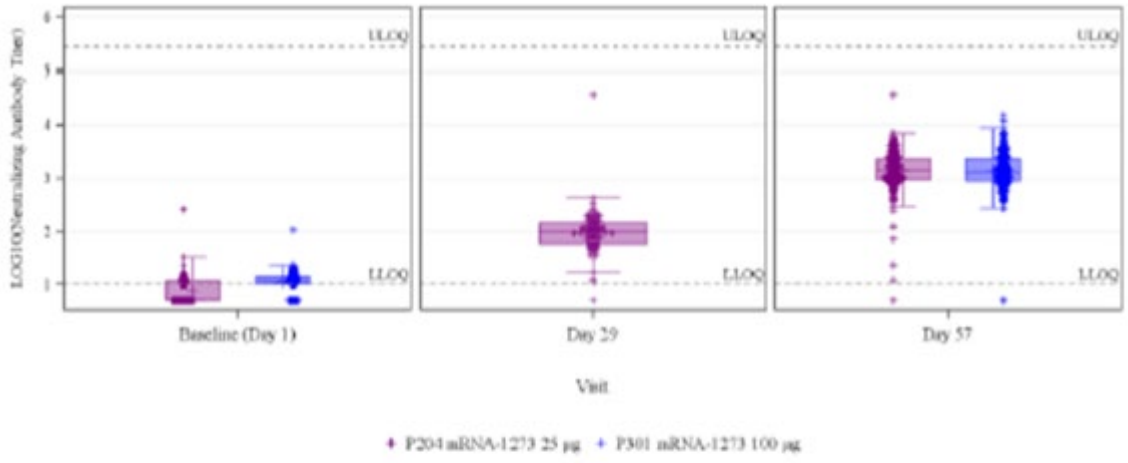
Table 14: Co-primary Immunobridging (Pseudovirus Neutralising Antibody Level) (Part 2 PPI Immunogenicity Subset) (2 to <6 Years)

	Study P204 2 to < 6 Years mRNA-1273 25 µg N = 264	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N = 295**
Baseline GMC	7.7	11.1
GMC observed at Day 57	n = 264 1410.0	n = 291 1390.8
GMFR (95% CI)[a] at Day 57 from baseline	183.3 (164.03, 204.91)	125.8 (112.99, 139.96)
GMC (95% CI) at Day 57	1410.015 (1273.782, 1560.820)	1390.781 (1262.487, 1532.113)
GMR (P204 Part 2 vs P301; model based) (95% CI)[b]	1.014 (0.881, 1.167)	
Participants achieving seroresponse, n (%)[c] at Day 57	261/264 (98.9)	289/291 (99.3)
95% CI[d]	96.7, 99.8	97.5, 99.9
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	-0.4 (-2.7, 1.5)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMC = geometric mean concentration; GMFR = geometric mean fold rise; GMR = geometric mean ratio; ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; PsNVA = pseudovirus neutralization assay; ULOQ = upper limit of quantification.
Based on PsVNA by PPD vaccine (VAC62). 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 to 25 years of age).
[a] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMC and GMFR, respectively, then back-transformed to the original scale for presentation.
[b] The log-transformed antibody levels are analyzed 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 (2 to < 6 years): Study P204 Table 14.2.3.1.1.3, Study P204 Table 14.2.1.1.3.1.3, and Study P204 Table 14.2.1.2.3.1.3

Figure 1: Box Plots of Pseudovirus Neutralising Antibody (Part 2 PP Immunogenicity Subset) (2 to <6Years)



Abbreviations: ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; 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.
Study P301 mRNA-1273 group includes young adults (18 to 25 years of age).
The ULOQ for selected P301 participants tested previously was different.
Box plot is based on log-transformed values.
Source (2 to < 6 years): Study P204 Figure 14.2.1.4.5.3

Part 1 PP Immunogenicity Subset (6 Months to < 2 Years)

The immunogenicity results from the Part 1 PP Immunogenicity subset for the 25-µg mRNA-1273 group in infants and children 6 months to < 2 years of age are presented.

The Day 57 (28 days after dose 2) nAb results of the infants and children (6 months to < 2 years) were compared with previously generated results from the PP Immunogenicity subset of 18- to 25-year-old participants in Study P301. Children receiving 25 µg mRNA-1273 demonstrated a nAb GMC of 1782.603 (Table 30), and 100% met the definition of seroresponse. Comparison of nAb GMC from Study P204 children (6 months to < 2 years) receiving 25 µg mRNA-1273 (n = 98) to Study P301 young adults (18 to 25 years; n = 295) yielded a GMR of 1.371 (95% CI: 1.123, 1.675). The difference in seroresponse rates at Day 57 between the 2 groups was 1.0% (95% CI: -2.8%, 3.0%).

Table 15: Part 1 Analysis of Pseudovirus Neutralizing Antibody Level and Seroresponse Rate at Day 57 by Pseudovirus Neutralization Assay (ID50) (Part 1 PP Immunogenicity Subset 25 µg Group) (6 Months to < 2 Years)

	Study P204 6 months to < 2 Years mRNA-1273 25 µg N = 98	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N = 295**
Baseline GMC	9.565	9.285
GMC observed at Day 57	n = 97 1782.603	n = 295 1299.855
GMFR (95% CI)[a] at Day 57 from baseline	188.484 (161.932, 219.389)	139.990 (126.103, 155.405)
GMC (95% CI) at Day 57	1782.603 (1498.398, 2120.713)	1299.855 (1176.638, 1435.974)
GMR (P204 vs P301; model based) (95% CI)[b]	1.371 (1.123, 1.675)	
Participants achieving seroresponse, n (%)[c] at Day 57	96/96 (100)	292/295 (99.0)
95% CI[d]	96.2, 100.0	97.1, 99.8
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	1.0 (-2.8, 3.0)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMFR = geometric mean fold ratio; GMR = geometric mean ratio; GMC = geometric mean concentration; ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; ULOQ = upper limit of quantification.
Based on PsVNA by Duke University Medical Center Laboratory.
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 to 25 years of age).
[a] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMC and GMFR, respectively, then back-transformed to the original scale for presentation.
[b] The log-transformed antibody levels are analyzed 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 (6 months to < 2 years): Study P204 Table 14.2.1.1.3.1.1, Study P204 Table 14.2.1.2.3.1.1, and Study P204 Table 14.2.3.1.1.1

Part 2 PP Immunogenicity Subset (6 Months to < 2 Years)

Part 2 PP Immunogenicity Subset was the pre-specified cohort for the assessment of the primary immunogenicity objective.
Table 15 summarises the analysis of Day 57 serum nAb levels (measured by PsVNA ID50 assay) for children 6 months to < 2 years of age in the Part 2 PP Immunogenicity Subset and the comparison with those from young adults (18 to 25 years of age) in Study P301.
Figure 2 depicts these results.

In the Part 2 PP Immunogenicity Subset (n = 230), baseline nAb GMC was below the LLOQ; Day 57 GMC was 1780.7 (95% CI: 1616.18, 1961.88; n = 230). On Day 57, 100% of children met criteria for seroresponse (*Table 15*). The geometric mean fold rise (GMFR) from baseline to Day 57 was 225.3 (95% CI: 200.40, 253.27).

The pre-specified success criteria for the primary immunogenicity objective were met (*Table 15*) thus enabling the inference of vaccine effectiveness from Study P301. The GMR of Day 57 nAb concentration from children 6 months to < 2 years of age in the Part 2 PP Immunogenicity Subset compared to Study P301 young adults 18 to 25 years was 1.280 (95% CI: 1.115, 1.470), meeting the non-inferiority success

criterion (ie, lower bound of the 95% CI for GMR ≥ 0.67); the GMR point estimate criterion (≥ 0.8) was also met. The difference in seroresponse rates between the 2 immunobridging groups was 0.7% (95% CI: -1.0%, 2.5%), also meeting the noninferiority success criterion (lower bound of the 95% CI of the seroresponse rate difference > -10%).

Table 16: Co- primary immunobridging (Pseudovirus Neutralising Antibody Level) (Part 2 PP Immunogenicity Subset) (6 Months to <2 Years)

	Study P204 6 months to < 2 Years mRNA-1273 25 µg N = 230	**Study P301 18 to ≤ 25 Years mRNA-1273 100 µg N = 295**
Baseline GMC	7.9	11.1
GMC observed at Day 57	n = 230 1780.7	n = 291 1390.8
GMFR (95% CI)[a] at Day 57 from baseline	225.3 (200.40, 253.27)	125.8 (112.99, 139.96)
GMC (95% CI) at Day 57	1780.658 (1606.375, 1973.849)	1390.781 (1269.081, 1524.152)
GMR (P204 Part 2 vs P301; model based) (95% CI)[b]	1.280 (1.115, 1.470)	
Participants achieving seroresponse, n (%)[c] at Day 57	230/230 (100)	289/291 (99.3)
95% CI[d]	(98.4, 100.0)	(97.5, 99.9)
Difference in seroresponse rate (P204 vs P301), % (95% CI)[e]	0.7 (-1.0, 2.5)	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMC = geometric mean concentration; GMFR = geometric mean fold ratio; GMR = geometric mean ratio; ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; LS = least squares; PP = per protocol; PsNVA = pseudovirus neutralization assay; ULOQ = upper limit of quantification.

Based on PsVNA by PPD vaccine (VAC62). 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 to 25 years of age).

[a] 95% CI is calculated based on the t-distribution of the log-transformed values or the difference in the log-transformed values for GMC and GMFR, respectively, then back-transformed to the original scale for presentation.

[b] The log-transformed antibody levels are analyzed 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.

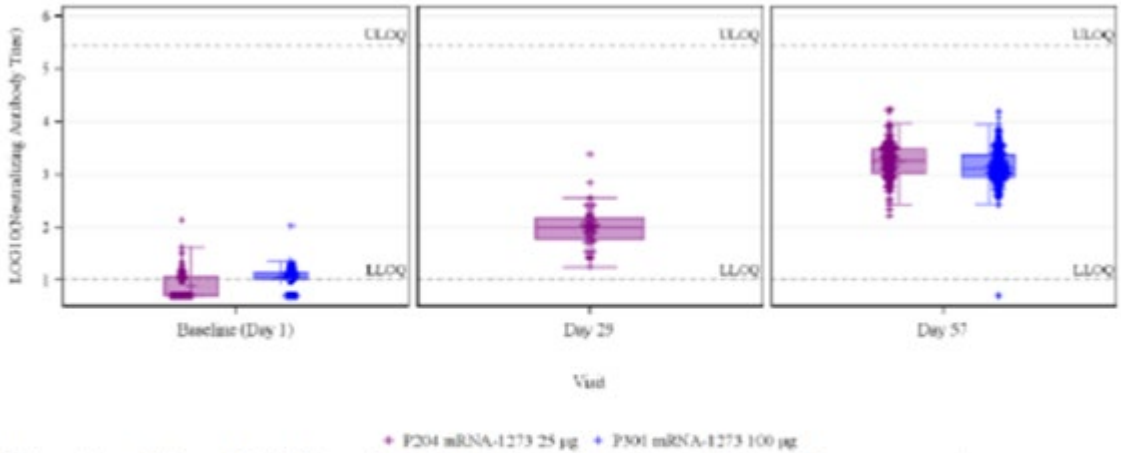
[c] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above the LLOQ. Percentages are based on the number of participants with non-missing data at baseline and the corresponding timepoint.

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

[e] 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Source (6 months to < 2 years): Study P204 Table 14.2.3.1.1.3, Study P204 Table 14.2.1.1.3.1.3, and Study P204 Table 14.2.1.2.3.1.3

Figure 2: Box Plot of Pseudovirus Neutralising Antibody (Part 2 PP Immunogenicity Subset) (6 Months to <2 Years)



Abbreviations: ID_{50} = 50% inhibitory dose; LLOQ = lower limit of quantification; 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 to 25 years of age).
The ULOQ for selected P301 participants tested previously was different.
Box plot is based on log-transformed values.
Source (6 months to < 2 years): Study P204 Figure 14.2.1.4.5.3

Efficacy in Children 2 to < 6 Years

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

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.

Table *17* summarises the descriptive analysis of SARS-CoV-2 infections and COVID-19 cases occurring at least 14 days after dose 2 in the PP Set for Efficacy. The analyses of efficacy were conducted in participants negative at baseline for both nasal swab RT-PCR and serology (Elecsys).

Based on the PP Set for Efficacy, there were 119 cases (4.6%) in the mRNA-1273 group meeting the CDC case definition (incidence rate 175 per 1000 person-years) and 61 cases (7.1%) in the placebo group (incidence rate 277 per 1000 person-years), and VE was 36.8% (95% CI: 12.5%, 54.0%). For cases meeting the P301 case definition, there were 71 cases (2.7%) in the mRNA-1273 group (incidence rate 104 per 1000 person-years) and 43 cases (5.0%) in the placebo group (incidence rate 194 per 1000 person-years). VE was 46.4% (95% CI: 19.8%, 63.8%).

Table 17: Summary of Efficacy Endpoint Analysis Results Starting 14 Days After Dose 2 (PP Set for Efficacy) (2 to < 6 Years)

Endpoint	**Part 2**	
	Placebo N=858	**mRNA-1273 25 µg N = 2594**
CDC case definition of COVID-19		
Cases, n/N1 (%)	61/858 (7.1)	119/2594 (4.6)
Incidence rate per 1000 person-years (95% CI)[a,b]	276.980 (211.868, 355.792)	175.023 (144.992, 209.441)
VE based on incidence rate (95% CI)[c]	0.368 (0.125, 0.540)	
P301 case definition of COVID-19		
Cases, n/N1 (%)	43/858 (5.0)	71/2594 (2.7)

Incidence rate per 1000 person-years (95% CI)	193.528 (140.057, 260.681)	103.761 (81.038, 130.880)
VE based on incidence rate (95% CI)[c]	0.464 (0.198, 0.638)	
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	33/858 (3.8)	79/2594 (3.0)
Incidence rate per 1000 person-years (95% CI)	153.725 (105.817, 215.887)	118.464 (93.789, 147.641)
VE based on incidence rate (95% CI)[c]	0.229 (-0.195, 0.493)	
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	93/858 (10.8)	198/2594 (7.6)
Incidence rate per 1000 person-years (95% CI)	433.362 (349.779, 530.898)	296.924 (257.004, 341.288)
VE based on incidence rate (95% CI)[c]	0.315 (0.114, 0.467)	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; N1 = number of participants at risk at 14 days after dose 2 for specific efficacy endpoint; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VE = vaccine efficacy.

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

Source (2 to < 6 years): Study P204 Table 14.2.8.1.1.2.1, Study P204 Table 14.2.7.1.1.2.1, Study P204 Table 14.2.6.1.1.2.1.1, and Study P204 Table 14.2.5.1.1.2.1

- *Sensitivity Analysis of All Reported Cases Regardless of Test Performed for Endpoints Starting 14 Days After Dose 2 in the PP Set for Efficacy (Part 2)*

As noted above, a sensitivity analysis of efficacy included all reported cases (COVID-19 and SARS-CoV-2 infection) regardless of test was performed. Table 17 summarises the sensitivity analysis performed on endpoints occurring 14 days or more after dose 2 in the PP Set for Efficacy. This analysis included endpoints derived based on RT-PCR (central and local laboratory-based), home testing, and cases lacking test modality identification. When evaluating all potential cases identified with any type of SARS-CoV-2 diagnostic test, VE 14 days after dose 2 was 28.5% using the CDC and 37.5% using the P301 definition.

Table 18: Summary of Sensitivity Analysis of All Reported Cases Regardless of Test Performed Starting 14 Days After Dose 2 (PP Set for Efficacy) (2 to < 6 Years)

	Part 2	
	Placebo N = 858	**mRNA-1273 25 µg N = 2594**
CDC case definition of COVID-19		
Cases, n/N1 (%)	81/858 (9.4)	179/2594 (6.9)
Incidence rate per 1000 person-years (95% CI)[a,b]	371.417 (294.959, 461.638)	265.496 (228.026, 307.367)
VE based on incidence rate (95% CI)[c]	0.285 (0.059, 0.453)	
P301 case definition of COVID-19		
Cases, n/N1 (%)	55/858 (6.4)	106/2594 (4.1)
Incidence rate per 1000 person-years (95% CI)	248.894 (187.501, 323.970)	155.607 (127.399, 188.203)

VE based on incidence rate (95% CI)[c]	0.375 (0.118, 0.553)	
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	40/858 (4.7)	94/2594 (3.6)
Incidence rate per 1000 person-years (95% CI)	188.616 (134.750, 256.841)	142.484 (115.142, 174.364)
VE based on incidence rate (95% CI)[c]	0.245 (-0.123, 0.483)	
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	120/858 (14.0)	273/2594 (10.5)
Incidence rate per 1000 person-years (95% CI)	566.030 (469.295, 676.834)	413.839 (366.200, 465.955)
VE based on incidence rate (95% CI)[c]	0.269 (0.086, 0.412)	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; N1 = number of participants at risk at 14 days after dose 2 for specific efficacy endpoint; PP = per protocol; RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VE = vaccine efficacy.

Table includes analysis of all cases, including those confirmed by RT-PCR (central and local laboratory-based), home test results, and cases that did not include test modality identification.

[a] Person-years is defined as the total years from the first injection date for Part 1 and the randomization 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 snapshot 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 is defined as 1 - ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Source (2 to < 6 years): 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 in Children 6 Months to < 2 Years

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

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.

Table *19* summarises the descriptive analysis of SARS-CoV-2 infections and COVID-19 cases occurring at least 14 days after dose 2 in the PP Set for Efficacy. All summaries of efficacy are performed in baseline nasal swab polymerase chain reaction (PCR) and Elecsys negative participants.

For cases meeting the CDC case definition, there were 51 cases (3.4%) in the mRNA- 1273 group (incidence rate 138 per 1000 person-years) and 34 cases (6.6%) in the placebo group (incidence rate 280 per 1000 person-years), and VE was 50.6% (95% CI: 21.4%, 68.6%). According to P301 case definition, there were 37 cases (2.4%) in the mRNA-1273 group (incidence rate 100 per 1000 person-years) and 18 cases (3.5%) in the placebo group (incidence rate 146 per 1000 person-years), and VE was 31.5% (95% CI: -27.7 %, 62.0%). Asymptomatic SARS-CoV-2 infection as defined occurred in 32 cases (2.1%) in the mRNA-1273 group and 11 cases (2.1%) in the placebo group. VE was 3.8% (95% CI: -112%, 52.8%).

Table 19: Summary of Efficacy Endpoint Analysis Results Starting 14 Days After Dose 2 (PP Set for Efficacy) (6 Months to < 2 Years)

	Part 2	
	Placebo N = 513	**mRNA-1273 25 µg N = 1511**
CDC case definition of COVID-19		
Cases, n/N1 (%)	34/513 (6.6)	51/1511 (3.4)

Incidence rate per 1000 person-years (95% CI)[a,b]	279.822 (193.785, 391.023)	138.239 (102.928, 181.759)
VE based on incidence rate (95% CI)[c]	0.506 (0.214, 0.686)	
P301 case definition of COVID-19		
Cases, n/N1 (%)	18/513 (3.5)	37/1511 (2.4)
Incidence rate per 1000 person-years (95% CI)	146.042 (86.553, 230.809)	99.981 (70.396, 137.811)
VE based on incidence rate (95% CI)[c]	0.315 (-0.277, 0.620)	
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	11/513 (2.1)	32/1511 (2.1)
Incidence rate per 1000 person-years (95% CI)	91.487 (45.670, 163.696)	87.988 (60.184, 124.213)
VE based on incidence rate (95% CI)[c]	0.038 (-1.115, 0.528)	
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	45/513 (8.8)	81/1511 (5.4)
Incidence rate per 1000 person-years (95% CI)	374.376 (273.073, 500.945)	222.821 (176.952, 276.946)
VE based on incidence rate (95% CI)[c]	0.405 (0.123, 0.592)	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; N1 = number of participants at risk at 14 days after dose 2 for specific efficacy endpoint; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VE = vaccine efficacy.

[a] Person-years is defined as the total years from the first injection date for Part 1 and the randomization 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 snapshot 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 is defined as 1 - ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Source (6 months to < 2 years): Study P204 Table 14.2.8.1.1.2.1, Study P204 Table 14.2.7.1.1.2.1, Study P204 Table 14.2.6.1.1.2.1.1, and Study P204 Table 14.2.5.1.1.2.1

- *Sensitivity Analysis of All Reported Cases Regardless of Test Performed for Endpoints Starting 14 Days After Dose 2 in the PP Set for Efficacy (Part 2)*

To account for the increased COVID-19 case numbers during the Omicron variant wave, results of home testing were also collected, starting in December 2021. According to protocol, families were encouraged in case of any positive home test to obtain a confirmatory RT PCR test, either at a local diagnostic lab or via an illness visit at the study site. Therefore, data for COVID-19 cases derived based on RT-PCR testing (performed at CLIA-certified central or local laboratory), based on home testing, or where the test modality was not identified were available.

A sensitivity analysis of efficacy included all reported cases (COVID-19 and SARS-CoV-2 infection) regardless of test performed. Table 19 summarises the sensitivity analysis performed on endpoints occurring 14 days or more after dose 2 in the PP Set for Efficacy. When evaluating all potential cases identified with any type of SARS-CoV-2 diagnostic test, VE 14 days after dose 2 indicated to be 53.5% using the CDC and 43.7% using the P301 definition.

