15 December 2022
EMA/3578/2023
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/0083/G

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.

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List of abbreviations

Ab	Antibody
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
bAb	Binding antibody(ies)
BD	Booster dose
CDC	US Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CTG	Cardiotocography
CTP	Clinical trial protocol
EC	European Commission
ECG	Electrocardiogram
eDiary	Electronic diary
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EoI	Extension of indication
ER	Emergency room
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
GFP	Green fluorescent protein
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
ID50	50% inhibitory dose
IM	Intramuscular(ly)
IP	Investigational product
JRA	Juvenile rheumatoid arthritis
LNP	Lipid nanoparticle
LLoQ	Lower limit of quantification
MAA	Marketing authorisation application
MAAE	Medically attended adverse event
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
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
nAb	Neutralising antibody(ies)
NI	Non-inferiority
PI	Product information
PIP	Paediatric Investigation Plan
PP	Per protocol
PPIS	Per-Protocol (PP) Immunogenicity Subset
PPIS-Neg	Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status
PPIS-Pos	Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PsVNA	Pseudovirus neutralisation assay
PT	Preferred term
PTSD	Post-traumatic stress disorder
RMP	Risk management plan
RSI	Request for supplementary information
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Solicited adverse reaction(s)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
SRR	Seroresponse rate
T1E	Type 1 error
UK	United Kingdom
US	United States of America
VE	Vaccine efficacy / effectiveness
WHO	World Health Organisation
yoa	Years of age

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Moderna Biotech Spain, S.L. submitted to the European Medicines Agency on 22 September 2022 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type II	I and IIIB
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 a 25 µg booster dose of Spikevax bivalent Original/Omicron BA.1 (12.5 µg elasomeran/12.5 µg davesomeran) in children (6 to < 12 years), based on interim results from study P204; this is a Phase 2/3, Three-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; As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.5 of the RMP has also been submitted. In addition, the Marketing authorisation holder MAH took the opportunity to implement editorial changes.

To update sections 4.8, 5.1, and 6.6 of the SmPC to include additional immunogenicity data for the paediatric population (6 to < 18 years) based on Real-World Safety studies.

The group of variations 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/0256/2022 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the P/0256/2022 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	22 September 2022
Start of procedure:	12 October 2022
PRAC Rapporteur Assessment Report	19 October 2022
PRAC members comments	23 October 2022
Updated PRAC Rapporteur Assessment Report	24 October 2022
CHMP Rapporteur Assessment Report	31 October 2022
PRAC Outcome	27 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur Assessment Report	4 November 2022
Request for supplementary information (RSI)	10 November 2022
PRAC Rapporteur Assessment Report	30 November 2022
CHMP Rapporteur Assessment Report	30 November 2022
PRAC members comments	5 December 2022
CHMP members comments	5 December 2022
Updated PRAC Rapporteur Assessment Report	6 December 2022
Updated CHMP Rapporteur Assessment Report	8 December 2022
Opinion	15 December 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV. Coronaviruses are also zoonotic, with different species causing disease in other mammals, such as bats and cats.

An outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease quickly spread globally (WHO 2020). This virus is not known to have previously caused disease in humans. The World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern on 30 January 2020 and declared COVID-19 a pandemic on 11 March 2020.

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids in 3 principal ways: 1) inhalation of respiratory droplets and aerosol particles; 2) deposition of respiratory droplets and aerosol particles on mucous membranes in the mouth, nose, or eye by direct splashes and/or sprays; and 3) touching mucous membranes with hands that have been soiled either directly by respiratory fluids or indirectly by contact with fomites (CDC 2021).

Transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic individuals has also been documented and may account for an estimated 59% of transmission (Johansson et al 2021).

Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and the distinctive symptoms of loss of taste or smell.

The genetic sequence of SARS-CoV-2 is constantly changing over time and new variants are emerging. After the onset of the Omicron wave, the demographics of hospitalised patients with COVID-19 shifted to younger age groups (UK Health Security Agency 2021; Abdullah et al 2022; Goga et al 2021).

Claimed therapeutic indication

Currently, the use of Spikevax (also referred to as mRNA-1273) for booster vaccinations for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV2 is authorised for individuals ≥ 12 years of age. The MAH submitted an application to request an amendment of this indication, to expand booster vaccination to individuals aged 6 through 11 years of age, using the modified variant vaccine Spikevax bivalent Original / Omicron BA.1 (also referred to as mRNA-1273.214, 12.5 µg elasomeran / 12.5 µg imelasomeran per dose). The dosing regimen is proposed to be an interval of at least 3 months (as for other age groups) following a primary series and/or previous booster dose with Spikevax or another authorised COVID-19 vaccine, based on extrapolation.