Table 20: Summary of Sensitivity Analysis Results of All Reported Cases Regardless of Test Performed Starting 14 Days After Dose 2 (PP Set for Efficacy) (6 Months to < 2 Years)

	Part 2	
	Placebo N = 513	**mRNA-1273 25 µg N = 1511**
CDC case definition of COVID-19		
Cases, n/N1 (%)	52/513 (10.1)	74/1511 (4.9)
Incidence rate per 1000 person-years (95% CI)[a,b]	433.888 (324.048, 568.986)	201.580 (158.284, 253.066)

VE based on incidence rate (95% CI)[C]	0.535 (0.324, 0.678)	
P301 case definition of COVID-19		
Cases, n/N1 (%)	30/513 (5.8)	51/1511 (3.4)
Incidence rate per 1000 person-years (95% CI)	245.656 (165.743, 350.690)	138.215 (102.910, 181.727)
VE based on incidence rate (95% CI)[C]	0.437 (0.085, 0.648)	
Asymptomatic SARS-CoV-2 infection		
Cases, n/N1 (%)	12/513 (2.3)	41/1511 (2.7)
Incidence rate per 1000 person-years (95% CI)	101.236 (52.310, 176.838)	113.519 (81.463, 154.002)
VE based on incidence rate (95% CI)[C]	-0.121 (-1.344, 0.422)	
SARS-CoV-2 infection (regardless of symptoms)		
Cases, n/N1 (%)	64/513 (12.5)	113/1511 (7.5)
Incidence rate per 1000 person-years (95% CI)	540.123 (415.961, 689.726)	313.136 (258.069, 376.476)
VE based on incidence rate (95% CI)[C]	0.420 (0.199, 0.577)	

Abbreviations: CDC = Centers for Disease Control and Prevention; CI = confidence interval; COVID-19 = coronavirus disease 2019; N1 = number of participants at risk at 14 days after dose 2 for specific efficacy endpoint; PP = per protocol; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; VE = vaccine efficacy.

[a] Person-years is defined as the total years from the first injection date for Part 1 and the randomization 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 snapshot 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 is defined as 1 - ratio of incidence rate (mRNA-1273 vs placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Source (6 months to < 2 years): 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

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study was amended 7 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 but the study seems overpowered for most of the endpoints.

Efficacy data and additional analyses

Immunobridging to infer effectiveness of vaccination from immune biological data of one population to the other is an accepted strategy for vaccines and has been used previously. Because there is currently no serologic correlate for protection, non-inferiority analyses based on post-vaccination antibody levels and response rates are usually recommended. As demonstrated by *in vitro* and *in vivo* studies, neutralising antibodies to the spike protein play a critical role in the prevention of COVID-19. In this study, antibody responses in children and young adults after vaccination with Spikevax were studied using assays to measure anti-spike binding and neutralising antibodies. Therefore, the results of the neutralising antibody response analyses are critical for demonstrating non-inferiority and assessing the acceptability of immunobridging.

The MAH presented immunogenicity results from study P204 on children in the age groups 2 to <6 years and 6 months to 2 years separately. Study P204 was set up in a Part 1 and a Part 2 for each age group in

order to define in Part 1 the most appropriate dose to move forward in Part 2. Study participants from Part 1 and Part 2 are not identical.

The nAb GMT in the dose group of 25µg mRNA-1273 for children 2 to <6 years in Part 1 was 1013.766 which was expectedly lower than the nAb GMT in the dose group of 50µg mRNA-1273 (1844.127). The nAb GMT in the comparator group from study P301 (100µg dose of mRNA-1273) was given as 1299.855. This part 1 was meant for dose finding and the number of participants in the age group 2 to < 6 years was limited (n=50). Part 1 in the age group 2 to <6 years led to the decision to move forward with 2 injections of each 25µg mRNA-1273 for both age groups.

In Part 2 PP Immunogenicity subset for children 2 to <6 years, 264 immunogenicity samples were analysed in the 25µg mRNA-1273 group and the nAb GMC compared to 295 immunogenicity samples from 18 to ≥25 year old adults from study P301. The resulting nAb GMCs were 1410.0 (2 to <6 years of age) and 1390.8 (18 to ≥25 years of age).
The GMR of Day 57 nAb concentration from children 2 to <6 years of age compared to young adults 18 to ≥25 years of age was 1.014 meeting the pre-specified non-inferiority criterion.
The difference in sero-response rates between these two groups was -0.4. Therefore, the pre-specified success criteria for the primary immunogenicity objective were met.
In Part 2 PP Immunogenicity subset for children 2 to <6 years of age 98.9% achieved sero-response as compared to 99.3% sero-response in young adults (18 to ≥25 years). The geometric mean fold rise (GMFR) from baseline to Day 57 was 183.3.

In the PP Immunogenicity subset Part 1 for children 6 months to < 2 years, 97 samples were analysed in the PP Immunogenicity subset and nAb GMTs compared to 295 samples from young adults (18 to ≥25 years).
Children receiving 25 µg mRNA-1273 demonstrated a nAb GMT of 1782.603, and 100% met the definition of sero-response. Comparison of nAb GMT from Study P204 children (6 months to < 2 years) receiving 25 µg mRNA-1273 to Study P301 young adults (18 to 25 years) yielded a GMR of 1.371. The difference in sero-response rates at Day 57 between the 2 groups was 1.0%. This supports the chosen dose for young children. As for children in the age group 2 years to <6 years, Part 1 was not intended for statistical analysis of the primary immunogenicity objective.

In the PP Immunogenicity subset Part 2 for children 6 months to < 2 years, 230 samples were analysed and nAb GMCs compared to 295 samples from young adults (18 to ≥25 years).
In the Part 2 PP Immunogenicity subset, baseline nAb GMC was below the LLOQ; Day 57 nAb GMC was 1780.7.
The GMR of Day 57 nAb concentration from children 6 months to < 2 years of age in the Part 2 PP Immunogenicity subset compared to Study P301 young adults 18 to ≥25 years was 1.280. The GMR point estimate criterion (≥ 0.8) was met.

On Day 57, 100% of children met criteria for sero-response. The difference in sero-response rates between the 2 immunobridging groups was 0.7%. The GMFR from baseline to Day 57 was 225.3. Therefore, the pre-specified success criteria for the primary immunogenicity objective were met.

For children below the age of 2 results were consistent between Part 1 and 2. For children above 2 years of age results for GMT, GMT ratio and sero-response were not consistent across parts. In Part 1 the GMT was lower in P204 than in P301, while in Part 2 P204 showed higher GMTs than P301. For sero-response rates it was the other way around (although based on very small differences in counts). Nevertheless, both age cohorts met the pre-specified non-inferiority-criteria based on data from the respective Parts 2. The difference in the nAb GMC value for immunogenicity samples from study P301 in Part 2 as compared to Part 1 (nAb GMT 1299.855) was explained by the MAH as to: Samples from Part 1 for 2 to <6-year-old children were analysed in the Duke University Medical Center. Testing was transferred to PPD Vaccine Laboratories for Part 2. The study P301 comparator subset was also retested at PPD Vaccine Laboratories to enable comparison for analysis of Part 2. Therefore, values for samples between Part 1 and Part 2 for 2 to <6-year-old children are not directly comparable but values within Part 1 or Part 2 are directly

comparable as analysis has been performed in the same laboratory. The MAH was asked to clarify whether samples from study P204 were analysed contemporaneously with samples from study P301, in particular at PPD for both Part 2 Immunogenicity subsets. The MAH confirmed contemporaneous testing at PPD.

In Part 2 PP Immunogenicity subset for children 2 to <6 years there were 24,2% two (2) years old children, 35,6% three (3) years old children, 29.2% four (4) years old children and 11.0% five (5) years old children participating.
In the Part 2 PP Immunogenicity subset for children 6 months to <2 years, 18.3% of children were ≥6 months and <1 year old. Accordingly, 81.7% of the children were ≥1 year to <2 years old. This age distribution is considered acceptable for an immunogenicity assessment of mRNA-1273 in children 6 month to <6 years.

The analysis presented for immunobridging was primarily based on Part 2 data, with data from Part 1 provided in support. It was noted that the MAH deviated from the original sample size for immunogenicity analyses without further explanation. It was planned to collect immunogenicity samples of approximately 396 subjects per age cohort in Part 2 who received mRNA-1273 leading to approximately 289 subjects in the immunogenicity PP set. For both age cohorts the numbers were substantially smaller with N=302 (N=264) in the immunogenicity (PP) set for children 2 to 6 years of age, and N= 274 (N=230) subjects in the respective analysis sets for children 6 months to 2 years of age. The timing of the primary immunogenicity analyses was not unambiguously defined and the chosen data cut-off might be arbitrary. Given the results and the minor deviation in the sample size, the impact on the final results is considered minor.

There was a notable overrepresentation of White participants in both Part 2 PP Immunogenicity subsets with 75.2% (6 months to < 2 years) and 71.2% (2 years to < 6 years) of participants in the respective age cohort. A bias on the results does not seem likely, however, cannot be excluded. For the European population the data is considered acceptable.

Vaccine efficacy (VE) was assessed as a secondary endpoint in part 2 of the study in children who had been tested negative for SARS-CoV-2 at baseline (by RT-PCR and serology) and who had received two doses of 25 µg Spikevax 28 days apart. VE was determined according to either of two case definitions: The CDC case definition reflecting less symptomatic disease and the P301 case definition reflecting more symptomatic disease. VE in the per-protocol set ranged from 32% (children <2 yoa, P301 definition) to 51% (children <2yoa, CDC definition) with children ≥2 and <6 yoa in between (47% P301 definition, 37% CDC definition). The MAH justifies these rather low efficacy results with the prevalence of the Omicron variant during the time of data collection. Indeed, as compared to research literature, point estimates of vaccine efficacy are consistent with the observed vaccine effectiveness after two doses of mRNA-1273 against Omicron in adults (e.g., 44% VE [95% CI: 35.1; 51.6%] at 14-90 days after dose 2; Tseng, 2022). Although it is noted that vaccine efficacy estimates for infants and children 6 months to under 2 years of age are more variable than for the older children 2-6 years of age, the consistency in vaccine efficacy seems to be applicable for both age groups (Tseng et al 2022; Andrews et al 2022). Nevertheless, more advanced efficacy data at a later stage should be submitted to verify this hypothesis and to exclude age effects.

Severe COVID-19 is very rare in children and no such cases were reported in study P204. Accordingly, efficacy against (predominant Omicron-related) severe outcomes, e.g. hospitalisation and death, could not be determined.

Sensitivity analyses determined VE against COVID-19 endpoints not only by RT-PCR results but also by test results derived only by home testing or cases lacking further test identification. Of note, VE derived upon these less stringent test results was similar to those determined using the prior strict case definitions. The increased number of cases identified in this sensitivity analysis also resulted in lower limits of 95% CIs that exceeded zero, supporting the assessment of VE using the protocol-specified case definitions.

In summary, reliable VE estimates are not available at this stage of development and current available efficacy results are of limited, albeit supportive, value due to the limitations noted above.

Despite some restrictions mentioned earlier, efficacy against symptomatic COVID-19 in children aged ≥6 months to <6 years are derived primarily on the basis of the co-primary immune-bridging endpoints.

2.4.3. Conclusions on the clinical efficacy

Overall, the MAH provided immunogenicity and efficacy data which supports an extension of the indication of mRNA-1273 in children below the age of 6.

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

- The MAH should provide the results from study mRNA-1273-P204, with an analysis of the secondary efficacy endpoint, based on a later data cut-off date to support the immunobridging, to be submitted by 30/06/2023 and a final clinical study report to be submitted by 31/03/2024.

2.5. Clinical safety

Introduction

On 06 January 2021, 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 23 July 2021, the indication had subsequently been extended to individuals ≥ 12 years of age (EMEA/H/C/005791/II/0021). On 10 November 2021 the procedure has started to extend the use of mRNA-1273 to include active immunisation to prevent coronavirus disease 2019 (COVID-19) in individuals 6 years to <12 years of age. This current procedure intends to extend the use of mRNA-1273 to include active immunisation to prevent COVID-19 in children 6 months to < 6 years of age. The safety assessment for the extension of indication of Spikevax to individuals 6 months to < 6 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 months to < 6 years of age, grouped in the age groups 2 years to < 6 years, and 6 months to < 2 years 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 study design of P204 in the younger age cohorts was similar to the design for the 6 years to < 12 year of age cohort. The study followed a pattern of age de-escalation, the older children (2 to < 6 years) were enrolled to Part 1 (to evaluate dose levels of 25 µg and 50 µg administered as a two-dose schedule one month apart, prior to younger children (6 months to < 2 years). Accordingly, a lower dose (25 µg) was evaluated in a group of 2 years to < 6 years old children in Part 1, a dose that proved less reactogenic than 2 injections of 50 µg of mRNA-1273. The youngest children (6 months to < 2 years) received 25 µg of mRNA-1273 in Part 1. In the blinded expansion phase (Part 2), participants received 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 21 Feb 2022.

Study population

Children with chronic disease (e.g., asthma, diabetes mellitus, cystic fibrosis, bronchial hyperactivity) 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 in adults, obesity 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.

Age Group 6 months < 2 years old

In part 1 of the trial no children with medical history were enrolled. In part 2 no obese children were enrolled and regarding to the medical history more children were enrolled in the mRNA-1273 vaccine group versus placebo group respectively 27 children (1.3%) compared to 2 children (0.3%) for chronic lung diseases and for the diagnosis of asthma were enrolled 22 children (1.2%) in the mRNA-1273 vaccine group compared to 2 children (0.3%) in the placebo group.

Age Group 2 years to < 6 years old

In Part 1 for both dose groups were enrolled 27 children obese with BMI >95th percentile; 9 children with chronic lung diseases; 8 children with asthma and no participant with diabetes mellitus. In part 2 of the trial, 106 children (10.5%) in the placebo and 326 children (10.8%) in the mRNA-1273 vaccine group were obese with BMI >95th percentile. The proportion of obese/non-obese children in the mRNA-1273 vaccine group was 326 out of a total of 3031 children comparable with the number of 106 out of 1007 in the placebo group. With regard to medical history the placebo and the number of participants enrolled was higher in the mRNA-1273 vaccine group versus placebo respectively with 103 (3.4%) children compare to 46 (4.6%) children for chronic lung diseases (including asthma) and 92 (3%) children versus 42 (2.2%) children for the diagnosis of asthma (including bronchial hyperactivity). The number of children enrolled for diabetes mellitus was similar with 1 participant for both mRNA-1273 vaccine group and placebo group.

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. For the age cohort 6 Months to < 2 Years: in part 1 of the trial, 94% of participants were seronegative at baseline, 4.7% were seropositive and for 1.3% the SARS-CoV-2 baseline status is not known. In part 2: 90% of participants in the placebo group and 89.4 % in the 25 µg dose group were SARS-CoV-2 seronegative at baseline, 6.5% versus 6% were seropositive, and for 3.6 % versus 4.5 % children in the 25 µg dose group, the SARS-CoV-2 baseline status is not known.

For the age cohort 2 years to < 6 years old: in part 1 of the trial, 92.8% of participants in the 25µg and 94.8% in the 50µg dose group were SARS-CoV-2 seronegative at baseline, 7.2% versus 3.9% were seropositive, and for 2 (1.3%) participants in the 50µg dose group, the SARS-CoV-2 baseline status is not known. In part 2, 89.2% of participants in the placebo group and 88.9 % in the 25 µg dose group were SARS-CoV-2 seronegative at baseline, 8.1% versus 8.8 % were seropositive, and for 2.7% versus 2.3% participants in the 25 µg dose group, the SARS-CoV-2 baseline status is not known.

Patient exposure and duration of follow-up

Age Group (6 Months to < 2 Years)

Disposition

Part 1

In Part 1, at the time of the data snapshot (21 February 2022) 150 participants received dose 1 and dose 2. No participants in Part 1 discontinued study vaccine due to an AE. A total of 3 (2.0%) participants in Part 1 withdrew from the study. Two (1.3%) participants discontinued study due to consent withdrawal, and one (0.7%) participant was lost to follow-up.

Table 21: Participant Disposition by Dose Level in Part 1 (FAS) (6 Months to < 2 Years)

	mRNA-1273 25 µg N = 150 n (%)
Received first injection	150 (100)
Received second injection	150 (100)
Did not receive any injection	0
Completed study vaccine schedule	150 (100)
Discontinued study vaccine[a]	0
Completed study[b]	0
Withdrew from study	3 (2.0)
Reasons for withdrawal from study	
Lost to follow-up	1 (0.7)
Withdrawal of consent	2 (1.3)

Abbreviations: AE = adverse event; FAS = full analysis set; IP = investigational product.
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] 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 (6 months to < 2 years): Study P204 Table 14.1.1.1.1

Part 2

In Part 2, at the time of the data snapshot, 1760 participants in the mRNA-1273 group and 590 participants in the placebo group had received dose 1 (a total of 2350 participants), and 1600 participants in the mRNA-1273 group and 529 participants in the placebo group had received dose 2 (a total of 2129 participants). A total of 9 (0.4%) participants discontinued study vaccine: 4 (0.2%) participants in the mRNA-1273 group and 5 (0.8%) in the placebo group. No participants in the mRNA-1273 group discontinued study vaccine due to an AE. A total of 34 (1.4%) participants in Part 2 withdrew from the study, including 19 (1.1%) participants in the mRNA-1273 group and 15 (2.5%) participants in the placebo group. Reasons to withdraw the study because of AE were in 1 participant (0.1%) in the mRNA-1273 group and in 1 participant (0.2%) related to COVID-19 in the placebo group.

Table 22: Participant Disposition in Part 2 (Randomisation Set) (6 Months to < 2 Years)

	Placebo N = 593 n (%)	mRNA-1273 25 µg N = 1762 n (%)	Total N = 2355 n (%)
Received first injection[a]	590 (99.5)	1760 (99.9)	2350 (99.8)
Received second injection	529 (89.2)	1600 (90.8)	2129 (90.4)
Did not receive any injection	3 (0.5)	2 (0.1)	5 (0.2)
Completed study vaccine schedule	529 (89.2)	1600 (90.8)	2129 (90.4)
Discontinued study vaccine[b]	5 (0.8)	4 (0.2)	9 (0.4)
Reason for discontinuation of study vaccine			
AE	1 (0.2)	0	1 (< 0.1)
COVID-19	1 (0.2)	0	1 (< 0.1)
Withdrawal of consent	3 (0.5)	1 (< 0.1)[c]	4 (0.2)
COVID-19 not related to infection	0	0	0
Other	3 (0.5)	1 (< 0.1)	4 (0.2)
Participant entered open-label or cross-over phase	0	1 (< 0.1)	1 (< 0.1)
Other	0	1 (< 0.1)	1 (< 0.1)
Missing	1 (0.2)	1 (< 0.1)	2 (< 0.1)
Completed study[d]	0	0	0
Withdrew from study	15 (2.5)	19 (1.1)	34 (1.4)
Reasons for withdrawal from study			
AE	1 (0.2)	1 (< 0.1)[e]	2 (< 0.1)
COVID-19	1 (0.2)	0	1 (< 0.1)
Other	0	1 (< 0.1)	1 (< 0.1)
Lost to follow-up	1 (0.2)	5 (0.3)	6 (0.3)
Physician decision	0	1 (< 0.1)	1 (< 0.1)
Withdrawal of consent	10 (1.7)	8 (0.5)	18 (0.8)
COVID-19 not related to infection	0	0	0
Other	10 (1.7)	8 (0.5)	18 (0.8)
Other	2 (0.3)	2 (0.1)	4 (0.2)
Missing	1 (0.2)	2 (0.1)	3 (0.1)

Demography (6 Months to < 2 Years)

Part 1

In the part 1 of the trial more males were enrolled compared to female participants with 55.3% versus 44.7%. The mean age was 0.9 years, the mean weight almost 10.78 kg and regarding participant's race are higher proportion of white subjects with 83.3% compared to 2% black race participants and 14.7 other races. Regarding to SARS-CoV-2 status 94% of participants were seronegative at baseline, 4.7% seropositive and for 2 (1.3%) participants the SARS-CoV-2 baseline status is not known. Of note, no placebo group is analysed.

Part 2

The proportion of female and male participants was overall balanced in the placebo and study vaccine group. In the placebo group, in total 49.2% of subjects were male and 50.8% female and in the mRNA-1273 group 51.7% male and 48.3 % female. The mean age was the same with 0.9, also the mean weight with 10.88 kg in both groups and according to participant's race higher proportion of enrolment of white subjects >75% compared to other races. Regarding SARS-CoV-2 status, in the placebo group, 90% of participants were seronegative at baseline, 6.5% seropositive and for 3.6 % status is not known, versus 89.4% seronegative, 6% seropositive and for 4.5% the SARS-CoV-2 baseline status is not known.

Study Duration (6 Months to < 2 Years)

Part 1

In Part 1, the median duration of follow-up was 263.0 days after dose 1 and 233.5 days after dose 2.

Table 23: Summary of Study Duration in Part 1 (Safety Set) (6 Months to < 2 Years)

	mRNA-1273 25 µg N = 150 n (%)
≥ 7 days since first injection, n (%)	150 (100)
≥ 35 days since first injection, n (%)	150 (100)
≥ 56 days since first injection, n (%)	150 (100)
≥ 7 days since second injection, n (%)	150 (100)
≥ 28 days since second injection, n (%)	150 (100)
≥ 56 days since second injection, n (%)	150 (100)
≥ 140 days since second injection, n (%)	149 (99.3)
Study duration from dose 1, days	
Median (min, max)	263.0 (134, 278)
Study duration from dose 2, days	
Median (min, max)	233.5 (101, 249)

Abbreviations: max = maximum; min = minimum.
Percentages are based on the number of participants in the Part 1 Safety Set.
Source (6 months to < 2 years): Study P204 Table 14.1.5.1

Part 2

In Part 2, the median duration of follow-up was 98.0 days after dose 1 and 68.0 days after dose 2. In Part 2, 1470 (83.5%) participants in the mRNA-1273 group and 482 (81.8%) participants in the placebo group have been followed for 28 days or more after dose 2. Further, 1138 (64.6%) participants in the mRNA-1273 group and 368 (62.5%) participants in the placebo group have been followed for 56 days or more after dose 2.

Table 24: Summary of Study Duration in Part 2 (Safety Set) (6 Months to < 2 Years)

	Placebo N = 589	mRNA-1273 25 µg N = 1761	Total N = 2350
Received first injection, n (%)	589 (100)	1761 (100)	2350 (100)
Received second injection, n (%)	528 (89.6)	1601 (90.9)	2129 (90.6)
≥ 7 days since first injection, n (%)	581 (98.6)	1729 (98.2)	2310 (98.3)
≥ 56 days since first injection, n (%)	490 (83.2)	1503 (85.3)	1993 (84.8)
≥ 7 days since second injection, n (%)	515 (87.4)	1578 (89.6)	2093 (89.1)
≥ 28 days since second injection, n (%)	482 (81.8)	1470 (83.5)	1952 (83.1)
≥ 56 days since second injection, n (%)	368 (62.5)	1138 (64.6)	1506 (64.1)
≥ 84 days since second injection, n (%)	91 (15.4)	276 (15.7)	367 (15.6)
Study duration from dose 1, days			
Median (min, max)	97.0 (1, 127)	98.0 (1, 127)	98.0 (1, 127)
Study duration from dose 2, days			
Median (min, max)	68.0 (0, 99)	68.0 (0, 99)	68.0 (0, 99)

Abbreviations: max = maximum; min = minimum.
Percentages are based on the number of participants in the Part 2 Safety Set.
Source (6 months to < 2 years): Study P204 Table 14.1.5.2

Age Group (2- to < 6-years-old)

Disposition

Part 1

In Part 1, at the time of the data snapshot (21 February 2022) 75 participants (100%) in the 25-µg group and 149 participants (100%) in the 50-µg group received dose 1 and dose 2. No participants in Part 1 discontinued study vaccine for any reason. One (0.4%) participant in the 50-µg group in Part 1 withdrew from the study to receive an authorised vaccine under EUA outside of the protocol. Details are provided in the table below.

Table 25: Participant Disposition by Dose Level in Part 1 (FAS) (2 to < 6 Years)

	mRNA-1273 25 µg N = 75 n (%)	mRNA-1273 50 µg N = 149 n (%)	Total N = 224 n (%)
Received first injection	75 (100)	149 (100)	224 (100)
Received second injection	75 (100)	149 (100)	224 (100)
Did not receive any injection	0	0	0
Completed study vaccine schedule	75 (100)	149 (100)	224 (100)
Discontinued study vaccine[a]	0	0	0
Completed study[b]	0	0	0
Withdrew from study	0	1 (0.7)	1 (0.4)
Reasons for withdrawal from study			
Participant receiving EUA vaccine outside protocol	0	1 (0.7)	1 (0.4)

Abbreviations: EUA = Emergency Use Authorization; FAS = full analysis set; IP = investigational product.
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] 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 (2 to < 6 years): Study P204 Table 14.1.1.1.1

Part 2

In Part 2, at the time of the data snapshot (21 February 2022), 3031 participants in the mRNA-1273 group and 1007 participants in the placebo group had received dose 1 (a total of 4038 participants) and 2960 participants in the mRNA-1273 group and 970 participants in the placebo group had received dose 2 (a total of 3930). A total of 41 (1.0%) participants discontinued study vaccine: 20 (0.7%) participants in the mRNA-1273 group and 21 (2.1%) in the placebo group. Reasons for discontinuation of study vaccine in the mRNA-1273 group were: withdrawal of consent 11 (0.4%) participants, subject entered open-label phase 5 (0.2%) participants, AE for 1 (0.1%) participant, lost to follow-up 1 (< 0.1%) participant, and other 1 (< 0.1%) participant. In the placebo group, reasons for discontinuation were: subject entered open-label phase for 15 (1.5%) participants, 5 (0.5%) participants received EUA vaccine outside of protocol, and withdrawal of consent in 1 (0.1%) participant. A total of 88 (2.2%) participants in Part 2 withdrew from the study, including 57 (1.9%) participants in the mRNA-1273 group and 31 (3.1%) participants in the placebo group. Reasons for study withdrawal in the mRNA-1273 group were withdrawal of consent 40 (1.3%) participants; lost to follow-up 7 (0.2%) participants, other 4 (0.1%) participant, and physician decision 2 (< 0.1%) participants. One participant (< 0.1%) in the mRNA-1273 group withdrew from the study due to an AE. No participant withdrew the study because of AE reason in the placebo group.

Table 26: Participant Disposition by Dose Level in Part 2 (Randomisation Set) (2 to < 6 Years)

	Placebo N = 1008 n (%)	mRNA-1273 25 µg N = 3040 n (%)	Total N = 4048 n (%)
Received first injection	1007 (> 99.9)	3031 (99.7)	4038 (99.8)
Received second injection	970 (96.2)	2960 (97.4)	3930 (97.1)
Did not receive any injection	1 (< 0.1)	9 (0.3)	10 (0.2)
Completed study vaccine schedule	970 (96.2)	2960 (97.4)	3930 (97.1)
Discontinued study vaccine[a]	21 (2.1)	20 (0.7)	41 (1.0)
Reason for discontinuation of study vaccine			
AE	0	1 (< 0.1)[b]	1 (< 0.1)
Lost to follow-up	0	1 (< 0.1)	1 (< 0.1)
Participant receiving EUA vaccine outside protocol	5 (0.5)	0	5 (0.5)
Withdrawal of consent	1 (< 0.1)	11 (0.4)[c]	12 (0.3)
Participant entered open-label or crossover phase	15 (1.5)	5 (0.2)	20 (0.5)
Other	0	1 (< 0.1)	1 (< 0.1)
Missing	0	1 (< 0.1)	1 (< 0.1)
Completed study[d]	0	0	0
Withdrew from study	31 (3.1)	57 (1.9)	88 (2.2)
Reasons for withdrawal from study			
AE	0	1 (< 0.1)[b]	1 (< 0.1)
Lost to follow-up	0	7 (0.2)	7 (0.2)
Participant receiving EUA vaccine outside protocol	8 (0.8)	0	8 (0.2)
Physician decision	0	2 (< 0.1)	2 (< 0.1)
Protocol deviation	2 (0.2)	0	2 (< 0.1)
Withdrawal of consent	17 (1.7)	40 (1.3)	57 (1.4)
COVID-19 not related to infection	1 (< 0.1)	4 (0.1)	5 (0.1)
Other	16 (1.6)	36 (1.2)	52 (1.3)
Other	3 (0.3)	4 (0.1)	7 (0.2)
Missing	1 (< 0.1)	3 (< 0.1)	4 (< 0.1)

Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; EUA = Emergency Use Authorization.
Percentages are based on the number of participants in the Part 2 Randomization Set.

[a] Defined as a participant who received the first injection but did not receive the second injection.
[b] One participant in the mRNA-1273 group was coded as discontinuing study vaccine and study due to an AE. Adverse events leading to discontinuation of study vaccine and from study are discussed in Section 2.5.5.1.5.3.2, and narratives are available in Module 5.3.5.1.
[c] Eleven participants in the mRNA-1273 group discontinued study vaccine due to withdrawal of consent. The verbatim reasons were reviewed, and none related to AEs. Where reasons were provided, many related to inability to comply with time commitments; some related to concern regarding visiting clinic sites during Omicron.
[d] Study completion is defined as a subject who completed the last scheduled procedure, regardless of number of injections. Follow-up in the study is currently ongoing.
Source (2 to < 6 years): Study P204 Table 14.1.1.1.2, Study P204 Listing 16.2.7.7.2, Study P204 Listing 16.2.7.1.2, and Study P204 Listing 16.2.7.8.2

Demography (2- to < 6-years-old)

Part 1

The proportion of female and male participants was overall balanced in Part 1 of the trial in both group doses, slightly more males were included. In the 25 µg dose group, in total 47.8% of subjects were female and 52.2% male and in the group dose 50 µg were 75% female and 80% male. The two dose groups were also balanced with regards to age, weight, and SARS-CoV-2 baseline serostatus. The mean age was 3.6 in the 25 µg dose and 3.8 in the 50 µg dose. According to participant' race in part 1, in the

group dose 25 µg there are included 71% white participants, 4.3 % black race subjects and 11.6 Asian subjects compare with the same higher proportion of 81% white subjects in the 50 dose group with 81% versus 4.5% black and 1.9% Asian. Regarding SARS-CoV-2 status, in the 25µg dose group 92.8% of participants were seronegative at baseline and 7.2% seropositive compared to the 50µg where 94.8% were seronegative at baseline, 3.9% seropositive, and for 2 (1.3%) participants the SARS-CoV-2 baseline status is not known.

Part 2

In part 2 the proportion of female and male participants were balanced between placebo and mRNA-1273 group with slightly more male participants. In the placebo group 50.6% were male and 49.4% female versus 50.9% and 49.1% respectively in the study vaccine group. Mean age was 3.0 in both groups, mean weight 16.02 versus 16.13kg. According to the participant's race both in placebo and 25 µg dose group higher enrolment has been of white participants, respectively (78.6; 75.8%) compare with other races (8.9%; 11%). Regarding SARS-CoV-2 status at baseline, in the placebo group 89.2% were seronegative, 8.1% seropositive and for 2.7% SARS-CoV-2 status is missing versus respectively 88.9%, 8.8% and 2.3% in the mRNA-1273 group.

Study Duration (2- to < 6-years-old)

Part 1

In Part 1, at the time of the data snapshot (21 February 2022), the median duration of follow-up from Part 1 in subjects 2 to < 6 years of age was 236.0 days for the 25-µg group and 266.0 days for the 50-µg group after dose 1 and 207.0 days for the 25-µg group and 237.0 days for the 50-µg group after dose 2. The 25-µg dose was the dose advanced to Part 2.

Table 27: Summary of Study Duration by Dose Level in Part 1 (Safety Set) (2 to < 6 Years), source: Table 9 Clinical Overview

	mRNA-1273 25 µg N = 69	mRNA-1273 50 µg N = 155	Total N = 224
≥ 7 days since first injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 35 days since first injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 56 days since first injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 7 days since second injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 56 days since second injection, n (%)	69 (100)	155 (100)	224 (100)
≥ 140 days since second injection, n (%)	69 (100)	155 (100)	224 (100)
Study duration from dose 1, days			
Median (min, max)	236.0 (224, 238)	266.0 (204, 307)	263.0 (204, 307)
Study duration from dose 2, days			
Median (min, max)	207.0 (189, 210)	237.0 (173, 274)	231.0 (173, 274)

Abbreviations: max = maximum; min = minimum.
Percentages are based on the number of participants in the Part 1 Safety Set.
Source (2 to < 6 years): Study P204 Table 14.1.5.1

Part 2

In Part 2, the median duration of follow-up was 103.0 days after dose 1 and 71.0 days after dose 2. Participants followed for 28 days or more post-dose 2 include 2713 (89.5%) participants in the mRNA-1273 group and 892 (88.6%) participants in the placebo group. Further, 2180 (71.9%) participants in the

mRNA-1273 group and 710 (70.5%) participants in the placebo group have been followed for 56 days or more after dose 2.

Table 28: Summary of Study Duration in Blinded Phase of Part 2 (Safety Set) (2 to < 6 Years)

	Placebo N = 1007	mRNA-1273 25 µg N = 3031	Total N = 4038
Received first injection, n (%)	1007 (100)	3031 (100)	4038 (100)
Received second injection, n (%)	970 (96.3)	2960 (97.7)	3930 (97.3)
≥ 7 days since first injection, n (%)	1004 (99.7)	3027 (99.9)	4031 (99.8)
≥ 56 days since first injection, n (%)	908 (90.2)	2765 (91.2)	3673 (91.0)
≥ 7 days since second injection, n (%)	957 (95.0)	2902 (95.7)	3859 (95.6)
≥ 28 days since second injection, n (%)	892 (88.6)	2713 (89.5)	3605 (89.3)
≥ 56 days since second injection, n (%)	710 (70.5)	2180 (71.9)	2890 (71.6)
≥ 84 days since second injection, n (%)	202 (20.1)	654 (21.6)	856 (21.2)
Study duration from dose 1, days			
Median (min, max)	102.0 (1, 127)	103.0 (0, 127)	103.0 (0, 127)
Study duration from dose 2, days			
Median (min, max)	70.0 (0, 99)	71.0 (0, 99)	71.0 (0, 99)

Abbreviations: max = maximum; min = minimum.
Percentages are based on the number of participants in the Part 2 Safety Set.
Participants received second injection after unblinding date are excluded. Study duration from second injection is 0 days for participants who received second injection with same unblinding date.
Source (2 to < 6 years): Study P204 Table 14.1.5.2

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 predefined 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 predefined in the CTP.

Solicited adverse reactions

Solicited local ARs assessed included pain, erythema, swelling, and axillary swelling or tenderness. The local ARs assessed were the same across all ages of the study. Solicited systemic ARs were categorised in two different sets depending on the participants' age. For participants aged 37 months and older, the solicited systemic ARs assessed included fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting. For participants aged 2 years to ≤ 36 months, the solicited systemic ARs assessed were fever, irritability/crying, sleepiness, and loss of appetite. Protocol-defined fever grades in participants aged 2 years to ≤ 36 months were the following: grade 1 = 38°C to 38.5°C, grade 2 = 38.6°C to 39.5°C, grade 3 = 39.6°C to 40°C, and grade 4 > 40.0°C. Protocol-defined fever grades in participants aged 37 months to < 6 years were the following: grade 1 = 38°C to 38.4°C, grade 2 = 38.5°C to 38.9°C, grade 3 = 39°C to 40°C, and grade 4 > 40°C. The systemic toxicity scales for the children 37 months to < 6 years of age were taken from the US FDA Guidance for industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007), while the toxicity scales for children 6 to ≤ 36 months of age were per the Sponsor's internal clinical standards. Any solicited AR that met either of the following criteria was also included in the analysis of unsolicited AEs: 1) solicited local or systemic ARs within an onset within 7 days but persisting beyond 7 days or an AR meeting the SAE criteria. 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.

Solicited Local Adverse Reactions (6 Months to < 2 Years)

Part 1

The incidence of solicited local ARs was slightly higher after dose 2 than dose 1. The most common solicited local AR was injection site pain, after any dose and the majority of solicited local ARs were grade 1 or 2. Three participants who received the 25-µg dose level of mRNA-1273 experienced grade 3 solicited local ARs after dose 2: erythema in 1 participant and swelling in 2 participants. There were no grade 4 solicited local ARs in Part 1. The majority of the solicited local ARs in participants in both groups occurred within the first 2 days after each dose and persisted for a median of 2 days in the 25-µg group. The only reported local ARs in Part 1 persisting beyond 7 days after dose 1 were erythema and axillary (or groin) swelling or tenderness (of note, no placebo group available, only 25 ug had been analysed).

Table 29: Summary of Solicited Local Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (6 Months to < 2 Years)

	Dose 1	Dose 2
	mRNA-1273 25 µg (N = 149) n (%)	mRNA-1273 25 µg (N = 150) n (%)
Solicited local adverse reactions – N1	149	150
Any solicited local adverse reactions	60 (40.3)	71 (47.3)
Grade 3	0	3 (2.0)
Pain – N1	149	150
Any	48 (32.2)	58 (38.7)
Grade 3	0	0
Erythema (redness) – N1	149	150
Any	11 (7.4)	20 (13.3)
Grade 3	0	1 (0.7)
Swelling (hardness) – N1	149	150
Any	14 (9.4)	18 (12.0)
Grade 3	0	2 (1.3)
Axillary (or groin) swelling or tenderness – N1	149	150
Any	15 (10.1)	11 (7.3)
Grade 3	0	0

Abbreviations: Any = grade 1 or higher; N1 = number of participants who submitted any data for the event.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). Pain is injection site pain or tenderness. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: grade 1 = 5-20 mm; grade 2 = >20-50 mm; grade 3 = > 50 mm; grade 4 = necrosis or exfoliative dermatitis. Toxicity grade for axillary (underarm or groin) swelling or tenderness is defined as: grade 1 = some swelling or tenderness but no interference with normal daily activities; grade 2 = swelling or tenderness that interferes with normal daily activities; grade 3 = swelling or tenderness that prevents normal daily activities; grade 4 = emergency room visit or hospitalization.
Source (6 months to < 2 years): Study P204 Table 14.3.1.1.1.1 and Study P204 Table 14.3.1.1.2.1

Part 2

Solicited local ARs were more common in the mRNA-1273 group than in the placebo group. Solicited local ARs in both groups were mostly grade 1 and 2; grade 3 local ARs occurred in a higher percentage of participants in the mRNA-1273 group than in the placebo group. No grade 4 solicited local ARs were reported in Part 2 of the study. In the mRNA-1273 group, the percentage of participants experiencing overall and grade 3 solicited local ARs was higher after the second dose compared with the first dose. After any dose, the most common solicited local AR was injection site pain; the most common grade 3 solicited local ARs were erythema and swelling. No grade 3 events of injection site pain or axillary (or groin) swelling or tenderness were reported in either treatment group. After any dose, the majority of the solicited local ARs that occurred within 7 days in the mRNA-1273 group in Part 2 had an onset within the first day after any dose. Solicited local ARs persisting beyond 7 days after any dose occurred infrequently; 1.2% of participants in the mRNA-1273 group and 0.3%in the placebo group. In the mRNA-1273 group, there was a similar number of participants with persisting solicited ARs persisting beyond 7 days after dose 1 (1.2%) and dose 2 (1.2%), and in the placebo group (0.3%) of participants had persisting events persisting after dose 1 (with no participants with persisting events after dose 2). In the mRNA-1273 group, the most frequently reported event persisting beyond 7 days was axillary (or groin) swelling or

tenderness, all of which were mild (grade 1) with a similar number of events reported after dose 1 and dose 2 (dose 1: 14 events, 0.8%; and dose 2:16 events, 1.0%). This was compared to 1 (0.2%) mild event in the placebo group. In the mRNA-1273 group, 1.4% of participants reported solicited local ARs with onset after 7 days after dose 1. No participants reported solicited local ARs with onset after 7 days after dose 2. The ARs with onset after 7 days reported after any dose were pain (0.2%), erythema (redness) (0.9%), swelling (hardness) (0.4%), and axillary (or groin) swelling or tenderness (0.2%). In the placebo group, no solicited local ARs with onset after 7 days were reported after any dose.

Table 30: Summary of Solicited Local Adverse Reactions (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (6 months to < 2 years)

	Dose 1		Dose 2	
	Placebo (N = 582) n (%)	mRNA-1273 25 µg (N = 1746) n (%)	Placebo (N = 526) n (%)	mRNA-1273 25 µg (N = 1596) n (%)
Solicited local adverse reactions – N1	582	1745	526	1596
Any solicited local adverse reactions	193 (33.2)	775 (44.4)	159 (30.2)	868 (54.4)
Grade 3	2 (0.3)	9 (0.5)	0	22 (1.4)

	Dose 1		Dose 2	
	Placebo (N = 582) n (%)	mRNA-1273 25 µg (N = 1746) n (%)	Placebo (N = 526) n (%)	mRNA-1273 25 µg (N = 1596) n (%)
Pain – N1	582	1744	526	1596
Any	175 (30.1)	652 (37.4)	135 (25.7)	738 (46.2)
Grade 3	0	0	0	0
Erythema (redness) – N1	582	1744	526	1596
Any	24 (4.1)	150 (8.6)	20 (3.8)	215 (13.5)
Grade 3	2 (0.3)	5 (0.3)	0	13 (0.8)
Swelling (hardness) – N1	582	1744	526	1596
Any	15 (2.6)	146 (8.4)	11 (2.1)	243 (15.2)
Grade 3	0	5 (0.3)	0	14 (0.9)
Axillary (or groin) swelling or tenderness – N1	582	1743	526	1596
Any	26 (4.5)	102 (5.9)	28 (5.3)	148 (9.3)
Grade 3	0	0	0	0

Abbreviations: Any = grade 1 or higher; N1 = number of participants who submitted any data for the event.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1). Pain is injection site pain or tenderness. Toxicity grade for injection site erythema (redness) or swelling (hardness) is defined as: grade 1 = 5-20 mm; grade 2 = >20-50 mm; grade 3 = > 50 mm; grade 4 = necrosis or exfoliative dermatitis. Toxicity grade for axillary (underarm or groin) swelling or tenderness is defined as: grade 1 = some swelling or tenderness but no interference with normal daily activities; grade 2 = swelling or tenderness that interferes with normal daily activities; grade 3 = swelling or tenderness that prevents normal daily activities; grade 4 = emergency room visit or hospitalization.
Sources (6 months to < 2 years): Study P204 Table 14.3.1.1.1.2.1 and Study P204 Table 14.3.1.1.2.2.1

Solicited local ARs (2- to < 6-years-old)

Part 1

The incidences of the solicited local ARs were higher after any dose in the 50-µg group compared to the 25-µg group. In both mRNA-1273 dose groups, the incidence of solicited local ARs was higher after dose 2 than dose 1 and the majority of solicited local ARs in both groups were grade 1 or 2 in severity. All grade 3 solicited local ARs were reported in the 50-µg group. There were no grade 4 solicited local ARs after any dose in any group in Part 1. After any dose, the most common solicited AR was injection site pain. Pain was the only grade 3 solicited local AR and 2 events of grade 3 pain occurred in the 50-µg group. The majority of the solicited local ARs in participants in both groups occurred within the first 2 days after any dose and persisted for a median of 2 days in both dose groups. Individual solicited local ARs persisting beyond 7 days, all of which occurred in in the 50-µg group, included injection site erythema, swelling, and axillary (or groin) swelling or tenderness after dose 1. Solicited local ARs persisting beyond 7 days after dose 2 were from 2 participants who reported grade 1 injection site axillary (or groin) swelling or tenderness.