The intended wording in section 4.1 is the follows:

Spikevax bivalent Original/Omicron BA.1 is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older who have previously received at least a primary vaccination course against COVID-19.

In support of the application, the MAH provided data showing the safety and immunogenicity of a booster dose of 25 µg of Spikevax (mRNA-1273) given to children aged 6 through 11 years of age. The data is derived from Study mRNA-1273-P204 (also referred to as P204), an ongoing Phase 2/3, 3-part, dose-escalation (open-label), age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 in children 6 months to 11 years.

The study population was evaluated in 3 discrete age groups (6 through 11 years, 2 to < 6 years, and 6 months to < 2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of mRNA-1273 in the primary series. For each of the three age groups, an open-label dose-finding (Part 1) phase preceded a blinded, placebo-controlled (Part 2) phase, which evaluated the selected dose of mRNA-1273 in a placebo-controlled fashion. Data regarding the mRNA-1273 primary series for all age groups in P204 has been previously submitted and primary series of 2 doses of 50 µg of mRNA-1273 (which is half of the primary dose for individuals 12 years and older), given 28 days apart is currently authorised for

use in children 6 through 11 years of age. In a subsequent amendment, the study protocol was revised to offer the mRNA-1273 primary series to P204 participants randomised to placebo once vaccination against COVID-19 was authorised in the respective age group. Following evidence of enhanced effectiveness of the adult booster dose, study P204 was amended to offer a 25 µg booster dose of mRNA-1273 to all children enrolled in the 6 through 11 years of age group. The dose could be administered starting 6 months post-dose 2 of the primary series.

In addition, the MAH submitted clinical data to support a single booster dose of 50 µg mRNA-1273 for children from 12 through 17 years of age who previously completed a primary vaccination series of two 100 µg doses administered approximately 1 month apart. The data is derived from Study mRNA-1273-P203 (also referred to as P203), an ongoing, Phase 2/3 study originally designed as a randomised (2:1 vaccine:placebo), observer-blind, placebo-controlled study evaluating the safety, reactogenicity, and immunogenicity/efficacy of a two-dose mRNA-1273 vaccine (100 µg) primary series in healthy adolescents 12 to 17 years (Part 1A). In May 2021, upon emergency authorisation of a non-study COVID-19 vaccine for use in adolescents, Study P203 transitioned to an open-label phase. In November 2021, Protocol Amendment 3 was implemented to evaluate administration of a 50 µg mRNA-1273 booster dose administered to ongoing study participants at least 5 months after completion of the mRNA-1273 primary series (Part 1C-1).

Based on the data submitted, the booster vaccination indication in children 6-11 years of age was also extended to the Spikevax (mRNA-1273) 0.1 mg/mL formulation, while noting that the administration of a 25 µg dose with the Spikevax (mRNA-1273) 0.2 mg/mL formulation is however not feasible. It is also noted that the MAH intends to further extend the booster vaccination indication to the Spikevax bivalent Original/Omicron BA.4-5 vaccine (mRNA-1273-222) in a future, separate procedure.

The approach is considered acceptable as booster vaccination with the bivalent Original/Omicron BA.1 vaccine (mRNA-1273.214) demonstrated superiority in eliciting neutralising antibodies (nABs) against Omicron BA.1 and BA.4-5 regardless of prior SARS-CoV-2 infection as compared to mRNA-1273 (Original) in adults.

2.1.2. About the product

The MAH is using its mRNA-based platform to develop mRNA-1273, a novel, lipid nanoparticle (LNP)-encapsulated, mRNA-based vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The proprietary LNPs encapsulating the mRNA increase its delivery efficiency and improve vaccine tolerability.

Prior to the emergence of the novel SARS-CoV-2 coronavirus, the MAH had developed an understanding of mRNA vaccine approaches against coronavirus based on prior experience in the development of mRNA vaccines against MERS-CoV. This preclinical effort led to the evaluation of several mRNA vaccine designs against MERS-CoV, the most effective of which were spike protein designs. Of these, a full-length spike protein modified to introduce 2 proline residues to stabilise the spike protein into a prefusion conformation (S-2P) showed improved performance versus the wild-type spike protein. These improvements included better expression of protein, stabilisation of the spike protein in the prefusion conformation, and improved immunogenicity in murine studies.

The coronavirus spike protein mediates attachment and entry of the virus into host cells by attachment followed by membrane fusion, making it a primary target for neutralising antibodies (Corti et al 2015; Wang L 2015; Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilised SARS-CoV-2 S-2P mRNA expresses well in mammalian cells and is in the pre-fusion conformation (Wrapp et al 2020).

Spikevax is delivered via intramuscular injection, and mRNA is subsequently delivered into cells, primarily antigen presenting cells at the injection site and draining lymph nodes. After delivery, the mRNA utilises the cell's translational machinery to produce the SARS-CoV-2 spike protein, which after proper assembly and processing is trafficked to the cell membrane for display to the immune system.

mRNA-1273 stimulates innate immune responses, resulting in the production of proinflammatory cytokines and type 1 interferon (Nelson et al 2020). This process activates B-cell and T-cell responses from the adaptive immune system. mRNA-1273 directly activates B-cells, including memory B-cells, resulting in the secretion of antibodies that bind and neutralise SARS-CoV-2 viruses. mRNA-1273 also directly activates T-cells, which eliminate infected cells and support B-cell responses. mRNA-1273 induces Th1-biased CD4 T-cell responses (Jackson et al 2020) and antigen-specific CD8 T-cells in humans (Zhang et al 2022).

To respond to emerging SARS-CoV-2 variants, the MAH is developing modified mRNA COVID-19 booster vaccines. The variant-matched bivalent COVID-19 mRNA vaccines contain equal amounts of two mRNAs that encode for the Spike protein of the ancestral SARS-CoV-2 and antigenically divergent variants of concern, each encapsulated into individual LNPs, and co-formulated into a single drug product. After delivery, both mRNAs are delivered to cells in the body where the two distinct spike protomers, each of which represents one of the three components of the spike trimer, are expressed. After expression these spike protomers assemble into the spike trimer and both homotrimers as well heterotrimers (mixed protomers from the ancestral spike and the Variant spike), form.

The inclusion of both the original and the variant spikes in the vaccine are intended to broaden immunity as significantly as possible. To that end, inclusion of the ancestral spike allows reactivation and boosting of memory immune cell populations, increasing immunity that was previously present. In addition, inclusion of the variant spike, which has novel functional epitopes present primarily on the receptor-binding domain and the N-terminal domain, allows new naïve immune populations to be engaged and new memory responses to be elicited. This likely broadens immunity not only to the spike antigens delivered but likely also against a broader diversity of spike proteins.

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

The MAH did not seek Scientific advice at the CHMP. The Study P204 protocol and SAP have been designed according to the MAH in accordance with both US FDA general guidance on COVID-19 vaccine development (Department of Health and Human Services (DHHS), Food and Drug Administration, and Center for Biologics Evaluation and Research (US) 2020, 2021) and product-specific guidance. Study P204 protocol development, paediatric study plan, and paediatric investigation plan were discussed with EMA, Health Canada, and other agencies as part of the authorisation pathway developed to expedite regulatory approval in each country.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

No new non-clinical data was submitted in this application, which is 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.

Overview of clinical studies

Study mRNA-1273 P301 (No new data submitted within this submission)

The pivotal study of mRNA-1273 in adults is mRNA-1273-P301 (also referred to as P301) is a Phase 3 efficacy, safety, and immunogenicity study that provides the primary clinical evidence of vaccine efficacy (VE) and safety in adults ≥18 years of age. The study was designed as a randomised, observer- and participant-blind, placebo-controlled study of the efficacy, safety, and immunogenicity of 2 doses of mRNA-1273 100 µg compared with placebo (Part A, Blinded Phase). In this study, more than 30,000 participants were randomised and > 96.7% participants received dose 2 of mRNA-1273. Vaccine efficacy was observed to be 94.1% with a median of 9 weeks of efficacy follow-up 93.2% after 5.3 months of median efficacy follow-up. Data from this study supported the US EUA; 18 December 2020), the Canadian Interim Order (23 December 2020), and the European Medicines Agency (EMA) Conditional Marketing Authorisation (6 January 2021).

Study mRNA-1273-P203

Study mRNA-1273-P203 (also referred as P203) is an ongoing US Phase 2/3, randomised, observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, and effectiveness of the mRNA-1273 vaccine in healthy adolescents. The goal of the study was to support an indication for use of mRNA-1273 (100 µg IM, given as 2 doses, 28 days apart) in the 12 to < 18 years of age group. The blinded study started in November 2020 and enrolled 3,732 participants.

In May 2021, upon emergency authorisation of a non-study COVID-19 vaccine for use in adolescents, Study P203 transitioned to an open-label phase. This allowed unblinding of study participants and crossover of those participants randomised to placebo to receive the mRNA-1273 primary series. In November 2021, Protocol Amendment 3 was implemented to evaluate administration of a 50 µg mRNA-1273 booster dose to ongoing study participants in Part 1A and Part 1B. A booster dose was administered at least 5 months after completion of the mRNA-1273 primary series in Booster Phase (Part 1C-1).

Study mRNA-1273 P204

Study mRNA-1273 P204 (also referred to as P204) is an ongoing Phase 2/3, 3-part, dose-escalation (open-label), age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in children 6 months to 11 years.