Table 31: Summary of Local Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (2- to < 6-year-olds)

	Dose 1		Dose 2	
	mRNA-1273 25 µg (N = 69) n (%)	mRNA-1273 50 µg (N = 152) n (%)	mRNA-1273 25 µg (N = 69) n (%)	mRNA-1273 50 µg (N = 154) n (%)
Solicited local adverse reactions – N1	69	152	69	154
Any solicited local adverse reactions	40 (58.0)	109 (71.7)	55 (79.7)	137 (89.0)
Grade 3 or above	0	2 (1.3)	0	2 (1.3)
Pain – N1	69	152	69	154
Any	39 (56.5)	104 (68.4)	54 (78.3)	136 (88.3)
Grade 3 or above	0	1 (0.7)	0	1 (0.6)
Erythema (redness) – N1	69	152	69	154
Any	4 (5.8)	23 (15.1)	6 (8.7)	22 (14.3)
Grade 3 or above	0	0	0	1 (0.6)
Swelling (hardness) – N1	69	152	69	154
Any	4 (5.8)	17 (11.2)	6 (8.7)	18 (11.7)
Grade 3 or above	0	1 (0.7)	0	0
Axillary (or groin) swelling or tenderness – N1	69	152	69	154
Any	1 (1.4)	10 (6.6)	1 (1.4)	16 (10.4)
Grade 3 or above	0	0	0	0

Abbreviations: Any = grade 1 or higher; N1 = number of participants who submitted any data for the event.
Note: Pain is injection site pain/tenderness. 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 (2 to < 6 years): Study P204 Table 14.3.1.1.1.1 and Table 14.3.1.1.2.1

Part 2

The solicited local ARs were more common in the mRNA-1273 group than in the placebo group after both doses. Solicited local ARs in both groups were mostly grade 1 and 2 in severity. In the mRNA-1273 group, the percentage of participants experiencing grade 3 solicited local ARs was higher after dose 2 when compared to dose 1 (1.2% versus 0.8%, respectively). After any dose, the most common solicited local AR was injection site pain; the most common grade 3 solicited local ARs were erythema, swelling, and pain. No grade 4 solicited local ARs were reported for either group in Part 2 of the study. The majority of the solicited local ARs in the mRNA-1273 group in Part 2 had a time to onset of 1 day after any dose with an event duration median of 2 days. The majority of the solicited local ARs in the placebo group also had a time to onset within 1 day of any dose with a median event duration of 1 day. Solicited local ARs persisting beyond 7 days occurred infrequently, in <1% of participants in either treatment group. In the mRNA-1273 group, solicited local ARs persisting beyond 7 days after dose 1 included injection site pain, erythema, swelling, and axillary (or groin) swelling or tenderness and in the placebo group, included injection site pain and axillary (or groin) swelling or tenderness. Solicited local ARs persisting beyond 7 days after dose 2 in the mRNA-1273 group included injection site pain, swelling, and axillary (or groin) swelling or tenderness while in the placebo group, there was a single event of injection

site pain persisting beyond 7 days after dose 2. In the mRNA-1273 group, 1.3% of participants reported solicited local ARs with onset after 7 days after dose 1. Fewer (0.1%) participants after dose 2 reported solicited local ARs with onset after 7 days. Only (< 0.1%) participant in the placebo group reported solicited local ARs with onset after 7 days post any dose and the reported was injection site erythema (redness).

Table 32: Summary of Solicited Local Adverse Reactions (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (2- to < 6-year-olds)

	Dose 1		Dose 2	
	Placebo (N = 970) n (%)	mRNA-1273 25 µg (N = 2957) n (%)	Placebo (N = 959) n (%)	RNA-1273 25 µg (N = 2938) n (%)
Solicited local adverse reactions – N1	970	2956	959	2938
Any solicited local adverse reactions	407 (42.0)	1874 (63.4)	404 (42.1)	2157 (73.4)
Grade 3 or above	4 (0.4)	23 (0.8)	0	34 (1.2)
Pain – N1	970	2954	959	2938
Any	382 (39.4)	1813 (61.4)	395 (41.2)	2099 (71.4)
Grade 3 or above	0	4 (0.1)	0	11 (0.4)
Erythema (redness) – N1	970	2955	959	2938
Any	14 (1.4)	164 (5.5)	15 (1.6)	259 (8.8)
Grade 3 or above	3 (0.3)	12 (0.4)	0	12 (0.4)
Swelling (hardness) – N1	970	2955	959	2938
Any	17 (1.8)	134 (4.5)	11 (1.1)	240 (8.2)
Grade 3 or above	2 (0.2)	10 (0.3)	0	13 (0.4)
Axillary (or groin) swelling or tenderness – N1	970	2954	959	2938
Any	56 (5.8)	205 (6.9)	31 (3.2)	267 (9.1)
Grade 3 or above	0	0	0	1 (< 0.1)

Abbreviations: Any = grade 1 or higher; N1 = number of participants who submitted any data for the event.
Note: Pain is injection site pain/tenderness. 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 (2 to < 6 years): Study P204 Table 14.3.1.1.1.2.1 and Table 14.3.1.1.2.2.1

Solicited Systemic Adverse Reactions (6 Months to < 2 Years)

Part 1

The overall incidences of solicited systemic ARs were similar after doses 1 and 2, occurring in the majority of participants receiving mRNA-1273 (71.8% after dose 1, versus 69.3% after dose 2). Grade 3 solicited systemic ARs were more common after dose 2 (2.0%) compared with after dose 1 (0.7%). Irritability/crying was the most commonly reported event, occurring in over 60% of participants after

each dose. There was one event of Grade 3 fever occurring in a 1-year-old male [FLD1]that started after the second dose on day 6 and resolved on post-dose day 8. The event was reported as moderate in intensity and related to vaccination. No other concurrent AEs were reported. No grade 4 solicited systemic ARs were reported in Part 1 of the study. The majority of the solicited systemic ARs in participants in Part 1 occurred within the first 2 days after each dose at both dose levels and persisted for a median of 3.0 days in the mRNA-1273 25 µg group. Solicited systemic ARs persisting beyond 7 days after any dose (11.3%) of participants were irritability/crying, loss of appetite, sleepiness, and fever. Irritability/crying was the most commonly reported of these, occurring in 12/150 (8.0%) participants. There were 2 grade 3 events of loss of appetite. Two participants (1.3%) reported solicited systemic ARs of fever with onset after 7 days after any dose.

Table 33: Summary of Solicited Systemic Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (6 Months to < 2 years

	Dose 1	Dose 2
	mRNA-1273 25 µg (N = 149) n (%)	mRNA-1273 25 µg (N = 150) n (%)
Solicited systemic adverse reactions – N1	149	150
Any solicited systemic adverse reaction	107 (71.8)	104 (69.3)
Grade 3	1 (0.7)	3 (2.0)
Fever – N1	149	150
Any	11 (7.4)	17 (11.3)
Grade 3	0	1 (0.7)

	Dose 1	Dose 2
	mRNA-1273 25 µg (N = 149) n (%)	mRNA-1273 25 µg (N = 150) n (%)
Irritability/crying – N1	149	150
Any	94 (63.1)	94 (62.7)
Grade 3	0	0
Sleepiness – N1	149	150
Any	39 (26.2)	42 (28.0)
Grade 3	1 (0.7)	0
Loss of appetite – N1	149	150
Any	28 (18.8)	38 (25.3)
Grade 3	0	2 (1.3)

Abbreviations: Any = grade 1 or higher; G = toxicity grade; N1 = number of participants who submitted any data for the event.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for Fever for subjects age 6 to ≤ 36 months is defined as: G1 = 38 - 38.4°C; G2 = 38.5 - 39.5°C; G3 = 39.6 - 40°C; G4 = > 40°C.
Source (6 months to < 2 years): Study P204 Table 14.3.1.1.1.1 and Study P204 Table 14.3.1.1.2

Part 2

The overall incidences of solicited systemic ARs were similar in the mRNA-1273 group (88.5%) and the placebo group (84.4%). In the mRNA-1273 group, solicited systemic ARs were similar after doses 1 (76.4%) and 2 (73.6%), and in the placebo group the incidence was slightly higher after dose 1 (72.3%) compared to dose 2 (66.5%). The majority of solicited systemic ARs were grade 1 to grade 2 in severity. Grade 3 and higher solicited systemic ARs after any dose were more common in the mRNA-1273 group (5.1%) than in the placebo group (3.8%). After any dose, the most frequently reported solicited systemic AR were similar between placebo and mRNA-1273: irritability/crying (77.7% vs 81.5%), followed by sleepiness (52.1% vs 51.1%), and loss of appetite (40.8% vs 45.7%). Incidences of grade 3 solicited systemic ARs of fever (1.5% vs 1.0%) and sleepiness (0.3% vs 0.3%). Grade 3 solicited systemic ARs of loss of appetite (placebo:0.5%; mRNA-1273: 1.4%) and irritability/crying (placebo: 1.7%; mRNA-1273:2.8%) were higher in the mRNA-1273 group. The only grade 4 solicited systemic ARs were reported for fever and they were similar with 0.2% for both groups. The majority of the solicited systemic ARs in participants in the mRNA-1273 group in Part 2 occurred within the first 2 days after any dose and persisted for a median of 2.0 days in the placebo group and 3.0 days in the mRNA-1273 group. Solicited systemic ARs persisting beyond 7 days after any dose were reported for 11.5% of participants in the placebo group and 12.6% of participants in the mRNA-1273 group, and were reported in similar proportions for fever (0.9% vs 1.7%), irritability/crying (8.7% vs 9.3%), sleepiness (2.6% vs2.0%), and loss of appetite (4.8% vs 3.9%). After any dose, 0.3% of participants in the placebo group and 0.7% of participants in the mRNA-1273 group reported solicited systemic ARs with onset after Day 7. Loss of appetite (0.3%) was the only event reported in the placebo group, and the most frequently reported solicited systemic AR in the mRNA-1273 group was fever (0.5%) followed by irritability/crying (0.2%), sleepiness (< 0.1%), and loss of appetite (< 0.1%).

Table 34: Summary of Solicited Systemic Adverse Reactions (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (6 Months to < 2 years)

	Dose 1		Dose 2	
	Placebo (N = 582) n (%)	mRNA-1273 25 µg (N = 1746) n (%)	Placebo (N = 526) n (%)	mRNA-1273 25 µg (N = 1596) n (%)
Solicited systemic adverse reactions – N1	582	1745	526	1596
Any solicited systemic adverse reactions	421 (72.3)	1334 (76.4)	350 (66.5)	1174 (73.6)
Grade 3 or above	11 (1.9)	46 (2.6)	12 (2.3)	47 (2.9)
Fever – N1	582	1743	526	1594
Any	49 (8.4)	191 (11.0)	44 (8.4)	232 (14.6)
Grade 3 or above	4 (0.7)	12 (0.7)	6 (1.1)	10 (0.6)
Irritability/crying – N1	581	1737	525	1589
Any	361 (62.1)	1175 (67.6)	307 (58.5)	1021 (64.3)
Grade 3 or above	6 (1.0)	24 (1.4)	5 (1.0)	25 (1.6)
Sleepiness – N1	581	1739	525	1589
Any	217 (37.3)	645 (37.1)	175 (33.3)	558 (35.1)
Grade 3 or above	1 (0.2)	4 (0.2)	1 (0.2)	1 (< 0.1)
Loss of appetite – N1	581	1737	525	1589
Any	152 (26.2)	524 (30.2)	132 (25.1)	510 (32.1)
Grade 3 or above	1 (0.2)	10 (0.6)	2 (0.4)	16 (1.0)

Abbreviations: Any = grade 1 or higher; G = toxicity grade; N1 = number of participants who submitted any data for the event.
Note: Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for solicited systemic adverse reactions other than fever 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. Toxicity grades for fever based on age group (6 months to < 2 years) are described in Section 2.5.5.1.3.2.
Source (6 months to < 2 years): Study P204 Table 14.3.1.1.1.2.1 and Table 14.3.1.1.2.2.1

Analysis of Fever in Part 2 (6 Months to < 2 Years)

Most fevers (defined as temperature ≥ 38°C, tympanic method of management preferred) were reported on Day 1 and 2 after either dose, and in both the mRNA-1273 and the placebo group. After both doses, the rate of fevers reported was higher in the mRNA-1273 group compared to the placebo group. For the remaining 5 days after Day 2 for either dose, the reported fever rates were similar between the mRNA-1273 group and the placebo group. Most of these participants reported a fever < 39°C, with a higher rate reported in the mRNA-1273 group after both dose 1 and dose 2. The rates of fevers between 39°C and 40°C were similar in all groups. Four participants in the mRNA-1273 group and one participant in the placebo group had fever of 40°C after any dose. All three fevers after Dose 2 which occurred in the mRNA-1273 group had additional, concurrent AEs reported that could have contributed to the incidence and severity of the fever (URI). One placebo recipient reported a fever over 40°C after Dose 1; this participant also had a concurrent AE of 'viral rash' reported at the time of fever.

Table 35: Onset of Fever ≥ 38°C in Part 2 (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (6 months to < 2 years)

	Dose 1		Dose 2	
	Placebo (N = 582) n (%)	mRNA-1273 25 µg (N = 1746) n (%)	Placebo (N = 526) n (%)	mRNA-1273 25 µg (N = 1596) n (%)
Fever - N1	582	1743	526	1594
Day 1, 30 Minutes After Vaccination (at Study Clinic)	5 (0.9)	11 (0.6)	3 (0.6)	13 (0.8)
Day 1, After Vaccination (at Home)	8 (1.4)	35 (2.0)	4 (0.8)	67 (4.2)
Day 2	9 (1.5)	44 (2.5)	13 (2.5)	89 (5.6)
Day 3	6 (1.0)	16 (0.9)	6 (1.1)	22 (1.4)
Day 4	8 (1.4)	18 (1.0)	4 (0.8)	8 (0.5)
Day 5	7 (1.2)	20 (1.1)	5 (1.0)	11 (0.7)
Day 6	2 (0.3)	26 (1.5)	4 (0.8)	11 (0.7)
Day 7	4 (0.7)	21 (1.2)	5 (1.0)	11 (0.7)

Abbreviations: N1 = number of participants who submitted any data for the event.
Source (6 months to < 2 years): Study P204 Table 14.3.1.3.1.2.1 and Study P204 Table 14.3.1.3.2.2.1

Local solicited ARs were reported in a higher percentage of participants in the mRNA-1273 group compared with the placebo group after each dose and at higher frequency after dose 2 (54.4%) compared to dose 1 (44.4%) in the mRNA-1273 group. Systemic ARs occurred at similar rates after doses 1 (76.4%) and 2 (73.6%) in the mRNA-1273 group. The majority of solicited ARs were grade 1 or grade 2. The incidence of grade 3 solicited ARs was infrequent in both groups (< 5%) and slightly higher in the mRNA-1273 group than in the placebo group after any dose.

Solicited systemic ARs (2- to < 6-year-olds)

Part 1

Overall solicited systemic ARs were more common after dose 2 than dose 1 at both dose levels and in both age groups (25 and 50 µg RNA-1273). The most commonly reported event in the 24-month- to ≤ 36-month-old age group occurring after either dose or dose level was irritability. The most commonly occurring Grade 3 event in this younger age group was fever, occurring only in the 50-µg group after both doses (4.2% after dose 1 and 11.5% after dose 2). In the 37-month- to < 6-year-old group, the most commonly occurring event after either dose or dose level was fatigue. The most commonly occurring Grade 3 event in this age group was fever after dose 2, occurring in 1.7% in the 25-µg group and 6.3% in the 50-µg group. Advancement of the 25-ug dose to Part 2 was based on the balance of reactogenicity and immunogenicity. Regarding reactogenicity of the two dosages, the higher rate and severity of solicited systemic ARs in the 50-µg group compared to the 25-µg group (particularly for fever) contributed to advancement of 25-µg to Part 2.

Table 36: Summary of Solicited Systemic Adverse Reactions (Part 1 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (2- to < 6-year-olds)

	24-month- to ≤ 36-month-olds				37-month- to < 6-year-olds			
	Dose 1		Dose 2		Dose 1		Dose 2	
	mRNA-1273 25 µg (N = 9) n (%)	mRNA-1273 50 µg (N = 24) n (%)	mRNA-1273 25 µg (N = 9) n (%)	mRNA-1273 50 µg (N = 26) n (%)	mRNA-1273 25 µg (N = 60) n (%)	mRNA-1273 50 µg (N = 128) n (%)	mRNA-1273 25 µg (N = 60) n (%)	mRNA-1273 50 µg (N = 126) n (%)
Any solicited systemic adverse reaction	5 (55.6)	8 (33.3)	8 (88.9)	20 (76.9)	16 (26.7)	54 (42.2)	29 (48.3)	85 (66.4)
Grade 3 or above	0	1 (4.2)	0	3 (11.5)	0	2 (1.6)	1 (1.7)	11 (8.6)
Fever – N1	9	24	9	26	60	128	60	128
Any	1 (1.1)	2 (8.3)	0	9 (34.6)	1 (1.7)	8 (6.3)	6 (10.0)	32 (25.0)
Grade 3 or above	0	1 (4.2)	0	3 (11.5)	0	0	1 (1.7)	8 (6.3)
Irritability/crying – N1	9	23	9	26	(-)	(-)	(-)	(-)
Any	5 (55.6)	6 (26.1)	6 (66.7)	18 (69.2)	(-)	(-)	(-)	(-)
Grade 3 or above	0	0	0	0	(-)	(-)	(-)	(-)
Sleepiness – N1	9	23	9	26	(-)	(-)	(-)	(-)
Any	2 (22.2)	3 (13.0)	2 (22.2)	10 (38.5)	(-)	(-)	(-)	(-)
Grade 3 or above	0	0	0	0	(-)	(-)	(-)	(-)
Loss of appetite – N1	9	23	9	26	(-)	(-)	(-)	(-)
Any	1 (11.1)	0	2 (22.2)	7 (26.9)	(-)	(-)	(-)	(-)
Grade 3 or above	0	0	0	2 (7.7)	(-)	(-)	(-)	(-)
Headache – N1	(-)	(-)	(-)	(-)	60	126	60	127
Any	(-)	(-)	(-)	(-)	5 (8.3)	13 (10.3)	11 (18.3)	33 (26.0)
Grade 3 or above	(-)	(-)	(-)	(-)	0	0	0	1(0.8)
Fatigue – N1	(-)	(-)	(-)	(-)	60	126	60	127
Any	(-)	(-)	(-)	(-)	8 (13.3)	43 (34.1)	21 (35.0)	70 (55.1)
Grade 3 or above	(-)	(-)	(-)	(-)	0	2 (1.6)	0	5 (3.9)
Myalgia – N1	(-)	(-)	(-)	(-)	60	126	60	127

	24-month- to ≤ 36-month-olds				37-month- to < 6-year-olds			
	Dose 1		Dose 2		Dose 1		Dose 2	
	mRNA-1273 25 µg (N = 9) n (%)	mRNA-1273 50 µg (N = 24) n (%)	mRNA-1273 25 µg (N = 9) n (%)	mRNA-1273 50 µg (N = 26) n (%)	mRNA-1273 25 µg (N = 60) n (%)	mRNA-1273 50 µg (N = 128) n (%)	mRNA-1273 25 µg (N = 60) n (%)	mRNA-1273 50 µg (N = 126) n (%)
Any	(-)	(-)	(-)	(-)	4 (6.7)	12 (9.5)	9 (15.0)	24 (18.9)
Grade 3 or above	(-)	(-)	(-)	(-)	0	1 (0.8)	0	1 (0.8)
Arthralgia – N1	(-)	(-)	(-)	(-)	60	126	60	127
Any	(-)	(-)	(-)	(-)	2 (3.3)	5 (4.0)	3 (5.0)	11 (8.7)
Grade 3 or above	(-)	(-)	(-)	(-)	0	1 (0.8)	0	0
Nausea/vomiting – N1	(-)	(-)	(-)	(-)	60	126	60	127
Any	(-)	(-)	(-)	(-)	2 (3.3)	7 (5.6)	5 (8.3)	16 (12.6)
Grade 3 or above	(-)	(-)	(-)	(-)	0	0	0	0
Chills – N1	(-)	(-)	(-)	(-)	60	126	60	127
Any	(-)	(-)	(-)	(-)	0	4 (3.2)	3 (5.0)	20 (15.7)
Grade 3 or above	(-)	(-)	(-)	(-)	0	0	0	0

Abbreviations: Any = grade 1 or higher; N1 = number of participants who submitted any data for the event.
(-) indicates that this assessment is not applicable to participants in this age group.
Note: Toxicity grade for solicited systemic adverse reactions other than fever 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. Toxicity grades for fever based on age group (2 years to ≤ 36 months or 37 months to < 6 years). Protocol-defined fever grades in participants aged 37 months to < 6 years were the following: grade 1 = 38°C to 38.4°C, grade 2 = 38.5°C to 38.9°C, grade 3 = 39°C to 40°C, and grade 4 > 40°C. Protocol-defined fever grades in participants 2 years to ≤ 36 months were the following: grade 1 = 38°C to 38.5°C, grade 2 = 38.6°C to 39.5°C, grade 3 = 39.6°C to 40°C, and grade 4 > 40.0°C. .
Source (2 to < 6 years): Study P204 Table 14.3.1.1.4.1.4 and Study P204 Table 14.3.1.1.4.1.5

Part 2

Solicited systemic ARs were more common in the mRNA-1273 group than in the placebo group after both doses. In the mRNA-1273 group solicited systemic ARs, including Grade 3 ARs, were more common after

dose 2 than dose 1; in the placebo group event rates were higher after dose 1 compared to dose 2 (Table 39). For both the mRNA-1273 and placebo group, most solicited systemic ARs were grade 1 to 2 in severity. In the younger age group (2-years to ≤ 36-months), after any dose, the most common solicited systemic ARs in either group, occurring in >20% of participants, were irritability/crying, sleepiness and loss of appetite. The most common grade 3 solicited systemic ARs in the mRNA-1273 group after any dose in >1% of participants in at least one dose group were irritability/crying, and fever ≥39.0°C; in the placebo group these were fever ≥39.0°C and irritability/crying. In the older age group (37-month- to < 6-years), after any dose, the most common solicited systemic AR was fatigue in >20% of participants. The most common grade 3 solicited systemic ARs, occurring in >1% of participants in at least one dose group, in the mRNA-1273 group were fatigue and fever and in the placebo group was fatigue. Fever was the only grade 4 solicited systemic AR reported in either group. Most solicited systemic ARs in the mRNA-1273 group occurred within the first 2 days after either dose and lasted for a median of 2 days. Solicited systemic ARs persisting beyond 7 days after any dose were reported in similar proportions in the placebo group (5.8%) as in the mRNA-1273 group (4.7%). Participants reporting solicited systemic ARs with onset after 7 days after any dose was similar in the mRNA-1273 and placebo group with 0.4%. Systemic ARs reported with an onset after 7 days after any dose in the mRNA-1273 group included fever, fatigue, irritability/crying, sleepiness, and loss of appetite, while systemic ARs reported with an onset after 7 days after any dose in the placebo group included events of fever, headache, and loss of appetite.