The study population was evaluated in 3 discrete age groups (6 years through 11 years, 2 years to <6 years, and 6 months to <2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of mRNA-1273 in the primary series. For each of the three age groups, an open-label dose-finding (Part 1) phase preceded a blinded, placebo-controlled (Part 2) phase which evaluated the selected dose of mRNA-1273 in a placebo-controlled fashion. Data regarding the mRNA-1273 primary series for all age

groups in P204 has been previously submitted and primary series of 50 µg is currently authorised for use in children from 6 through 11 years of age. In a subsequent amendment, the protocol was revised to offer the mRNA-1273 primary series to P204 participants randomised to placebo once vaccination against COVID-19 was authorised in the respective age group. Following evidence of enhanced effectiveness of the adult booster dose, study P204 was amended to offer a booster dose of 25 µg mRNA-1273 to all children enrolled in the 6 through 11 years age group, which could be administered starting 6 months post-dose 2 of the primary series.

2.3.2. Clinical efficacy

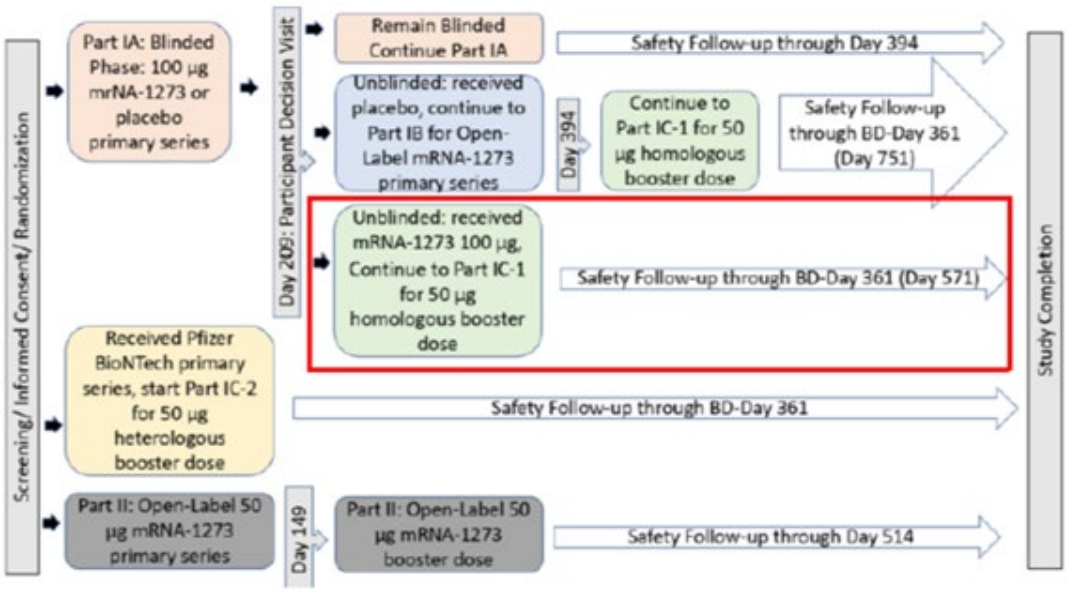
Study mRNA-1273-P203 (adolescent 12 – 17 years of age)

Study Overview

Study P203 is an ongoing, Phase 2/3 study originally designed as a randomised (2:1 vaccine:placebo), observer-blind, placebo-controlled study evaluating the safety, reactogenicity, and effectiveness of a two dose mRNA-1273 vaccine (100 µg) primary series in healthy adolescents 12 to 17 years (Part 1A, Figure 1). The blinded study started in November 2020 and enrolled 3,732 participants. Results from the Blinded Phase were previously submitted and reviewed by the Agency (EUA 27073 Amendment 191, submitted 09 Jun 2021; EUA 27073 Amendment 373, submitted 24 March 2022). Results supported administration of mRNA-1273 as two 100 µg doses 28 days apart in adolescents between ≥ 12 and 17 years of age. On 17 Jun 2022, the US Food and Drug Administration (FDA) granted EUA of the mRNA-1273 vaccine for adolescents 12 through 17 years of age.

In May 2021, upon emergency authorisation of a non-study COVID-19 vaccine for use in adolescents, Study P203 transitioned to an open-label phase. This allowed unblinding of study participants and crossover of those participants randomised to placebo to receive the mRNA-1273 primary series (Part 1B, Figure 1).

Figure 1: Overall Design Schema



Abbreviations: BD = booster dose; EUA = Emergency Use Authorization
Parts 1A, 1B, and 1C-1 are described in the text above. Part 1C-2 offered an mRNA-1273 BD to eligible participants who completed a primary COVID-19 vaccination series with a non-Moderna mRNA COVID-19 vaccine under EUA. Part II is evaluating a 50 µg primary series and BD in adolescents between 12 and 17 years of age. Neither Part 1C-2 nor Part II are discussed in this submission but rather included in this Figure for completeness.

Clinical Development of mRNA-1273 in Children

Study mRNA-1273-P204 (children 6 - 11 years of age)

P204 Study Overview: Study P204 is an ongoing Phase 2/3, 3-part, dose-escalation (open-label), age de- escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 in children 6 months to 11 years.

The study population was evaluated in 3 discrete age groups (6 through 11 years, 2 to <6 years, and 6 months to <2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of mRNA-1273 in the primary series. For each of the three age groups, an open-label dose-finding (Part 1) phase preceded a blinded, placebo-controlled (Part 2) phase which evaluated the selected dose of mRNA-1273 in a placebo-controlled fashion. Data regarding the mRNA-1273 primary series for all age groups in P204 has been previously submitted and primary series of 50 µg is currently authorised for use in children from 6 through 11 years. In a subsequent amendment, the protocol was revised to offer the mRNA-1273 primary series to P204 participants randomised to placebo once vaccination against COVID-19 was authorised in the respective age group.

Overview of P204 Booster Phase (Children 6 through 11 years of age): Following evidence of enhanced effectiveness of the adult BD, study P204 was amended to offer a BD (mRNA-1273, 25 µg) to all children enrolled in the 6 through 11 years of age group, which could be administered starting 6 months post-dose 2 of the primary series.

Participants receiving a BD were followed for safety and immunogenicity. Safety assessment included monitoring of solicited adverse reactions (SAR; collected for 7 days after BD), collection of all unsolicited adverse events (AEs) (up to 28 days after BD) and collection of serious AEs (SAEs), medically-attended AEs (MAAEs), AEs of special interest (AESI) and AEs leading to discontinuation through the entire study period post-BD. Serum samples were collected for immunogenicity analysis at the pre-booster visit (BD Day 1) and again on Day 29 post-BD. Serum levels of SARS-CoV-2 specific antibody (Ab) were measured. Data presented in this submission encompasses that from the start of the Booster Phase up to the time of the data cut (16 May 2022).

This submission describes the post-booster data for participants who received a primary series of 50 µg mRNA-1273 (from Part 1, open-label, or Part 2, randomised) and subsequently received a 25 µg BD ("Booster group") at least 6 months after Dose 2. Data from these children are presented and discussed in combination. Data for participants who received placebo during the randomised blinded phase of the study and subsequently received a BD following cross-over vaccination ("placebo-mRNA-1273-Booster") are included in the tables and listings accompanying this submission. This "placebo-mRNA-1273-Booster" group is not discussed in the submission as the group is small (n=3) and had less follow-up time than children randomised to mRNA-1273 primary series. Additionally, post-BD data from children in Part 1 who received the 100 µg primary series (as part of the Part 1 dose-finding phase) is included in the tables and listings but not discussed in the submission. Analysis and summary tables, and listings of individual level data accompany this submission.

Methods

Study participants

Disposition – Study P203 (adolescent 12 – 17 years of age)

A total of 1,346 participants 12 to 17 years of age who completed the 100 µg mRNA-1273 primary series in Study P203 Part 1A, received a 50 µg mRNA-1273 BD (Table 1). A total of 11 participants

(0.8%) in the mRNA-1273 booster group discontinued the study due to withdrawal of consent by participant (6 participants), lost to follow up (4 participants), and "other" reasons (1 participant). "Other" reasons from withdrawal or discontinuation from study were due to logistical issues with compliance with protocol procedures. No participants discontinued the study due to AEs.

Table 1: Participant Disposition After Booster Dose Full Analysis Set (Booster Dose)

	mRNA-1273-Booster N = 1346 n (%)
Received booster injection	1346 (100)
Completed study[1]	1 (<0.1)
Discontinued from study	11 (0.8)
Reason for discontinuation from study	
Lost to follow up	4 (0.3)
Withdrawal of consent by participant	6 (0.4)
COVID-19 non-infection related[2]	1 (<0.1)
Other	5 (0.4)
Other	1 (<0.1)
Adverse event	0
Protocol deviation	0

Abbreviations: BD = booster dose

[1] Study completion is defined as a participant who completed 12 months of follow up after the BD. A total of 1334 participants are still in the 12-month follow-up period.

[2] "COVID-19 non-infection related" refers to situations related to pandemic conditions (eg, reluctance to attend study site visits because of concerns regarding SARS-CoV-2 transmissibility) rather than to SARS-CoV-2 infection or COVID-19 in the study participant.