Table 37: Summary of Solicited Systemic Adverse Reactions Other than Fever (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (2- to < 6-year-olds)

	24-month- to ≤ 36-month-olds				37-month- to < 6-year-olds			
	Dose 1		Dose 2		Dose 1		Dose 2	
	Placebo (N = 320) n (%)	mRNA-1273 25 µg (N = 944) n (%)	Placebo (N = 330) n (%)	mRNA-1273 25 µg (N = 963) n (%)	Placebo (N = 650) n (%)	mRNA-1273 25 µg (N = 2013) n (%)	Placebo (N = 629) n (%)	mRNA-1273 25 µg (N = 1975) n (%)
Any solicited systemic adverse reaction	198 (61.9)	612 (65.0)	194 (58.8)	651 (67.6)	290 (44.6)	983 (48.8)	234 (37.2)	1163 (58.9)
Grade 3 or above	10 (3.1)	21 (2.2)	2 (0.6)	31 (3.2)	15 (2.3)	48 (2.4)	11 (1.7)	104 (5.3)
Fever – N1	320	942	330	962	650	2013	627	1974
Any	25 (7.8)	106 (11.3)	35 (10.6)	182 (18.9)	33 (5.1)	155 (7.7)	28 (4.5)	316 (16.0)
Grade 3 or above	4 (1.3)	6 (0.6)	0	15 (1.6)	5 (0.8)	24 (1.2)	2 (0.3)	62 (3.1)
Irritability/crying – N1	319	941	330	963	(-)	(-)	(-)	(-)
Any	163 (51.1)	513 (54.5)	148 (44.8)	523 (54.3)	(-)	(-)	(-)	(-)
Grade 3 or above	6 (1.9)	12 (1.3)	2 (0.6)	10 (1.0)	(-)	(-)	(-)	(-)
Sleepiness – N1	319	941	330	963	(-)	(-)	(-)	(-)
Any	92 (28.8)	285 (30.3)	89 (27.0)	347 (36.0)	(-)	(-)	(-)	(-)
Grade 3 or above	0	2 (0.2)	0	1 (0.1)	(-)	(-)	(-)	(-)
Loss of appetite – N1	319	941	330	963	(-)	(-)	(-)	(-)
Any	71 (22.3)	225 (23.9)	69 (20.9)	294 (30.5)	(-)	(-)	(-)	(-)
Grade 3 or above	1 (0.3)	7 (0.7)	0	8 (0.8)	(-)	(-)	(-)	(-)
Headache – N1	(-)	(-)	(-)	(-)	650	2013	629	1975
Any	(-)	(-)	(-)	(-)	78 (12.0)	232 (11.5)	51 (8.1)	310 (15.7)
Grade 3 or above	(-)	(-)	(-)	(-)	2 (0.3)	5 (0.2)	1 (0.2)	8 (0.4)
Fatigue – N1	(-)	(-)	(-)	(-)	650	2013	629	1975
Any	(-)	(-)	(-)	(-)	236 (36.3)	807 (40.1)	185 (29.4)	956 (48.4)
Grade 3 or above	(-)	(-)	(-)	(-)	11 (1.7)	21 (1.0)	8 (1.3)	45 (2.3)
Myalgia – N1	(-)	(-)	(-)	(-)	650	2013	629	1975

	24-month- to ≤ 36-month-olds				37-month- to < 6-year-olds			
	Dose 1		Dose 2		Dose 1		Dose 2	
	Placebo (N = 320) n (%)	mRNA-1273 25 µg (N = 944) n (%)	Placebo (N = 330) n (%)	mRNA-1273 25 µg (N = 963) n (%)	Placebo (N = 650) n (%)	mRNA-1273 25 µg (N = 2013) n (%)	Placebo (N = 629) n (%)	mRNA-1273 25 µg (N = 1975) n (%)
Any	(-)	(-)	(-)	(-)	60 (9.2)	200 (9.9)	47 (7.5)	310 (15.7)
Grade 3 or above	(-)	(-)	(-)	(-)	2 (0.3)	5 (0.2)	3 (0.5)	9 (0.5)
Arthralgia – N1	(-)	(-)	(-)	(-)	650	2013	629	1975
Any	(-)	(-)	(-)	(-)	32 (4.9)	124 (6.2)	28 (4.5)	168 (8.5)
Grade 3 or above	(-)	(-)	(-)	(-)	1 (0.2)	2 (< 0.1)	0	3 (0.2)
Nausea/vomiting – N1	(-)	(-)	(-)	(-)	650	2013	629	1975
Any	(-)	(-)	(-)	(-)	50 (7.7)	137 (6.8)	30 (4.8)	194 (9.8)
Grade 3 or above	(-)	(-)	(-)	(-)	2 (0.3)	7 (0.3)	0	6 0.3)
Chills – N1	(-)	(-)	(-)	(-)	650	2013	629	1975
Any	(-)	(-)	(-)	(-)	40 (6.2)	129 (6.4)	31 (4.9)	245 (12.4)
Grade 3 or above	(-)	(-)	(-)	(-)	0	1 (< 0.1)	2 (0.6)	10 (1.0)

Abbreviations: Any = grade 1 or higher; N1 = number of participants who submitted any data for the event.
(-) indicates that this assessment is not applicable to participants in this age group.
Note: Toxicity grade for solicited systemic adverse reactions other than fever 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. Toxicity grades for fever based on age group (2 years to ≤ 36 months or 37 months to < 6 years). Protocol-defined fever grades in participants aged 37 months to < 6 years were the following: grade 1 = 38°C to 38.4°C, grade 2 = 38.5°C to 38.9°C, grade 3 = 39°C to 40°C, and grade 4 > 40°C. Protocol-defined fever grades in participants 2 years to ≤ 36 months were the following: grade 1 = 38°C to 38.5°C, grade 2 = 38.6°C to 39.5°C, grade 3 = 39.6°C to 40°C, and grade 4 > 40.0°C.
Source (2 to < 6 years): Study P204 Table 14.3.1.1.4.19 and Study P204 Table 14.3.1.1.4.20

Analysis of Fever in Part 2 (2- to < 6-year-olds)

Fever has been reported in both treatment groups after any dose, with a higher frequency in the study vaccine group after dose 2 and most commonly reported on Day 1 or Day 2 after vaccination.

Table 38: Onset of Fever ≥38°C in Part 2 (Part 2 – First Injection Solicited Safety Set, Second Injection Solicited Safety Set) (2- to < 6-year-olds)

	Dose 1		Dose 2	
	Placebo (N = 970) n (%)	mRNA-1273 25 µg (N = 2957) n (%)	Placebo (N = 959) n (%)	mRNA-1273 25 µg (N = 2938) n (%)
Fever - N1	970	2955	957	2936
Day 1, 30 Minutes After Vaccination (at Study Clinic)	3 (0.3)	13 (0.4)	0	11 (0.4)
Day 1, After Vaccination (at Home)	16 (1.6)	52 (1.8)	14 (1.5)	158 (5.4)
Day 2	9 (0.9)	78 (2.6)	11 (1.1)	243 (8.3)
Day 3	5 (0.5)	26 (0.9)	8 (0.8)	20 (0.7)
Day 4	5 (0.5)	22 (0.7)	6 (0.6)	15 (0.5)
Day 5	6 (0.6)	18 (0.6)	7 (0.7)	17 (0.6)
Day 6	6 (0.6)	33 (1.1)	13 (1.4)	11 (0.4)
Day 7	8 (0.8)	19 (0.6)	4 (0.4)	23 (0.8)

Abbreviations: N1 = number of participants who submitted any data for the event.
Source (2 to < 6 years): Study P204 Table 14.3.1.3.1.2.1 and Study P204 Table 14.3.1.3.2.2.1

Reported fevers lasted for a median duration of 1 day after any dose in both treatment groups (Study P204 [2 to < 6 years] Table 14.3.1.4.1.2 and Study P204 [2 to < 6 years] Table 14.3.1.4.2.2).

The majority of the reported fevers were in the range of ≥ 38 to 38.9°C after any dose in both treatment groups. Initially there were reported 13 events of grade 4 fever events determined, therefore 3 of the 13 fever events were incorrectly reported as grade 4, given that none of these 3 participants recorded any elevated temperature. The 10 confirmed events were discussed further as: 8 (0.3%) in the mRNA-1273 group and 2 (0.2%) in the placebo group. The 8 events in the study vaccine group occurred mostly after dose 2, with 3 of the 8 events occurring after dose 1 and 5 of the 8 events after dose 2. Four of the 10 events of grade 4 fever reported concurrent AEs including: 3 (of 8) in the mRNA-1273 group (upper respiratory tract infection; croup; bilateral viral pneumonia) and 1 (of 2) in the placebo group (COVID-19 infection).

Unsolicited Adverse Events

In both parts of the trial, unsolicited AEs after any dose were collected during the 28 days after each injection and are divided in the 2 age cohorts and respective parts.

Unsolicited Adverse Events (6 Months to < 2 Years)

Part 1

The summary of unsolicited AEs reported in Part 1 is provided in the table below. MAAEs reflect those anticipated in paediatric populations and in a study conducted in the winter and during the Omicron variant surge. The most commonly reported SOC for MAAEs was infections and infestations (19.3% out of total of 30.0%) reflecting typical childhood infectious diseases in this age group.

Table 39: Summary of Subjects Reporting at Least One Unsolicited Adverse Event up to 28 Days After Any Dose (Part 1 – Safety Set) (6 Months to < 2 Years)

Category	mRNA-1273 25 µg (N = 150)
Unsolicited TEAEs regardless of relationship to study vaccination	
All	80 (53.3)
Serious	2 (1.3)
Fatal	0
Medically attended	45 (30.0)
Leading to discontinuation from study vaccine	0
Leading to discontinuation from participation in the study	0
Severe	4 (2.7)
Special Interest (AESI)	1 (0.7)
Unsolicited TEAEs related to study vaccination	
All	23 (15.3)
Serious	0
Fatal	0
Medically attended	4 (2.7)
Leading to discontinuation from study vaccine	0
Leading to discontinuation from participation in the study	0
Severe	2 (1.3)
Special Interest (AESI)	0

Abbreviation: TEAE= treatment-emergent adverse event.
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity grade=0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
Source (6 months to < 2 years): Study P204 Table 14.3.1.7.1.1

The most common reported unsolicited AEs reported, i.e. those reported by more than 1% for part 1 were: pyrexia (9.3%), upper respiratory tract infection (8.7%), irritability (8.0%), teething (7.3%), otitis media (6.0%), rhinorrhoea (6.0%), decreased appetite (6.0%), hand-foot- and foot and- mouth diseases (4.0%), cough (3.3%), injection site lymphadenopathy (2.7%) and the other symptoms in lower percentages. Four (2.7%) participants experienced 6 severe TEAEs reported within 28 days of any dose, including decreased appetite (2) febrile convulsion (1), this AE was also reported as an SAE. Three events of cough, wheezing and urticarial occurred in one participant 21 days after dose 2 and were assessed as not related by the investigator.

Part 2

The incidence of unsolicited AEs was similar between the mRNA-1273 group and the placebo group. Serious unsolicited TEAEs within 28 days of any dose were reported in few (0.5%) participants in the mRNA-1273 group and 0 participants in the placebo group. MAAEs were also reported in similar proportions in the two groups: 27.6% in the mRNA-1273 group and 27.3% in the placebo group.

Table 40: Summary of Subjects Reporting at Least One Unsolicited Adverse Event up to 28 Days After Any Dose (Part 2 – Safety Set) (6 months to < 2 years)

Category	Placebo (N = 589)	mRNA-1273 25 µg
Unsolicited TEAEs regardless of relationship to study vaccination		
All	284 (48.2)	869 (49.3)
Nonserious	284 (48.2)	868 (49.3)
Serious	0	8 (0.5)
Fatal	0	0
Medically attended	161 (27.3)	486 (27.6)
Leading to discontinuation from study vaccine	1 (0.2)	1 (< 0.1)
Leading to discontinuation from participation in the study	1 (0.2)	0
Severe	4 (0.7)	21 (1.2)
Special Interest (AESI)	0	3 (0.2)
Unsolicited TEAEs related to study vaccination		
All	71 (12.1)	292 (16.6)
Nonserious	71 (12.1)	292 (16.6)
Serious	0	1 (< 0.1)
Fatal	0	0
Medically attended	3 (0.5)	23 (1.3)
Leading to discontinuation from study vaccine	0	1 (< 0.1)
Leading to discontinuation from participation in the study	0	0
Severe	3 (0.5)	12 (0.7)
Special Interest (AESI)	0	2 (0.1)

Abbreviation: TEAE = treatment-emergent adverse event.
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity grade = 0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
Source (6 months to < 2 years): Study P204 Table 14.3.1.7.1.2

The TEAEs experienced in the mRNA-1273 group were comparable with those in the placebo group. The unsolicited AEs higher in the placebo group compared with the mRNA-1273 group by at least 1% were: upper respiratory tract infection, COVID-19, and otitis media. The unsolicited AEs higher in the mRNA-1273 group compared with the placebo group by at least 1% were: croup infectious, diarrhoea, and injection site lymphadenopathy. Twenty-one (1.2%) participants in the mRNA-1273 group and 4 (0.7%) participants in the placebo group reported at least 1 severe TEAE within 28 days of any dose during Part 2. Unsolicited severe TEAEs in the mRNA-1273 group of Part 2 had the following PTs: respiratory tract infection viral, bronchiolitis, gastroenteritis viral, mastoiditis, pneumonia, respiratory syncytial virus infection, rhinovirus infection, food allergy, decreased appetite, electrolyte imbalance, irritability, febrile convulsion, urticaria, pyrexia, and radial head dislocation. All events were reported once except for irritability (n = 8, 0.5%), decreased appetite (n = 3, 0.2%), and febrile convulsion (n = 2, 0.1%). Unsolicited severe TEAEs in the placebo group of Part 2 had the following PTs: respiratory tract infection viral, hand-foot-and-mouth disease, decreased appetite, irritability, and pyrexia. The only event occurring more than once was pyrexia (n = 2, 0.3%) both occurring at Day 7 after most recent dose of IP and both considered related. The TEAEs involving RTIs up to 28 days showed comparable frequencies in reporting rates, therefore imbalances of several respiratory related infections were noted, occurring with greater frequency in the mRNA-1273 group compared to the placebo group. According to MAH the 3:1 randomisation scheme, low event rates, and multiple comparisons all increase the possibility that these

imbalances occurred by chance and are not suggestive of a safety concern. The events of pneumonia, RSV infection, and croup are summarised for the 6 months to <2-year-old age group.

- **Croup infectious** were reported for 2 (0.3%) placebo participants and 23 (1.3%) participants of mRNA-1273.
- **Respiratory Syncytial Virus Infection** was reported for 3 (0.5%) placebo participants and 14 (0.8%) participants of mRNA-1273.
- **Pneumonia**: No cases in the placebo group and 3 (0.2 %) participants of mRNA-1273.

Unsolicited AEs considered being vaccine related (6 Months to < 2 years)

Part 1

The most common AEs considered being vaccine related in Part 1 of the study reported within 28 days included irritability (7.3%), decreased appetite (4.7%), injection site lymphadenopathy (2.7%) and somnolence (2.7%). According to MAH the majority of AEs were consistent with the known reactogenicity profile of mRNA-1273.

Part 2

Mostly the AEs considered being vaccine related in Part 2 reported within 28 days were balanced between the placebo and mRNA-1273 groups. The most frequently reported unsolicited AEs considered being vaccine related in both groups belonged to the SOC were: general and administration disorders with 4.7% in the mRNA-1273 group and 1.4% in the placebo group and the leading symptoms in this SOC were pyrexia with 1.5 % vs 0.7%, followed by injection site lymphadenopathy (1.4 % vs 0.2%), injection site erythema (1.1 % versus 0.2%), injection site induration (0.5% versus 0.2 %). The second most common SOC was skin and cutaneous disorders with 0.6% in the mRNA-1273 group versus 0.2% in the placebo group.

Unsolicited Adverse Events (2- to < 6-year-olds)

Part 1

As of 21st February 2022, a total of 23.2% of participants in the 25-µg group of Part 1 and 36.1% of participants in the 50-µg group reported at least 1 unsolicited TEAE. The incidence of medically attended adverse events (MAAEs) was lower in the 25-µg group compared to the 50-µg group (7.2 % versus 20.6%). The most commonly reported SOC for MAAEs was infections and infestations (19.3% out of 30.0%) reflecting typical childhood infectious diseases in this age group. In the 25-µg group, 7.2% of participants reported at least 1 TEAE determined by the investigator to be related to IP compared to 11% of participants in the 50-µg group. None of the experienced MAAEs in the 25-µg group experienced were considered to be related to IP or severe TEAEs while in the 50-µg group, 1.9% participants reported MAAEs considered by the investigator to be related to study IP and 2.6% participants experienced severe TEAEs within 28 days of any dose, 1.9% of which were considered related to study vaccine.

Table 41: Summary of Subjects Reporting at Least 1 Unsolicited Adverse Event up to 28 Days After Any Dose (Part 1 – Safety Set) (2- to < 6-year-olds)

Category	mRNA-1273 25 µg (N = 69) n (%)	mRNA-1273 50 µg (N = 155) n (%)
Unsolicited TEAEs regardless of relationship to study vaccination		
All	16 (23.2)	56 (36.1)
Serious	0	0
Fatal	0	0
Medically attended	5 (7.2)	32 (20.6)
Leading to discontinuation from study vaccine	0	0
Leading to discontinuation from participation in the study	0	0
Severe	0	4 (2.6)
Special Interest (AESI)	0	0
Unsolicited TEAEs related to study vaccination		
All	5 (7.2)	17 (11.0)
Serious	0	0
Fatal	0	0
Medically attended	0	3 (1.9)
Leading to discontinuation from study vaccine	0	0
Leading to discontinuation from participation in the study	0	0
Severe	0	3 (1.9)
Special Interest (AESI)	0	0

Abbreviation: TEAE= treatment-emergent adverse event.
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity grade=0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
Source (2 to < 6 years): Study P204 Table 14.3.1.7.1.1

The most common reported unsolicited AEs, i.e. those reported by more than 1% for part 1 were mostly higher in the 50-µg group compare to the 25-µg group: upper respiratory tract infection (7.7% vs 0), pyrexia (7.7% vs 2.9%), injection site erythema (4.5% vs 4.3%), cough (3.9% vs 5.8%), rhinorrhoea (3.9% vs 1.4%). Four participants in the 50-µg group experienced severe TEAEs: 2 events of fatigue and 2 events of pyrexia. Two of the events of fatigue and one event of pyrexia were considered related to study IP by the investigator and all events were considered resolved or recovered according to the investigator.

Part 2

The experienced unsolicited TEAEs within 28 days after vaccination were in similar proportions of participants in the mRNA-1273 (40.0%) and in the placebo group (37.5%). MAAEs considered related to study vaccination were reported in a higher proportion of participants in the mRNA-1273 group (1.0%) than in the placebo group (0.3%), although rates were ≤ 1% in either group.

Table 42: Summary of Subjects Reporting at Least 1 Unsolicited Adverse Event up to 28 Days After Any Dose (Part 2 – Safety Set) (2- to < 6-year-olds)

Category	Placebo (N = 1007)	mRNA-1273 25 µg
Unsolicited TEAEs regardless of relationship to study vaccination		
All	378 (37.5)	1212 (40.0)
Nonserious	378 (37.5)	1211 (40.0)
Serious	1 (< 0.1)	4 (0.1)
Fatal	0	0
Medically attended	221 (21.9)	662 (21.8)
Leading to discontinuation from study vaccine	0	0
Leading to discontinuation from participation in the study	0	0
Severe	9 (0.9)	21 (0.7)
Special Interest (AESI)	1 (<0.1)	5 (0.2)
Unsolicited TEAEs related to study vaccination		
All	80 (7.9)	286 (9.4)
Nonserious	80 (7.9)	286 (9.4)
Serious	0	0
Fatal	0	0
Medically attended	3 (0.3)	30 (1.0)
Leading to discontinuation from study vaccine	0	0
Leading to discontinuation from participation in the study	0	0
Severe	8 (0.8)	18 (0.6)
Special Interest (AESI)	1 (<0.1)	2 (<0.1)

Abbreviation: TEAE = treatment-emergent adverse event.
Note: Percentages are based on the number of safety participants. Solicited adverse reactions with toxicity grade = 0 that lasted beyond Day 7 or started after Day 7 are not included in this table.
Source (2 to < 6 years): Study P204 Table 14.3.1.7.1.2

The most common reported unsolicited AEs reported, i.e. those reported by more than 1% for part 2 were comparable between the mRNA-1273 group and the placebo group, with the exception of higher incidence of injection site erythema in the mRNA-1273 group in 38 participants (1.3%) compare to the placebo group in 2 participants (0.2%) and COVID-19 incidence with 93 participants (3.1%) in the mRNA-1273 and with 55 participants (5.5%) in the placebo group. Twenty-two participants in the mRNA-1273 group and 9 participants in the placebo group reported at least 1 severe TEAE within 28 days of any dose during Part 2. The majority of severe events considered related to IP occurred within the first week after injection and were generally related to childhood illnesses according to the investigator.