Percentages are based on the number of participants (N) in Full Analysis Set for Part C.

Source: Table 14.1.1.1.5.

Analysis Populations – P203

A description of the analysis sets in Study P203 and the number of participants included in each analysis set are provided in Table 2.

Table 2: Analysis Sets

Analysis Set	mRNA-1273-Booster N (%)	Description
FAS[1]	1346 (100)	All participants who received BD in Part C.
mITT1[1]	653 (48.5)	All participants in the FAS for Part C who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) pre-booster dose and received one booster dose without wrong treatment, ie, all FAS participants excluding those with pre-booster positive or missing RT-PCR test or serology test and those who received the wrong BD (ie, dose received in Part C is not as assigned).
Immunogenicity subset[2]	372 (100)	All participants selected for immune testing, with baseline (pre-Dose 1) SARS-CoV-2 status available, and baseline (pre-Dose 1) and at least 1 post-booster antibody assessment for the analysis endpoint.
PP Immunogenicity Subset [PPIS][2]	327 (88.1)	Participants selected for the Immunogenicity Subset who received 2 doses of mRNA-1273 in Part A per schedule, received a BD in Part C, had a negative SARS-CoV-2 status at baseline (pre-Dose 1 of Part A), had BD-Day 1 and BD-Day 2 Ab assessment for the analysis endpoint, and had no major protocol deviations that impacted key or critical data. The PP Immunogenicity Subset was used for analyses of immunogenicity in Part C by pre-booster SARS-CoV-2 status (negative [PPIS-Neg] and positive [PPIS-Pos]).
PP Immunogenicity Subset – Pre-booster SARS-CoV-2 Negative[2]	257 (69.1)	Participants who are in PP Immunogenicity Subset (Part C, BD) and are pre-booster SARS-CoV-2 negative, defined as no virologic or serologic evidence of SARS-CoV-2 infection on or before BD-Day 1 (pre-booster).
Safety Set[3]	1346 (100)	All participants who received a BD in Part C.
Solicited Safety Set[3]	1294 (96.1)	All participants who received a BD in Part C and contribute any solicited AR data (ie, have at least 1 post-booster-solicited safety assessment in Part C). The Solicited Safety Set was used for the analyses of solicited ARs in Part C.

Abbreviations: Ab = antibody; bAb =; BD = booster dose; AR = adverse reaction; BD = booster dose; FAS = full analysis set; mITT1 = modified intent-to-treat-1; PP = Per-Protocol; RT-PCR = reverse-transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[1] Percentage (%) was calculated using number of participants in FAS as denominator.

[2] Percentage (%) was calculated using number of participants in Immunogenicity subset as denominator.

[3] Percentage (%) was calculated using number of participants in Safety set as denominator.

Source: Table 14.1.2.1.5

Of note,

Table 2 *contains a typo in the definition of the PPIS where it should read "BD-Day 29 Ab assessment" rather than "DB-Day 2 assessment".*

PP Immunogenicity Subset

The Per-Protocol (PP) Immunogenicity Subset supported the primary immunogenicity analysis between adolescents boosted in P203 and the young adult (18 to 25 years) comparator group from the pivotal P301 study.

The P203 Immunogenicity Subset included 372 participants in the mRNA-1273 Booster group; of these, 45 participants were excluded from the PP Immunogenicity Subset for the following reasons: 26 had no immunogenicity data at BD-Day 29, 14 had positive baseline SARS-CoV-2 status in Part A of the study, and 5 had no immunogenicity data at BD-Day 1.

The PP Immunogenicity Subset included 295 P301 young adults 18 through 25 years of age, whose immune response elicited by the primary series (Day 57) were used to compare the immune response elicited by a BD in young adults 12 through 17 years of age (P203, Day 29 post-booster). The same P301 young adults PP Immunogenicity Subset (N = 295) has been used as the reference/comparison group for immunobridging of the primary series in participants 6 months to 17 years old.

The CHMP noted that the immunogenicity subset contains 372 participants which is about 28% of the FAS and it was clarified that the first ~400 enrolled participants in study P203 Part C who received a booster vaccination and met pre-specified criteria (participant in FAS and SARS-CoV-2 status not missing) were selected for the immunogenicity subset. Therefore, selection was not based on any stratification but was conducted arbitrarily. Although an undetermined bias in the populations cannot be excluded, this method was considered acceptable by the CHMP.

Disposition – Study P204 (children 6 – 11 years of age)

A total of 1,294 participants 6 through 11 years of age received the mRNA-1273 25 µg BD (Table 3). One participant discontinued the study due to withdrawal of consent. Withdrawal for this participant was not related to AEs.

Table 3: P204 Participant Disposition After Booster Dose Full Analysis Set (6 through 11 years)

	mRNA-1273 25 µg – Booster N=1294 n (%)
Received Booster Injection in Part 2	1294 (100)
Completed Study[a]	0
Discontinued from Study	1 (<0.1)
Reason for Discontinuation from Study	
Adverse Event	0
COVID-19 Infection	0
SAR/Reactogenicity Event	0
Other	0
Death	0
Lost to Follow-up	0
Physician Decision	0
Pregnancy	0
Protocol Deviation	0
Study Terminated by Sponsor	0
Participant Received Another COVID-19 Vaccine Under EUA	0
Withdrawal of Consent by Participant	1 (<0.1)
COVID-19 Non-Infection Related[b]	0
Other	1 (<0.1)
Other	0

Abbreviations: COVID-19 = coronavirus disease 2019; EUA = emergency use authorization; SAR = serious adverse reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

Percentages are based on the number of participants in Full Analysis Set.

[a] Study completion is defined as a participant who completed 12 months of follow-up after the booster dose.

[b] "COVID-19 non-infection related" refers to situations related to pandemic conditions (eg, reluctance to attend study site visits because of concerns regarding SARS-CoV-2 transmissibility) rather than to SARS-CoV-2 infection or COVID-19 in the study participant.

Source: Study P204 Table 14.1.1.2.2

Demographics and Baseline Characteristics

The demographics and baseline characteristics of participants in the Study 204 Safety Set are presented in

Table 4. The race and ethnicity demographics of the boosted participants were similar to that in the original P204 study as well as that from the MAH's study P301. Accordingly, results obtained can be generalised to various populations of children in this age group (the MAH references Creech et al. 2022). The demographics of the Safety Set was similar to that of the immunogenicity set. Approximately 33% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Table 4: P204 Participant Demographics and Baseline Characteristics Safety Set (6 through 11 years)

	mRNA-1273 25 µg – Booster N=1294 n (%)
Age (Years)	
n	1294
Mean (SD)	8.5 (1.62)
Median	8.0
Min, Max	6, 11
Sex, n (%)	
Male	672 (51.9)
Female	622 (48.1)
Race, n (%)	
White	850 (65.7)
Black	142 (11.0)
Asian	101 (7.8)
American Indian or Alaska Native	6 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)
Multiracial	153 (11.8)
Other	24 (1.9)
Not Reported	14 (1.1)
Unknown	3 (0.2)
Ethnicity, n (%)	
Hispanic or Latino	202 (15.6)
Not Hispanic or Latino	1079 (83.4)
Not Reported	10 (0.8)
Unknown	3 (0.2)
Race and Ethnicity Groupa, n (%)	
White non-Hispanic	699 (54.0)
Communities of Color	593 (45.8)
Missing	2 (0.2)
Weight (kg)	

	mRNA-1273 25 µg – Booster N=1294 n (%)
N	1294
Mean (SD)	33.69 (11.379)
Median	30.82
Min, Max	15.4, 103.7
Pre-booster SARS-CoV-2 Statusb, n (%)	
Negative	763 (59.0)
Positive	432 (33.4)
Missing	99 (7.7)

Abbreviations: bAb = binding antibody; BD = booster dose; COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SD = standard deviation.

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

[b] Pre-booster SARS-CoV-2 Status: Negative is defined as having a negative RT-PCR test and a negative serology test (based on bAb specific to SARS-CoV-2 nucleocapsid) at the time of BD. Positive is defined as having either positive RT-PCR test or positive serology (anti-SARS -CoV-2 nucleocapsid) on the date of BD.

Source: Study P204 Table 14.1.3.13.2.

The CHMP noted that participants who elected to receive a booster vaccination and volunteered to participate in the immunogenicity subset, i.e. had blood samples collected at pre-specified visits in the booster phase, were selected. Therefore, selection was not based on any stratification but was conducted arbitrarily. Although an undetermined bias in the populations cannot be excluded, this method was considered acceptable by the CHMP.

The MAH provided summary tables of demographics for safety and immunogenicity sets for participants in studies P203, P204 and P301 (see

Table 5 and Table 6). In the summary of demographics in Per-Protocol Immunogenicity Subsets the distribution of gender is balanced. There is an imbalance in race and ethnicity between the study groups ranging from 77.4% White Non-Hispanic in study P203, and 62.1% in study P204, to 49.5% in study P301. This imbalance, however, is not considered detrimental to the results.