TEAEs involving respiratory tract infections (RTIs) up to 28 days showed imbalances of several respiratory related infections occurring with greater frequency in the mRNA-1273 group compared to the placebo group. According to MAH the 3:1 randomisation scheme, low event rates, and multiple comparisons all increase the possibility that these imbalances occurred by chance and are not suggestive of a safety

concern. The events of pneumonia, RSV infection, and croup are summarised for the 6 months to <2-year-old age group.

- **Croup infectious** were reported for 6 (0.6%) placebo participants and 17 (0.6 %) participants of the mRNA-1273 group.
- **Pneumonia** was reported in 0 participants in placebo group compared with 13 participants (0.4%) of the mRNA-1273 group.
- **Respiratory Syncytial Virus Infection** was reported for 1 (0.1%) placebo participants and 11 (0.4 %) participants of the mRNA-1273 group.

Unsolicited AEs considered being vaccine related (2- to < 6-year-olds)

Part 1

The incidence of AEs considered being vaccine related in Part 1 of the study were more frequently in the 50-µg group (17/155; 11.0%) compared to the 25-µg group (5/69; 7.2%). The most frequently reported unsolicited AEs considered being vaccine related in both groups belonged to the SOC of General disorders and administration site conditions (5.8% versus 10.3 % subjects) in the 25µg and the 50µg dose group).Leading symptom in this SOC in the 50µg dose group vs 25µg dose was injection site erythema (4.5% vs 4.3%), followed by fatigue (1.9% vs 0), injection site swelling(1.3% vs 1.4%), while chest pain was reported in 1 participant (1.4%) in the 25µg dose and no participants in the 50µg dose group.

Part 2

The incidence of AEs being vaccine related to Part 2 were comparable between the mRNA-1273 group and the placebo group (9.4% vs 7.9%, respectively). The most frequently reported unsolicited AEs considered being vaccine related in both groups belonged to the SOC of General disorders and administration site conditions (5.6% of subjects versus 3.9% of subjects) in the mRNA-1273 group and the placebo group. Leading symptom in this SOC in the placebo group compared to the mRNA-1273 group were fatigue (2.1% vs 1.5%), pyrexia (1.5% vs 1.2%) while chest pain was not experienced in the placebo group and to 2 participants (<0.1) in the mRNA-1273 group.

Serious adverse event/deaths/other significant events

Serious Adverse Events/ deaths in Part 1 (6 Months to < 2 Years)

In the mRNA-1273 vaccine group, a total of 1.3% in Part 1 and 0.5% in Part 2 experienced SAEs and the events reported were either consistent with childhood disease or could be explained by pre-existing conditions and not be related with the study vaccine by the investigator. In Part 2, no SAEs were reported in the placebo group. No deaths have been reported in the study.

Part 1

Two participants reported 4 SAEs in the vaccine group that occurred within the 28-day. A 7-month-old male in the vaccine group experienced 3 severe (grade 3) concurrent SAEs of cough, wheezing, and urticaria 21 days after dose 2. These events were considered to be due to an anaphylactic reaction to food[FLD2] and have been resolved within the same day. A 1-year-old male in the vaccine study group experienced a severe (grade 3) SAE of febrile convulsion of 5 minutes' duration 10 days after dose 2. The participant first developed a maculo-papular rash, with an onset 2 days the event of febrile seizure (39°C) and has been hospitalised. In the vaccine study group, 1 SAE (grade 2) of rhinovirus infection with an onset of more than 28 days after dose 2 (149 days after dose 2) has been reported in a 1-year-old

female. The participant was hospitalised due to respiratory distress and bronchiolitic symptoms and was also diagnosed with left otitis media.

Part 2

In part 2, overall, there have been 9 reported SAEs experienced by eight participants in the study vaccine group within the 28-day follow-up period after any dose. Two events reported in the same participant (fever and febrile seizure) where considered related to the study vaccine in the assessment from the investigator. The participant a 1-year- old female in the vaccine group[FLD3], approximately 6 hours after dose 1 experienced a severe SAE of fever (temperature of 103.1°F), that persisted until the next day when the parent/guardian[FLD4] heard the child crying, describing that the child was limp[FLD5]. At the emergency room the participant vitals revealed heart rate 170 beats per minute, temperature 39.1°C, respiratory rate 32 breaths per minute, and oxygen saturation 97% and the diagnosis of febrile seizure was established by the ER physician. Treatment for the pyrexia and febrile convulsion included paracetamol and ibuprofen, the participant stayed 4 hours in ER for observation and the two events were resolved two days after the onset[FLD6]. In the sponsor position it was stated that this case was confounded by an additional mild (grade 1) AE of rash maculo-papular on trunk that was reported 3 days after the event of fever. Even though the vaccine is known to cause fever, a differential diagnosis should include a viral illness, e.g. HHV6. This disease is characterized by three to five days of high fever that resolves abruptly and is followed by development of a rash. HHV-6 infection has been associated with febrile seizures. The investigator assessed the events of pyrexia and febrile convulsion to be related to the IP while the Sponsor does not agree with the Investigator assessment that the event of febrile seizure was related to the IP. Given the short TTO of the fever and the additional AE of rash macular-papular suggestive of a viral illness, these confounders provide a more plausible explanation for the occurrence of the reported events. The participant was continuing in the study at the time of the data cut.

The other 7 SAEs (grade 3) assessed as not related to the study vaccine within the 28-day were diagnosed as following: febrile convulsion; electrolyte imbalance secondary to dehydration in the setting of RSV infection; metapneumovirus infection; foreign body in respiratory tract; mastoiditis in the setting of neutropenia and adenovirus infection; bronchiolitis; rhinovirus infection. The SAEs with an onset of more than 28 days after any dose were 7 events in the mRNA-1273 vaccine group and 1 event in the placebo group in the participants were considered not related to mRNA-1273 by the investigator.

No deaths have been reported in the study as of the data snapshot, 21st February 2022.

Discontinuation From IP or Study Participation

No participants aged 6 months to < 2 years old in Part 1 were discontinued the study and in part 2 there were 3 participants withdrawn the study, one in the study vaccine group and the 2 others in the placebo group. The participant in the mRNA-1273 vaccine group, a 1-year-old male, [FLD7]experienced an unsolicited TEAE of urticaria of mild intensity (rash on torso) that started the same day as dose 1 leading to discontinuation from study vaccine and no treatment was reported for urticaria. The event has been assessed as related to the study vaccine by the investigator and the event was considered to be resolved on the next day[FLD8].

Two other participants in the placebo group experienced TEAE of COVID-19 leading to discontinuation from study vaccine. The participant, a 7-month-old [FLD9]female, ten days after the 1st dose of the vaccine, on [FLD10]Study Day 10, experienced a mild TEAE of COVID-19 and the treatment included ibuprofen and paracetamol. The event of COVID-19 was considered to be resolved on [FLD11]Study Day 20. The event was not related to the IP according to the investigator, and the withdrawal from study on [FLD12]Study Day 27 was due to dose delay and relocation[FLD13]. The other case of withdrawn the study

due to TEAE of COVID-19 started 10 days after dose 1 and the event was not related to study IP according to the investigator. The narrative for the last case in the placebo group is not provided.

Serious Adverse Events/ deaths in Study (2- to < 6-year-olds)

In part 1, no SAEs were reported for this age group

In part 2, in the study vaccine group there were in total 6 SAEs reported from 4 participants within 28 days of any dose. All six events were reported as resolved and none were considered related to the study vaccine by the investigator. The 6 SAEs cases reported were reported as per below:

The event of severe (grade 3) metapneumovirus infection was reported in a 3-year-old female participant that started 8 days after dose 1. T[FLD14]he participant started having cough and fever (body temperature not reported) and was treated with respiratory fluticasone propionate and salbutamol. The participant has been diagnosed [FLD15]with human metapneumovirus. The next day[FLD16], the participant visited the primary care physician and resulted negative for influenza virus and SARS-CoV-2. [FLD17]Three days later the participant was hospitalised and was put on 2 L of oxygen via nasal cannula and later increased to 4 L. Additional treatments included dexamethasone and fluticasone propionate and was discharged[FLD18], 8 days after the start of the event.

The event of a viral pneumonia with bronchial hyperreactivity and respiratory distress (all severe, grade 3), was reported in a 2-year-old male and has started 14 days after the 1st vaccine dose. T[FLD19]he participant had rhinorrhoea, congestion, and wet cough and was treated orally with ibuprofen and paracetamol. After 2 days[FLD20] the participant had fever (max 106.3°F), presented the next day to the primary physician and has been diagnosed with viral left lower lobe pneumonia and left acute suppurative otitis media and was treated with amoxicillin. [FLD21]Two days later the participant developed respiratory distress and reactive airway disease, and he developed high fever the night before, purple lips, decreased energy, tachypnea, belly breathing, tracheal tugging, chest tightness, perioral cyanosis and was hospitalised the same day. Treatment included rectal paracetamol for fever and IV dexamethasone and respiratory salbutamol and participant was discharged two days later. [FLD22]

Placebo Group

within 28 days of any dose, 1 participant in the placebo group experienced 1 SAE of moderate (grade 2) abdominal wall abscess was experienced by a 2-year-old male participant which started 28 days after dose 2 and led to hospitalisation (Table 49). The event was considered resolved after 29 days and was not considered related to study IP by the investigator. One participant in the placebo group, a 2-year-old female, experienced 2 SAEs after 28 days following any dose. The events, both requiring hospitalisation, included a severe (grade 3) rhinovirus infection and a moderate (grade 2) asthma. Both events started 83 days after dose 2 and resolved with sequelae (intermittent asthma) after 14 days. The events were not considered to be related to study IP by the investigator. Beyond 28 days after dose 2, 5 participants experienced 5 SAEs. All of these events required hospitalisation. All events resolved and were not considered related to mRNA-1273 by the investigator. The events included:

No deaths have been reported in the study as of the data snapshot.

Discontinuation From IP or Study Participation

No participant in Part 1 was discontinued from IP or the study due to an AE. In Part 2 one participant, a 4-year-old-male in the vaccine group, on [FLD23]Study Day 1 experienced a mild AE of urticaria [FLD24] on the same day as dose 1 leading to discontinuation from study vaccine. Treatment for the urticaria included levocetirizine (1.25 mg, oral, once on Study Day 1[FLD25]) and ibuprofen (150 mg, oral, once on

Study Day[FLD26] 1). The second IP dose was withdrawn due to the urticarial and the event was considered related to study IP by the investigator.

Adverse Events of Special Interest (6 Months to < 2 Years)

AESIs were assessed as those occurring within 28 days of any injection and across the study duration.

In part 1 of the study, in the vaccine group one participant, a 1-year-old male experienced 1, severe AESI (also an SAE for overnight hospitalisation) of febrile convulsion that started 10 days after dose 2. An event of rash maculo-papular was reported with an onset 2 days before the event of febrile seizure, fever 39°C was documented, the electroencephalogram has resulted normal. Treatment included oral paracetamol and ibuprofen. The participant was discharged and the event was determined by the investigator to not be related to the study vaccine.

In part 2 of the study, 3 AESIs were reported by 3 participants in the vaccine group within 28 days and one additional was reported by 1 participant across the study duration. One severe grade 3 AESI and SAE of febrile convulsion of 5 minutes' duration was reported in a 1-year-old male 21 days after dose 1. [FLD27]The participant experienced febrile seizures with the highest fever at 101.0°F for the next 2 days. At hospital, unspecified tests have been conducted and treatment included paracetamol. Consultations with Infectious disease specialist and rheumatologist have been done with some suspected diagnoses but not a finalised one. There is not clear information if the second IP dose was only a delay or it has not been administered to the subject. There is also misleading information if the event was related or not to the IP based on the narrative information.

Another case with febrile convulsion was reported in a 1-year-old female, approximately 6 hours after receiving the 1st dose. The same case is described in details in the section of the SAEs. A mild AESI of liver injury was reported in a 9-month-old female, [FLD28]occurring 2 days after dose 2. Prior the participant has a viral gastroenteritis-type illness and has been recommended that subject's LFTs be monitored while breastfeeding. The [FLD29]laboratory results required by her primary doctor on the previous day resulted with these abnormal values alanine aminotransferase: 390 (high), aspartate aminotransferase: 349 (high) and [FLD30]these laboratory tests were reported on the next day as acute liver injury. It was also confirmed that the subject stopped breastfeeding more than 3 months prior. This event was determined to be related to mRNA-1273 by the investigator, although might be other multiple plausible causes for the increased LFTs, including recent illness (viral gastroenteritis). After 28 days,1 moderate AESI (also a SAE), was reported in a 1-year-old male in the vaccine group, who experienced an erythema multiforme that occurred 35 days after dose 1 and it was determined to not be related to study IP by the investigator.

In the Placebo group no AESIs were reported within 28 days one AESI was reported by 1 participant occurring beyond 28 days. A 1-year-old male experienced 1, severe AESI (also a SAE) of acute respiratory failure that occurred 29 days after dose 1 and resolved after 3 days with hospitalisation. The investigator assessed the event as not related to study IP.

Other Events of Interest Reported after the Data Snapshot (6 Months to < 2 Years)

Two events of interest in two participants were reported after the data cut of this IA: one event of MIS-C in the placebo group and one event of Kawasaki's disease in the mRNA-1273 group. Both events occurred in participants who were 2 years old (at the time of screening), and the onset of the events were beyond 28 days after receiving dose 2 (day 113 and day 79, respectively). The MIS-C event occurred in the placebo group and the Kawasaki's disease in the mRNA-1273 group. Both events were assessed as not related by the Investigator.

Adverse Events of Special Interest (2- to < 6-year-olds)

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 in Study P204 are listed in Table below.

Table 43: Adverse Events of Special Interest

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

Adverse Event	Additional Notes
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 $\geq$ 0.3 mg/dl ($\geq$ 26.5 µmol/L) within 48 hours; OR o Increase in serum creatinine to $\geq$ 1.5 times baseline, known or presumed to have occurred within prior 7 days OR o Urine volume $\leq$ 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

Adverse Event	Additional Notes
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 × 109/L • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome (Hemolysis-Elevated Liver enzymes-Low Platelets)
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-Barré 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

Adverse Event	Additional Notes
	• Chronic Fatigue Syndrome (Includes Myalgic encephalomyelitis and Post viral fatigue syndrome) • Myasthenia gravis

In part 1 of the study, the AEIs were assessed for the two group doses 25-µg group and 50-µg group. No participants experienced an AESI within 28 days of any dose in both 2 group doses.

One mild event of epilepsy was reported beyond 28 days after any dose in a 3-year-old female participant. The event started 126 days after dose 2 and was reported as resolved after 13 days. The event was considered by the investigator to be not related to the study vaccine.

In part 2 of the study, the AEIs were assessed in the vaccine and in the placebo group.
Vaccine Group: Five AESIs were reported in 5 participants occurring within 28 days of any dose.
One mild AE of food allergy was reported as not related in a 2-year-old male participant with known food allergy. The event occurred 17 days after dose 2 and resolved after 1 day and was reported as not related by the investigator.

A SAE (mild/grade 1) event of seizure was reported in a 4-year-old male participant, 22 days after dose 2 and the control at the emergency room resulted with a normal neurological exam, the participant was afebrile and well appeared. The event was considered to be not related to the study vaccine by the investigator. One mild event of erythema multiforme occurred in a 3-year-old female 3 days after dose 1[FLD31]. According to the narrative the patient was taking Amoxicillin for Otitis Media[FLD32]. It was reported that the participant received Amoxicillin 2 days before the onset of the event. The participant restarted taking amoxicillin for a week one month[FLD33] later for the same diagnose of otitis media. The participant experienced other events of erythema multiforme, one episode occurred 36 days after dose 2 [FLD34]and the other event occurred 45 days after dose 2 [FLD35]and was ongoing at the time of the assessment. All these 3 AEIs were considered to be not related to study IP by the investigator. For all the events cetirizine was used as treatment of choice for erythema. It is not clear why these 3 episodes have been assessed as not related to the study IP, for the first episode amoxicillin has been taken 2 days before the onset of the event while the second episode of the event started almost 4 weeks after the second course of amoxicillin was interrupted. Another participant, a 3-year-old male experienced a mild event of erythema multiforme occurred 3 days after dose 2 and it was assessed to be related to the IP.

One event of moderate chest pain was reported in a 4-year-old male participant, five days after the 2nd dose of the vaccine. In the narrative submitted, the participant [FLD36]complained [FLD37]that he had discomfort, localised to the left side of his chest, no fever reported. The participant has been evaluated by a cardiologist, the electrocardiogram and high sensitivity troponin have resulted within normal limits. No specific follow-up was planned unless new or recurrent symptoms occurred. No treatment for the chest pain was reported and the event was considered by the investigator to be related to study IP.

Placebo group:

Two AESIs were reported in a 3-year-old female participant in 1 participant in this group occurring within 28 days. A severe (grade 3) event of Henoch-Schönlein purpura occurred 3 days after dose 2 and was considered by the investigator to be related to study IP. Additionally, 5 days after dose 2, the participant experienced a mild (grade 1) event of glucosuria. It was considered by the investigator not to be related to study IP and was judged to have resulted from the use of exogenous steroids to treat the initial event of Henoch-Schönlein purpura. The same participant experienced 2 additional AESIs, mild events of ageusia and anosmia occurred 45 days after dose 2 [FLD38]concurrent with moderate COVID-19 (symptomatic) event. The two AESIs were considered not to be related to the study IP by the investigator. One case of MIS-C was reported in a placebo recipient 37 days after an event of asymptomatic COVID-19.

Events of Clinical Interest Based on the MedDRA SMQs of Hypersensitivity (6 Months to < 2 Years)

Part 1

A total of 20 hypersensitivity events experienced in 15 participants (10.0%) in part 1 of the study in the mRNA-1273 group. None of these hypersensitivity events occurred within 48 hours of any dose. The most commonly reported events were: wheezing (4 [2.7%] participants), conjunctivitis (3 [2.0%] participants), dermatitis contact, drug eruption, eczema and urticarial have the same frequency of (2 [1.3%] participants), and perioral dermatitis, Periorbital swelling, rash (including rash maculo-papular and rash vesicular) do have the same frequencies with (1 [0.7%] participants).

One 1-year-old female, in the vaccine group experienced 2 hypersensitivity events of perioral dermatitis and rash vesicular that occurred 7 days after dose 1. The events were determined to be related to study treatment. A 7-month-old male in the vaccine group experienced 3 severe concurrent SAEs of cough, wheezing, and urticaria 21 days after dose 2. These events were considered to be due to an anaphylactic reaction to food [FLD39]and to be related to the study IP by the investigator.

Part 2

The hypersensitivity events were generally balanced between placebo and vaccine group. In the placebo group, there were 5 hypersensitivity events reported by 4 participants within 48 hours after any dose. All events were grade 1 and none were related to study treatment. The most commonly reported events in the vaccine group and placebo group are summarised in the table below:

In the vaccine group, there were 9 hypersensitivity events (7 grade 1 and 2 grade 2 events) reported by 9 participants within 48 hours after any dose. Four of these events (2 cases of urticaria with hives, [FLD40]flushing, and rash) were determined to be related to treatment, and assessed as nonserious, grade 1 events. There were 2 AEs of anaphylactic reaction in the vaccine group, one attributed as "anaphylaxis to food product" and the other as "anaphylaxis[FLD41], both not related to the study IP.

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."

Events of Clinical Interest Based on MedDRA Cardiomyopathy SMQs in (6 Months to < 2 Years)

Part 1

No AEs of myocarditis or pericarditis were identified based on analysis of cases reported in Part 1 under the MedDRA Cardiomyopathy SMQ. There was one participant, an 8-month-old male participant in the vaccine group with medical history of otitis media acute, and upper respiratory tract infection experienced concurrent nonserious mild AEs of dyspnoea (due to nasal congestion), pyrexia, fatigue, nasal congestion, rhinorrhoea, and decreased appetite, as well as cough, and diarrhoea, starting 27 days after dose 1. The event was considered not related to the study IP by the investigator and the participant received dose 2 and was continuing the study at the time of the data cut.

Table 44: Summary of PTs Within the MedDRA Cardiomyopathy SMQs – Narrow and Broad Scope (Part 1 – Safety Set) (6 months to < 2 years)

Preferred Term	mRNA-1273 25 µg (N = 150) n (%)
Number of subjects reporting Cardiomyopathy	1 (0.7)
Number of cardiomyopathy	1
Dyspnoea	1 (0.7)

Note: Percentages are based on the number of safety subjects. Based on MedDRA version 23.0. Cardiomyopathy is identified through selected narrow and broad SMQ.
Source (6 months to < 2 years): Study P204 Table 14.3.1.22.3.15.2.1

Part 2

No AEs of myocarditis or pericarditis were identified in Part 2 and there were no participants in Part 2 (placebo or mRNA-1273) that experienced an event included in both narrow and broad under the MedDRA Cardiomyopathy SMQ.

Additional Analysis of Myocarditis and Pericarditis

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. Two PTs were identified in the safety database using the algorithm: irritability and vomiting in children < 12 years of age. For both Parts 1 and 2, this analysis identified only 1 participant, a 1-year-old female in the mRNA-1273 group in Part 2 reported PT of irritability and vomiting. This child had no relevant medical history and reported concurrent nonserious mild AEs of vomiting, irritability, and pyrexia 22 days after dose 2. The event of vomiting was resolved the same day, and the event of irritability the next day. The investigator assessed the events of vomiting and irritability to be not related to mRNA-1273 and the participant was continuing in the study at the time of the data cut. However, the information was provided in the clinical overview and the narrative has not been found, the MAH is required to submit the respective narrative (OC).

Table 45: Summary of PT Reported – Ad hoc Summary of Additional PT Reported Under CDC Definition of Myocarditis/Pericarditis – Part 2 (6 months to < 2 years)

	Placebo (N = 589) n (%)		mRNA-1273 25 µg (N = 1761) n (%)	
Preferred Term	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
Vomiting, Irritability	0	0	0	1 (< 0.1)

Source: Study P204 Listing 16.2.7.16.2

Events of Clinical Interest Based on the MedDRA SMQs of Hypersensitivity (2- to < 6-year-olds)

No events of anaphylaxis or other events indicative of clinically significant hypersensitivity reactions were reported in Part 1. In total, 11 participants in Part 1 experienced a total of 12 events of potential hypersensitivity reactions. All events were reported as non-serious. The 11 participants included 1 (1.4%) in the 25-µg mRNA-1273 group and 10 (6.5%) in the 50-µg group. In the 25-µg group the only PT reported within the hypersensitivity SMQs using the narrow and broad standard was a single event of rhinitis allergic that was assessed by the investigator as not related to study vaccination. In the 50-µg group in Part 1, only one event was assessed by the investigator as related to vaccination. This was a mild event of injection site rash that started 11 days after dose 1 and resolved 2 days after. The remaining 10 events in 9 participants were assessed by the Investigator as not related to vaccination and, of these, 8 events in 7 participants occurred within 28 days of vaccination (median time to onset 16 days, range 2 to 27 days). One mild (grade 1) event of urticaria papular on upper back occurred 1 day after dose 2 and resolved 3 days later; the aetiology was reported as unknown by the Investigator. The same participant developed a mild (grade 1) non-urticarial rash maculo-papular 26 days after dose 2 that resolved after 4 days later. Another participant experienced one event of mild (grade 1) erythema (red spot on right foot) 2 days after vaccination that resolved 3 days later; the Investigator confirmed this event was not related to the vaccination. One participant experienced an event of dermatitis contact[FLD42], and another participant experienced mild (grade 1) facial eczema on day 25. Two events of blister were reported in 2 participants and both events resolved; one event was a mild (grade 1) foot blister that occurred 16 days after dose 2 and the second event of blistering fingertips from an unknown source occurred 14 days after dose 2. One participant experienced moderate (grade 2) wheezing 27 days after dose 2 that resolved 5 days later; the Investigator confirmed the aetiology of this event was unknown. Two events of conjunctivitis occurred beyond 28 days after dose 2 (148 days and 177 days respectively).

Table 46: Events of Clinical Interest After Any Dose Based on the MedDRA SMQs of Hypersensitivity Narrow and Broad Scope in Part 1 (Part 1 – Safety Set) (2- to < 6-year-olds)

Preferred Term	mRNA-1273 25 µg (N = 69) n (%)	mRNA-1273 50 µg (N = 155) n (%)
Number of Subjects Reporting Hypersensitivity Events	**1 (1.4)**	**10 (6.5)**
Number of Subjects Reporting Related Hypersensitivity Events	**0**	**1**
Number of Events of Hypersensitivity	**1**	**11**
Blister	0	2 (1.3)
Conjunctivitis	0	2 (1.3)
Dermatitis contact	0	1 (0.6)
Eczema	0	1 (0.6)
Erythema	0	1 (0.6)
Injection site rash	0	1 (0.6)
Rash maculo-papular	0	1 (0.6)
Rhinitis allergic	1 (1.4)	0
Urticaria papular	0	1 (0.6)
Wheezing	0	1 (0.6)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Queries.
Note: Percentages are based on the number of safety participants. Hypersensitivity is identified through selected narrow and broad SMQ.
Source (2 to < 6 years): Study P204 Table 14.3.1.22.3.2.2.1 and Study P204 Listing 16.2.7.19.2.1

In Part 1, only 2 events were reported on the day of or day after dose administration. These events were urticaria papular and erythema. The event of urticaria with the verbatim term of "urticarial mild papular rash on upper back" occurred in a 5-year-old female participant and started on the day of dose 2. The event was reported as mild, unrelated, and reported as resolved in 3 days. The event of erythema [FLD43]occurred in a 5-year-old female participant and started the day after dose 2. The event was reported as mild, not related, and reported as resolved in 3 days. Beyond 48 hours of any dose, 1 event was reported with the PT wheezing. The event was reported in a 2-year-old male participant 26 days after dose 2. The event was reported as moderate, not related, and resolved 5 days after onset.

Part 2

One event of anaphylactic reaction was reported in the mRNA-1273 group in Part 2 with the verbatim term of anaphylaxis due to laxative[FLD44]. The number of participants in Part 2 reporting events within the narrow hypersensitivity SMQ and the combined narrow and broad hypersensitivity SMQ was 139 (4.6%) in the mRNA-1273 group, reporting a total of 151 events, and 39 (3.9%) participants in the placebo group, reporting a total of 45 events, respectively (Table 53). In the mRNA-1273 group in Part 2, the most commonly reported PTs (> 10 events) within hypersensitivity SMQs were urticaria, conjunctivitis, seasonal allergy, and rash. In the placebo group in part 2, the most commonly reported PTs within the hypersensitivity SMQ (> 4 events) were similar to the mRNA-1273 group; conjunctivitis, urticaria and rash. In total, 32 (1.1%) participants in the mRNA-1273 group reported PTs included in the narrow and broad hypersensitivity SMQs that were considered related to study IP, all mild to moderate. In the placebo group, 7 (0.7%) participants reported related events in the hypersensitivity SMQs. One event of Henoch-Schönlein purpura was severe (grade 3), and the remaining 6 events were either mild (grade 1) or moderate (grade 2). In the mRNA-1273 group and the placebo group, the SOC with the most common hypersensitivity SMQ PTs was skin and subcutaneous tissue disorders.

Fourteen events were reported within 48 hours of vaccination in the mRNA-1273 group, 8 of which were reported as related. Of these, 4 events were in the SOC of skin and subcutaneous tissue disorders (urticaria, erythema, rash and rash erythematous), 2 in the SOC of general disorders and administration site conditions (2 events of injection site rash), 1 in the SOC of eye disorders (eye swelling), and 1 in the SOC of gastrointestinal disorders (lip swelling). The event of lip swelling was reported as a mild MAAEs in a 3-year-old male. It was reported to start on the day of dose 2 and lasted for 31 days. No other events were reported for this participant. In the placebo group, 8 events were reported within 48 hours of vaccination and, of these, one event was assessed as related by the Investigator; the event was a mild (grade 1) rash that started 2 days after dose 1 and resolved 2 days later. In the mRNA,1273 group, no participant had more than 1 event within the hypersensitivity SMQ reported the same day or the day after any dosing. Twelve events reported in the hypersensitivity SMQ in the mRNA-1273 group and they were as per below: two events of erythema multiforme which are described in details in the part of AESIs. An anaphylactic reaction with the verbatim term as anaphylaxis due to laxative[FLD45] reported in a 3-year-old female participant, 32 days after dose 1 and the treatment consisted with diphenhydramine[FLD46] and dexamethasone and the event was considered related to study IP by the investigator. An event of bronchial hyperreactivity was reported in a 2-year-old male participant, 4 days after dose 1, the treatment was albuterol and the event was considered not related to study IP by the investigator.

Two events, both severe of bronchial hyperreactivity and respiratory distress were reported in a 2-year-old male participant, they occurred 14 days after dose 1, treatment included albuterol and the events were considered not related to study IP by the investigator. Other 5 events of bronchial hyperreactivity were reported with an onset >7 days after the last dose and were considered not related to study IP by the investigator. Four events of hypersensitivity were reported in the mRNA group and included in the verbatim term of "seasonal or environmental allergies" and all events were considered not related to study IP by the investigator. An event of drug hypersensitivity, [FLD47]was reported in a 4-year-old female participant, 29 days after dose 2 and the treatment included diphenhydramine [FLD48]and the event was considered not related to study IP by the investigator.

Cases of Clinical Interest Based on MedDRA Cardiomyopathy SMQs (2- to < 6- year-olds)

Part 1

The events recorded within the enhance surveillance for myocarditis/pericarditis based on cardiomyopathy SMQ for part 1 are summarised in Table *47* below.

Table 47: Summary of PTs Within the MedDRA Cardiomyopathy SMQs – Narrow and Broad Scope (Part 1 – Safety Set) (2- to < 6-year-olds)

Preferred Term	mRNA-1273 25 µg (N = 69) n (%)	mRNA-1273 50 µg (N = 155) n (%)	Total (N = 224) n (%)
Number of subjects reporting events	1 (1.4)	1 (0.6)	2 (0.9)
Number of events	1	1	2
Chest pain	1 (1.4)	0	1 (0.4)
Dyspnoea	0	1 (0.6)	1 (0.4)

Source (2 to < 6 years): Study P204 Table 14.3.1.22.3.15.2.1

No cases of myocarditis or pericarditis were reported in part 1 of the study. There were 2 participants in total in Part 1 who reported events included within the Cardiomyopathy SMQ, both narrow and broad, one per each group dose.

In the 25-µg group, there was one 4-year-old male participant with concurrent events of non-serious mild chest pain and back pain 4 days after dose 1. The event was considered related to study IP by the investigator and the child was treated with acetaminophen. It is stated that the participant received dose 2 with no additional cardiac AEs reported, however there was not found a narrative for this case (OC).

In the 50-µg group there was one 5-year-old female participant with medical history of asthma who reported concurrent events of non-serious, mild dyspnoea, urticaria papular, and abdominal pain upper, 2 days after dose 2. The child was treated with fluticasone propionate, salbutamol sulfate, and acetaminophen. The event of dyspnoea was considered to be resolved 3 days later. The investigator assessed the event of dyspnoea to be not related to the IP. The participant was continuing in the study at the time of the data snapshot.

Part 2

Table 48: Summary of PTs Reported by Subjects Within the MedDRA Cardiomyopathy SMQs (Part 2 – Safety Set) (2- to < 6-year-olds)

Preferred Term	Placebo (N = 1007) n (%)	mRNA-1273 25 µg (N = 3031) n (%)	Total (N=4038) n (%)
Number of subjects reporting events	2 (0.2)	5 (0.2)	7 (0.2)
Number of events	2	5	7
Dyspnoea	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Chest pain	0	2 (< 0.1)	2 (< 0.1)
Mental status changes	0	1 (< 0.1)	1 (< 0.1)
Palpitations	1 (< 0.1)	0	1 (< 0.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Queries
Source (2 to < 6 years): Study P204 Table 14.3.1.22.3.15.2.2

No AEs of myocarditis or pericarditis were reported in Part 2. In Part 2, with a 3:1 randomisation rate (mRNA-1273:placebo), there were a total of 7 participants who reported 7 events within the Cardiomyopathy SMQ, both narrow and broad: 5 participants in the mRNA-1273 group and 2 participants in the placebo group. The 5 participants in the mRNA-1273 group reported 5 events and the 2 participants in the placebo group reported 2 events.

In the mRNA-1273 group there were 2 events of dyspnoea in 2 participants, 2 events of chest pain in 2 participants, and 1 event of mental status change in one participant (Study P204 [2 to < 6 years] Table 14.3.1.22.3.15.2.2). The two events of chest pain were both reported after dose 2. The first report of a nonserious mild AE of chest pain was in a 3-year-old male participant occurring 2 days after dose 2 and resolving within 15 to 20 minutes. No other relevant nonserious AEs were reported by the participant. The investigator assessed the event of chest pain to be related to the IP. The participant was continuing in the study at the time of the data cut. The second report was in a 4-year-old male participant who 4 days after dose 2 experienced a nonserious moderate AE of chest pain, localised to the left side, that resolved within 30 minutes. The PI ordered a follow up evaluation, and the participant was seen by cardiologist. An ECG, highly sensitive troponin and physical examination were all within normal levels. No

other relevant nonserious AEs were reported by the participant. The investigator assessed the event of chest pain to be related to the IP. The participant was continuing in the study at the time of the data cut.

Two events of dyspnoea were reported in two participants, both after dose 1. One 4-year-old male participant with concurrent events of non-serious mild AE of dyspnoea, fatigue, vomiting, and loss of consciousness (described as brief less than 1 minute) one day after dose 1 that resolved within 1.5 hours. The investigator assessed the event of dyspnoea to be related to the IP. Participant did not receive dose 2 per parents/guardian's request. The participant was continuing in the study at the time of the data cut. The second report in a 3-year-old female participant with medical history of seasonal allergies, with concurrent events of nonserious mild AE of dyspnoea, oropharyngeal pain (sore throat NOS; started prior to the event of dyspnoea) and cough (cough; started prior to the event of dyspnoea), 21 days after dose 1. The event of dyspnoea was considered to be resolved 3 days later. The investigator assessed the event of dyspnoea to be not related to the IP. The participant received dose 2 and was continuing in the study at the time of the data cut. There was one event of nonserious moderate AE of mental status changes in a 2-year-old female participant with relevant medical history of hypoxemic ischemic encephalopathy, occurring 5 days after dose 1 and resolving the same day. Participant was evaluated by a neurologist. The event was considered not related by the investigator. Participant received dose 2 with no additional AEs reported.

Placebo group:

In the placebo group there were 2 events within the Cardiomyopathy SMQs in 2 participants, 1 event of dyspnoea in 1 participant, and 1 event of palpitations in another participant.

A 3-year-old female participant experienced concurrent nonserious mild AE of dyspnoea, bronchiolitis (started prior to the event of dyspnoea) and ear infection (bilateral ear infection; started during to the event of dyspnoea) 26 days after dose 1. The event of dyspnoea resolved 3 days later. The event was an MAAE and resulted in delay of dosing of the participant. The event was considered by the investigator not to be related to study IP.

One event of concurrent nonserious moderate AEs of palpitations and cyanosis (cyanosis of lip) occurred in a 2-year-old male participant, 2 days after dose 1 and resolved the same day. The event was an MAAE, and the participant was treated with prednisone and cetirizine[FLD49] as a result of the event. The investigator considered the events to be not related to study IP.

Additional Analysis of Myocarditis and Pericarditis (2- to < 6-year-olds)

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), there were no additional Preferred Terms not already captured in the Cardiomyopathy SMQ above, that were identified in the safety database using this algorithm.

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. No AEs of myocarditis or pericarditis were identified in Part 1 and 2 for both age groups under the MedDRA Cardiomyopathy SMQ. Overall, only 1 participant reporting PT included in the algorithm in the part 2 of the age group 6 months to < 2 years old. The narrative has not been found, the MAH is required to provided it. A 1-year-old female in the mRNA-1273 group in Part 2 reported PT of irritability and vomiting. This participant had no relevant medical history and reported concurrent nonserious mild AEs of vomiting, irritability, and pyrexia, 22 days after dose 2. The event of vomiting was resolved the same day, and the event of irritability the next day. The investigator assessed the events of vomiting and irritability to be not related to mRNA-1273. The MAH is required to submit the narrative of this case as the information has been provided in the clinical overview.

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. However, MAH is asked to provide the narrative for the event of chest pain in a one 4 year old participant 4 days after dose 1 in the 25-µg group. 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 small to finally assess the safety signal of myo-and pericarditis.

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

There were in total 4 participants withdrawing the study in the two age groups, 2 cases considered related and 2 cases considered not related to the study IP according by the investigator, summarised as per below:

Group age: 6 months to < 2 years old

No participant discontinued the study in part 1, and there were 3 participants who withdrawn the study in part 2, one in the vaccine group and the two others in the placebo group.

A 1-year-old male[FLD50] experienced an unsolicited TEAE of urticaria of mild intensity (rash on torso) that started the same day as dose 1 leading to discontinuation from study vaccine and no treatment was reported for urticaria. The event has been assessed as related to the study vaccine by the investigator and the event of was considered to be resolved on the next day[FLD51].

Two other participants in the placebo group experienced TEAE of COVID-19 leading to discontinuation from study vaccine. A 7-month-old [FLD52]female, ten days after the 1st dose of the vaccine, on [FLD53]Study Day 10, experienced a mild TEAE of COVID-19 and the treatment included ibuprofen and paracetamol. The event of COVID-19 was considered to be resolved on [FLD54]Study Day 20. The event was not related to the IP according to the investigator, and the withdrawal from study on [FLD55]Study Day 27 was due to dose delay and relocation[FLD56]. The other case of withdrawn the study due to TEAE of COVID-19 started10 days after dose 1 and the event was not related to study IP according to the investigator.

Group age: 2 years to < 6 years old

No participant discontinued the study in part 1 and there was one participant in part 2. A 4-year-old-male in the vaccine group, on [FLD57]Study Day 1 experienced a mild AE of urticaria [FLD58] on the same day as dose 1 leading to discontinuation from study vaccine. Treatment for the urticaria included levocetirizine (1.25 mg, oral, once on Study Day 1[FLD59] and ibuprofen (150 mg, oral, once on Study Day 1[FLD60]). The second IP dose was withdrawn due to the urticarial and the event was considered related to study IP by the investigator.

Post-marketing experience

Post-marketing very rare cases of myocarditis and pericarditis have occurred 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 study design of P204 in the younger age cohorts was similar to the design for the 6 to < 12 year of age cohort. For each of the 2 younger age groups, children were enrolled first to Part 1 for dose selection and subsequently to Part 2. Part 1 evaluated dosages of mRNA-1273 in an open-label fashion and led to the selection of a dosage for evaluation in the larger, blinded, placebo-controlled Part 2. As the study followed a pattern of age de-escalation, the older children (2 to < 6 years) were enrolled to Part 1 (to evaluate dose levels of 25 µg and 50 µg administered as a two-dose schedule one month apart) prior to younger children (6 months to < 2 years). Accordingly, a lower dose (25 µg) was evaluated in a group of 2 to < 6-year-old children in Part 1, a dose that proved less reactogenic than 2 injections of 50 µg of mRNA-1273. The youngest children (6 months to < 2 years) received 25 µg of mRNA-1273 in Part 1 with a less reactogenicity profile compared to the 50 µg dose. The data snapshot provided for the extension of indication to the paediatric population from 6 months to < 6 years of age is 21 Feb 2022; data from Part 1 and Part 2 of Study P204 are available and include at least 2 months (56 days) post-dose 2 follow-up from over 1000 exposed subjects per age group from Part 2 (2180 subjects 2 to < 6 years and 1138 subjects 6 months to < 2 years).

Demography and baseline characteristics

Demographics and baseline characteristics were well balanced in both age cohorts between dose groups and between placebo and mRNA-1273 group. The majority of participants in both age groups and parts of the study were SARS-CoV-2 seronegative at baseline. Regarding the race characteristics there were >75% white race participants enrolled.

Local and systemic reactogenicity

The data on local and solicited systemic AEs clearly documents that infants are affected by the vaccination. As such, 70 - 89% of children suffered from injection site pain as most common local AR after the second dose. The local solicited ARs for the two age cohorts were higher after dose 2 compared to dose 1 and more frequent in the mRNA-1273 compared to placebo group. The most common local ARs after any dose was injection site pain. The local ARs were mostly of grade 1 and 2 and the grade 3 events were mostly erythema and swelling for both group ages. No grade 4 event have been reported. Nevertheless, age associated aspects on erythema and swelling should has been asked to be further discussed. The MAH has explained that the toxicity grading for erythema (redness) and swelling (hardness) differ between the two age groups and a lower threshold for meeting Grade 1, 2 or 3 has been specified for the younger age group as described in the relevant table. It is explained that the disparities in the event rates between the two age groups tend to grow proportionally smaller as severity increases, but there were no grade 4 events reported. Another factor may be that erythema and swelling might be more detectable in smaller children whose soft tissue is more pliable than in older children. The difference of any pain in the 2 age group is explained that the youngest participants 6month to <2 year age category may not have the capacity to explicitly complain of pain and to demonstrate it by the behavioural aspect of irritability/crying. The definition of solicited systemic ARs in different between age group has been asked to be explained in more detail. The MAH responded that the solicited ARs were assessed based on 2 sets of age appropriate ARs: for the children 37 months to 5 years assessment was done for fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills and for the children 24 to 36 months were assessed for fever, irritability/crying, sleepiness and loss of appetite. There were used 3 approaches to measure pain symptoms: self-report, behavioural indicators and physiologic indicators. The MAH was based on the fact that with age increase the ability of self-reporting improves, thus the events for ages 37 months and older has consisted of more verbally related assessment. For this age group, nausea has been assessed, abdominal pain has not been collected as a solicited AR in any of the mRNA-1273 studies.

Solicited systemic ARs were similar after dose 1 and dose 2 and were comparable between the study vaccine group and the placebo group. The most common solicited systemic ARs across groups were irritability/crying, sleepiness and loss of appetite for the younger age group. The majority of solicited systemic ARs were grade 1 to grade 2 in severity, within the first 2 days after any dose and persisted for a median of 2.0 days. There was one grade 3 event of fever and no grade 4 event in part 1 and in part 2 the grade 3 solicited systemic ARs of loss of appetite and irritability/crying were higher in the mRNA-1273 group compared with the placebo group. In the older age group the most common solicited systemic AR in either group, occurring in >20% of participants, was fatigue. The most common grade 3 solicited systemic ARs, in >1% of participants in at least one dose group, in the mRNA-1273 group were fatigue and fever and in the placebo group was fatigue. As requested, the MAH has adequately provided summary tables on the Grade 3 solicited ARs: after the 1st dose, after the 2nd dose, and after any dose

and unsolicited severe (Grade 3) TEAEs up to 28 days after any dose. The median duration for all events was less than 3 days. According to the age groups the Grade 3 ARs with the longest duration were: pain with a maximum duration of 13 days, after dose 2, in the 6 years to <12 year age group, and irritability with a max duration of 18 days in 6 month to <2 year age group. The grade 3 or higher unsolicited TEAEs were reported infrequently with the highest event rate in the mRNA-1273 25µg 6 month to <2 year age group (1.2% of participants) versus 0.7 % participants in the 2 years to <6 years age group. The tables regarding the unsolicited Severe TEAE are endorsed. It is observed that pyrexia /fatigue were the most commonly reported severe events in the age group 2 years to <6 years, while irritability and decreased appetite were the most commonly reported severe events in participants 6 months to <2 years of age. It is agreed upon that the events which were more reported are age appropriate.

Unsolicited AEs

The incidence of unsolicited AEs irrespective of causality for both age cohorts was higher in the 50µg mRNA-1273 vaccine group compared with the 25µg dose group and also was higher in the mRNA-1273 vaccine group compared with the placebo group.

In the age group 6 months < 2 years in part 1, unsolicited AEs irrespective of causality up to 28 days after any dose were reported by 53.3% of subjects and the incidence of medically attended adverse events (MAAEs) was 30%. The most common reported unsolicited AEs reported were: pyrexia (9.3%), upper respiratory tract infection (8.7%), irritability (8.0%). In part 2, unsolicited AEs irrespective of causality up to 28 days after any dose were comparable between the 25µg mRNA-1273 vaccine group compared to placebo, respectively by 49.3% and 48.2 %. The MAAES were also comparable between the 2 groups (27.6% versus 27.3%).

For the age cohort 2 years to < 6 years old in part 1, unsolicited AEs irrespective of causality up to 28 days after any dose were reported from 23.2% subjects in the 25-µg group and 36.1% in the 50-µg group. The incidence of MAAEs was lower in the 25-µg group compared to the 50-µg group (7.2 % versus 20.6%). The most common reported unsolicited AEs were mostly higher in the 50-µg group compared to the 25-µg group: upper respiratory tract infection (7.7% vs 0), pyrexia (7.7% vs 2.9%) and injection site erythema (4.5% vs 4.3%). In part 2 the experienced unsolicited TEAEs within 28 days after vaccination were in similar proportions of participants in the mRNA-1273 (40.0%) and (37.5%) in the placebo group. MAAEs considered related to study vaccination were higher in the mRNA-1273 group (1.0%) than in the placebo group (0.3%). The most common reported unsolicited AEs were comparable between the mRNA-1273and the placebo group, with the exception of higher incidence of injection site erythema in the mRNA-1273 group reported by 1.3% subjects compare to 0.2% subjects and COVID-19 incidence reported in 3.1% subjects in the mRNA-1273 versus 5.5% participants in the placebo group.

Unsolicited AEs considered being vaccine related

The majority of ARs being vaccine related for the age group 6 months < 2 years are respectively for part 1 irritability (7.3%) and decreased appetite (4.7%) and these conditions are already covered in the SmPC. There are no AEs considered to be vaccine related in part 1 to be considered for inclusion into section 4.8 of the SmPC. In part 2, for both study vaccine group and placebo most common were general and administration disorder and the leading symptoms were pyrexia, followed by injection site lymphadenopathy and they are also included in the SmPC. However, questions are submitted to the MAH regarding narratives and clarification regarding to some unsolicited events belonging to these age cohort. For the age group 2 years < 6 years, the most common unsolicited ARs being vaccine related belonged to the SOC of General disorders and administration site conditions were higher in the 50µg dose group versus 25µg dose and more in the mRNA-1273 compared to the placebo group, subsequently the 25µg

dose was the final dose chosen in the study. However, imbalances were observed regarding the respiratory tract infections (RTIs) including Croup Infections, Pneumonia and RSV infection for both age cohorts with higher frequency in the mRNA-1273 group compared to the placebo group. According to MAH the 3:1 randomisation scheme, low event rates, and multiple comparisons all increase the possibility that these imbalances occurred by chance and are not suggestive of a safety concern.

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. In both age groups, children with at least one medical history have been enrolled, however no data on immunocompromised or "instable" children have been provided. The MAH was required to provide relevant literature reports with suggestive data on the role of the Covid-19 vaccine on correspondent children < 6 years old. Upon request the MAH has provided the literature research and the search string regarding immunocompromised or 'instable' children. There have been retained 302 articles and the overall review did not describe a direct impact of COVID-19 vaccines on Immunocompromised or instable children. The MAH states that most of the articles describe that immunocompromised child do not appear at increased risk of severe infection compared to the general paediatric population (Millen et al,2021) or that vaccination with a mRNA COVID-19 vaccine carried any additional risk other than those observed during clinical trials. Relevant literature was included and is acknowledged.

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.

Serious adverse events

As of data snapshot, for the age cohort of 6 months to 2 years the SAEs were higher in the mRNA-1273 vaccine group. In part 1 there were 4 SAEs experienced from 2 participants and they were not related to the study IP. In part 2 there were 9 SAEs reported from 8 participant. Two events reported in the same participant (fever and febrile seizure) where considered related to the study vaccine in the assessment by the investigator. The other 7 SAEs assessed as not related to the study vaccine within the 28-day were diagnosed as following: febrile convulsion; electrolyte imbalance secondary to dehydration in the setting of RSV infection; metapneumovirus infection; foreign body in respiratory tract; mastoiditis in the setting of neutropenia and adenovirus infection; bronchiolitis; rhinovirus infection. For the age cohort 2 years to 6 years, in part 1, there were no SAEs reported. In part 2, in the study vaccine group there were in total 6 SAEs reported from 4 participants within 28 days of any dose and all events were considered not related to the study vaccine by the investigator. There were two events of interest in two participants reported after the data cut: one event of Multisystem Inflammatory Syndrome in Children (MIS-C) in the placebo group and one event of Kawasaki's disease in the mRNA-1273 group. Both events occurred in participants who were 2 years old (at the time of screening), and the onset of the events were beyond 28 days after receiving dose 2 (day 113 and day 79, respectively). Both events were assessed as not related by the Investigator. No other events of autoimmune disease, 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, also the subjects enrolled were white and healthy individual or with stable chronic diseases and no data on immunocompromised children has been provided. No deaths have been reported in the study.

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 small to finally assess the safety signal of myo-and pericarditis.

Finally, the MAH is asked for data on an increase in SARS-CoV-2-positive UAI (Upper Airway Infections), such as laryngotracheobronchitis (croup) with Omicron, leading to hospitalisation. This has been described in literature recently, but is not reflected within the current data set**.** Upon request, the MAH replied that there were no differences noted in the incidence of UAIs and has acknowledged that the relatively few numbers of cases and generality of symptoms collected may prelude an adequate assessment. Therefore, continuous monitoring is required upon on cases of COVID-19 leading to hospitalisations or on the cases of croup associated with COVID-19.

2.5.2. Conclusions on clinical safety

This type II variation aims to include children aged 6 months to <6 years of age to the label of Spikevax. The database for evaluation of the safety profile of mRNA-1273 in the paediatric population 6 months to < 6 years of age derives from study P204. It is part of 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 data snapshot supporting the extension of indication to the paediatric population from 6 months to < 6 years of age is 21 Feb 2022. The follow up period of at least 2 months (56 days) post-dose 2 include over 1000 exposed subjects per age group from Part 2 (2180 subjects 2 to < 6 years and 1138 subjects 6 months to < 2 years). However, the duration of follow up is relatively limited. The selection of the 25µg dose of mRNA-1273 is justified by the lower local and systemic reactogenicity compared to 50µg mRNA-1273. But still, also the 25 µg dose is reactogenic. This is reflected not only in the incidence of overall solicited and unsolicited ARs but also considering the fever analyses.

There were two events of interest in two participants reported after the data cut: one event of Multisystem Inflammatory Syndrome in Children (MIS-C) in the placebo group and one event of Kawasaki's disease in the mRNA-1273 group. Both events occurred beyond 28 days after receiving dose 2 and were assessed as not related by the Investigator. No other events of autoimmune disease, 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.

Data on certain subgroups such immunocompromised subjects are not covered in the current dataset. Several clarifying questions were posed and have been addressed by the MAH.

The majority of reported unsolicited AEs considered being related to the vaccine are already covered in the SmPC. After assessment of the available clinical information, so far, no AE being vaccine related is considered for inclusion into section 4.8 of the SmPC.

In conclusion, the clinical safety profile in children from 6 months to <6 years appears comparable to the clinical safety observed in older children (6 to <12 years). No new safety signals were identified during trial P204 until the data cut-off. However, as the safety follow-up was relatively short, especially for the younger cohort, an update with regard to SAEs, AESIs and MAAEs with a later cut-off than February 21, 2022 was requested. The MAH commits to providing longer term safety analyses in the interim CSR planned for Q2 2023. This CSR will contain a minimum of 6 months of safety follow-up on at least 1000 individuals in each age cohort, with all individuals surpassing Day 57. The safety profile of mRNA-1273 available so far appears to be consistent with that observed in older children and adults, the commitment of the MAH to provide an interim CSR at a later date is considered acceptable.

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 submitted 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 4.1 is acceptable.

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

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 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	Safety, tolerability, reactogenicity, and effectiveness of up to 3 doses of elasomeran 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-associated enhanced respiratory disease (VAERD) Long-term safety	Study start	15 Mar 2021
			Final CSR	31 Mar 2024
Category 3 – Required pharmacovigilance activities				
Study 20-0003 Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of	Safety and reactogenicity of a 2-dose vaccination schedule 28 days apart, at different dose levels.	Anaphylaxis Myocarditis Pericarditis Long-term safety	Interim CSR	01 May 2021
			Final CSR (Main Study)	01 Nov 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
2019-nCoV Vaccine (mRNA-1273) in Healthy Adults Study status: Ongoing	IgG ELISA at Day 57. Neutralizing Ab using different assays, SARS-CoV-2 spike-specific T-cell responses.			
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 Study status: Ongoing	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 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	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?	Anaphylaxis Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	Protocol submission	30 Jun 2021
			Interim Updates	30 Sep 2021, 31 Mar 2022, 30 Sep 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study status: Ongoing	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 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	Long-term safety Interaction with other vaccines Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders		31 Mar 2023,
			Final study report	31 Dec 2023
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:	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 Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	- To describe utilization of COVID-19 Vaccine Moderna in pregnancy			
Study mRNA-1273-P902 Moderna mRNA-1273 Observational pregnancy outcome study Study status: Ongoing	Evaluate outcomes of pregnancies and birth in females exposed to elasomeran 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
			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 individuals with	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
	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 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	Characterize natural history of and risk factors for myocarditis temporally	Myocarditis	Protocol submission	28 February 2022

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Natural history and clinical outcomes of vaccine associated myocarditis Study status: Planned	associated with Moderna COVID-19 vaccination in children and young adults		Interim report	30 Aug 2022 28 Feb 2023 30 Aug 2023 28 Feb 2024 30 Aug 2024
			Final study report	28 February 2025

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)
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	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)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Additional risk minimisation measures: None	• 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)
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)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC 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 the age of 6 years of age SARS-CoV-2 infections cause mostly asymptomatic or mild disease. Therefore, any conclusions on 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 and 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 (PIMS, 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 months to < 6 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. There is 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. However, no vaccine is authorised for now to younger groups of 6 months to 6 years of age.

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 randomised (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 months to < 6 years age group were provided.

3.2. Favourable effects

In the absence of a correlate of protection, neutralising Ab titres lay the basis for protection against SARS-CoV-2 infection and/or Covid-19 disease. For children aged ≥6 to <12 years, immunobridging has been applied previously.

The MAH is providing results for children 6 months to < 6 years of age that demonstrate non-inferiority of the neutralising Ab response as well as sero-response rate as compared to young adults (18 to ≤25 years) from study P301 in which mRNA-1273 vaccine efficacy has been established. Based on these immunobridging results efficacy can be inferred for infants and children (6 months < 6 years).

VE data are available to support immunobridging.

3.3. Uncertainties and limitations about favourable effects

The study plans remained rather vague and together with the observed deviations in the conduct of study are not up to the usual standard of a confirmatory trial (e.g. the timing and sample size of primary immunogenicity analyses, the definition of analysis sets concerning the combination/separation of parts

and age groups, and 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. Nonetheless, the presented analyses, observed effects and the magnitude of deviations in sample size render these concerns less pronounced.

Available VE estimates are relatively imprecise, also due to limited follow-up being available at this point in time.

No data are available from children with a risk of more severe disease. Unless there is a severe immune defect associated with an 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. If the results regarding the higher GM in children can be confirmed by the requested analyses, a longer duration of protection is also conceivable in this population.

The impact on transmission is currently unknown.

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

3.4. Unfavourable effects

Spikevax is reactogenic. Overall, for the 2 age cohort groups the incidences of the solicited ARs were higher after any dose in the 50-µg group compared to the 25-µg group and higher in the mRNA-1273 dose groups compare to placebo groups. In general, in the mRNA-1273 dose groups, the incidence of solicited local ARs was higher after dose 2 than dose 1.

In the age group 6 months to < 2 years the most common solicited local ARs was injection site pain, the local ARs were of grade 1 and 2, with 3 cases of grade 3 in part 1 (1 erythema and 2 swelling). In part 2 the grade 3 ARs where more in the mRNA-1273 group compared to placebo group, the most common grade 3 solicited local ARs were erythema and swelling. In the age group of 2 years to < 6 years, the incidence of the solicited local ARs was dose-dependent and was higher in the 50-µg than in the 25-µg group after any injection (respectively 71.7% vs 58% after dose 1 and 89% vs 79.7% after dose 2). In both mRNA-1273 dose groups, the incidence was higher after dose 2. The majority of the solicited local ARs were grade 1 or 2 in severity. In part 1, injection site pain was the most common local ARs, the only grade 3 solicited local AR and the 2 events of grade 3 pain occurred in the 50-µg group. In part 2, the solicited local ARs were more common in the mRNA-1273 group than in the placebo group and were mostly grade 1 and 2 in severity. The most common grade 3 solicited local ARs were erythema, swelling, and pain. No grade 4 events were reported in both parts of the study.

The solicited systemic ARs for the age group 6 months to < 2 years, were similar after dose 1 and dose 2 and were comparable between the study vaccine group and the placebo group. In part 1 Irritability/crying was the most commonly reported event, reported by 60% of participants after each dose, followed by sleepiness and loss of appetite. The majority of solicited systemic ARs were grade 1 to grade 2 in severity. There was one grade 3 event of fever and no grade 4 event in part 1. In part 2 the grade 3 solicited systemic ARs of loss of appetite and irritability/crying were higher in the mRNA-1273 group compared with the placebo group. The only grade 4 solicited systemic ARs were reported for fever and

were similar with a frequency of 0.2% between the mRNA-1273 and placebo group. In the younger age group (2-years to ≤ 36-months), after any dose, the most common solicited systemic ARs in either group, occurring in >20% of participants, were irritability/crying, sleepiness and loss of appetite. The most common grade 3 solicited systemic ARs in the mRNA-1273 group after any dose in >1% of participants in at least one dose group were irritability/crying, and fever ≥39.0°C. In the older age group (37-month- to < 6-years), after any dose, the most common solicited systemic AR in either group, occurring in >20% of participants, was fatigue. The most common grade 3 solicited systemic ARs, occurring in >1% of participants in at least one dose group, in the mRNA-1273 group were fatigue and fever and in the placebo group was fatigue. Fever was the only grade 4 solicited systemic AR reported in either group.

Regarding the unsolicited ARs in the age group of 6 months to < 2 years in part 1, unsolicited AEs irrespective of causality up to 28 days after any dose were reported by 53.3% of subjects and the most common were: pyrexia (9.3%), upper respiratory tract infection (8.7%), irritability (8.0%). In part 2, the unsolicited AEs were comparable between the 25µg mRNA-1273 vaccine group (49.3%) and placebo group (48.2 %).

For the age group 2 years to < 6 years, the number of subjects reporting unsolicited AEs up to 28 Days after any vaccination in part 1 was higher in the 50 µg dose group (36.1%) compared to the 25 µg dose group (23.1%) and in part 2 was comparable between the mRNA-1273 group (40.0%) and the placebo group (37.5%). In part 2 the experienced unsolicited AEs within 28 days after vaccination were in comparable proportions of participants in the mRNA-1273 (40.0%) and (37.5%) in the placebo group, with the exception of higher incidence of injection site erythema in the mRNA-1273 group reported by 1.3% subjects compare to 0.2% subjects and COVID-19 incidence reported in 3.1% subjects in the mRNA-1273 versus 5.5% participants in the placebo group.

Study Part 1 (dose finding): Based on the provided data from Part 1 (in the age group from 2-<6 years), showing marked imbalances regarding reactogenicity and unsolicited adverse events, the decision to choose the 25µg dose is supported. However, exploring a further reduced dose would have been preferred from a safety perspective, especially for the younger age group from 6 months to 2 years.

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 months to <6 years compared to the 6 years to <12 years of age. However, the MAH is required to provide tables of reactogenicity comparison between these two age groups.

Not unexpectedly, rare ADR 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.

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.

3.6. Effects Table

Table 49: Effects Table for [insert product name and indication] <(data cut-off: …)>.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Immunogenicity			**2-<6y N = 264**	**18-25y N = 295**		
	GMR (nAb) (95% CI)	**1.014** (0.881, 1.167)			Non-inferiority demonstrated	
	Difference in nAb Seroresponse rate at day 57 (95% CI)	**-0.4** (-2.7, 1.5)			Non-inferiority demonstrated	
			6mo-<2y N = 230	**18-25y N = 295**		
	GMR (nAb) (95% CI)	**1.280** (1.115, 1.470)			Non-inferiority demonstrated	
	Difference in nAb Seroresponse rate at day 57 (95% CI)	**0.7** (-1.0, 2.5)			Non-inferiority demonstrated	
Vaccine Efficacy	VE based on incidence rate (95% CI)		**2-<6y N = 2594**	**2-<6y N = 858**		
	CDC case definition of COVID-19		**0.368** (0.125, 0.540)		Short FU, SARS-Cov2 variants; only supportive	
	P301 case definition of COVID-19		**0.464** (0.198, 0.638)		Short FU, SARS-Cov2 variants; only supportive	
			6mo-<2y N = 1511	**6mo-<2y N = 513**		
	CDC case definition of COVID-19		**0.506** (0.214, 0.686)		Short FU, SARS-Cov2 variants; only supportive	
	P301 case definition of COVID-19		**0.315** (-0.277, 0.620)		Short FU, SARS-Cov2 variants; only supportive	
Unfavourable Effects						
Age Group: 6 months < 2		Part 1 25 µg	Part 2 25 µg	Placebo		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
years						
Grade 3 solicited local adverse reaction (any dose)		3/150 (2.0%)	30/1758 (1.7%)	2/585 (0.3%)		
Grade 3 systemic adverse reaction (any dose)		4/150 (2.7%)	85/1758 (4.8 %)	21/585 (3.6 %)		
Any solicited systemic AR Grade 4		0	4/1758 (0.2)	1/585 (0.2%)		
Unsolicited AR/ Related unsolicited AE		23/150 (15.3%)			Part 2 , Imbalances of several respiratory related infections; higher in the mRNA-1273 group compared to the placebo.	
Serious AEs		2/150 (1.3%)			All SAE considered not related, no deaths reported	
Age Group: 2 years < 6 years	Part 1	Part 1	Part 2	Part 2		
	25 µg	50 µg	25 µg	Placebo		
Grade 3 solicited local adverse reaction (any dose)	0	4/152 (2.6%) Any Pain 88.4%	54/3015 (1.8 %) Any Pain (71.3 %)	4/997 (0.4 %)		
Grade 3 systemic adverse reaction (any dose)	1/69 (1.4 %)	15/154 (9.7 %)	188/3015 (6.2%)	35/997 (3.5 %)		
Any solicited systemic AR Grade 4	0	1/154 (0.6 %)	2/997 (0.2%)	11/3015 (0.4%)		
Unsolicited AR/ Related unsolicited AE	5/69 (7.2 %)	17/155 (11.0%)	286/3031 (9.4 %)	80/1007 (7.9 %)	Part 2 , Imbalances of several respiratory related infections; higher in the mRNA-1273 group compared to the placebo	
Serious AE	-	-	4/3031 (0.1 %)	1/1007 (<0.1 %)	All SAE considered not related, no deaths reported	

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 from 6 months to <6 years can be inferred by successful immunobridging. A non-inferior immune response with respect to neutralising antibody levels and seroresponse rates is suggested by the presented data.

Whether vaccination can prevent PIM-S is currently unknown.

The safety database overall could be sufficient. The known unfavourable effects are acceptable – even though Spikevax is reactogenic, the ADRs are mostly 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 post-marketing data in older age strata 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 infants and young children is generally milder than in the older population, there are individuals that suffer considerably from the direct consequences of the infection. The reactogenicity profile of the vaccinated paediatric population overall is considered acceptable. The benefits of preventing COVID-19 with potential irreversible and long-lasting consequences outweigh the identified risks of vaccination, especially in children at risk of severe COVID-19.

3.8. Conclusions

The overall benefit-risk of Spikevax is considered favourable.

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 and IIIB

Extension of indication to include immunisation of paediatric individuals from 6 months through 5 years of

age based on results from the study P204 (KidCove); this is a phase 2/3, two-part, open-label, dose-escalation, age de-escalation and randomised, 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. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. The MAH also took the opportunity to implement minor editorial changes in the product information. A revised RMP version 4.1 has been approved.

The variation leads to amendments to the Summary of Product Characteristics and the Package Leaflet, and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

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

Paediatric data

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Spikevax-H-C-005791-II-0067'

6. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 19 October 2022