Table 5: Summary of Demographics in Safety Sets: mRNA-1273 booster recipients in P203 (12-<18 years) and P204 (6-<12 years), and mRNA-1273 primary series recipients in P301 (18-25 years)

	P203 12-<18 years Booster 50 µg N=1346 n (%)	P204 6-<12 years Booster 25µg N= 1294 n (%)	P301 18-25 years Primary Series 100 µg N=878 n (%)
Sex			
Female	655 (48.7)	622 (48.1)	454 (51.7)
Male	691 (51.3)	672 (51.9)	424 (48.3)
Race			
White	1140 (84.7)	850 (65.7)	631 (71.9)
Black	43 (3.2)	142 (11.0)	84 (9.6)
Asian	66 (4.9)	101 (7.8)	85 (9.7)
American Indian or Alaska Native	7 (0.5)	6 (0.5)	4 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)	1 (<0.1)	2 (0.2)
Multiracial	71 (5.3)	153 (11.8)	28 (3.2)
Other	10 (0.7)	24 (1.9)	27 (3.1)
Not Reported	4 (0.3)	14 (1.1)	10 (1.1)
Unknown	4 (0.3)	3 (0.2)	7 (0.8)
Ethnicity			
Hispanic or Latino	171 (12.7)	202 (15.6)	283 (32.2)
Not Hispanic or Latino	1164 (86.5)	1079 (83.4)	591 (67.3)
Not reported	11 (0.8)	10 (0.8)	2 (0.2)
Unknown	0	3 (0.2)	2 (0.2)
Race and Ethnicity group			
White Non-Hispanic	999 (74.2)	699 (54.0)	404 (46.0)
Communities of Color	346 (25.7)	593 (45.8)	474 (54.0)
Missing	1 (<0.1)	2 (0.2)	0

Source: P203 booster–Table 14.1.3.14.1, P204 6-<12 years booster–Table 14.1.3.13.2, P301 primary series–Table 14.1.3.2.4

Table 6: Table 6 Summary of Demographics in Per-Protocol Immunogenicity Subsets–Pre-booster SARS-CoV-2 Negative (PPIS-Neg) for P203 (12-<18 years) and P204 (6-<12 years), and Per-Protocol Immunogenicity Subset (PPIS) for P301 (18-25 years)

	P203 12-<18 years Booster 50 µg N= 257 n (%)	P204 6-<12 years Booster 25 µg N= 95 n (%)	P301 18-25 years Primary Series 100 µg N= 295 n (%)
Sex			
Female	126 (49.0)	49 (51.6)	152 (51.5)
Male	131 (51.0)	46 (48.4)	143 (48.5)
Race			
White	225 (87.5)	73 (76.8)	206 (69.8)
Black	4 (1.6)	5 (5.3)	29 (9.8)
Asian	9 (3.5)	5 (5.3)	30 (10.2)
American Indian or Alaska Native	0	1 (1.1)	3 (1.0)
Native Hawaiian or Other Pacific Islander	0	1 (1.1)	2 (0.7)
Multiracial	15 (5.8)	7 (7.4)	14 (4.7)
Other	3 (1.2)	0	8 (2.7)
Not Reported	1 (0.4)	2 (2.1)	3 (1.0)
Unknown	0	1 (1.1)	0
Ethnicity			
Hispanic or Latino	32 (12.5)	15 (15.8)	77 (26.1)
Not Hispanic or Latino	223 (86.8)	78 (82.1)	216 (73.2)
Not reported	2 (0.8)	1 (1.1)	0
Unknown	0	1 (1.1)	2 (0.7)
Race and Ethnicity group			
White Non-Hispanic	199 (77.4)	59 (62.1)	146 (49.5)
Communities of Color	58 (22.6)	35 (36.8)	149 (50.5)
Missing	--	1 (1.1)	

Source: P203 booster–Table 14.1.3.14.3, P204 6-<12 years booster-Table 14.1.3.15.2.

Analysis Sets – Study P204

The following relevant analysis sets are defined: The FAS for Booster Dose Analysis consists of all participants who received at least one booster dose. Participants will be analysed according to their treatment group (mRNA-1273-Booster, or Placebo-mRNA-1273-Booster) if applicable. Immunogenicity Subset for booster dose consists of a) a subset of participants in the FAS (Booster Dose Analysis) and b) have baseline (pre-dose 1 of mRNA-1273) SARS-CoV-2 status available, and c) have baseline (pre-dose 1 of mRNA-1273) and at least one post-booster antibody assessment for the analysis endpoint. The Per-Protocol (PP) Immunogenicity Subset consists of all participants in Immunogenicity Subset for Booster Dose Analysis who meet all the following criteria: a) Received 2 doses of planned doses of mRNA-1273 vaccination in Part 1 open-label phase or Part 2 blinded phase per schedule b) Received booster dose in Booster Dose Analysis c) Had a negative SAS-CoV-2 status at baseline (pre-dose 1 of mRNA-1273) d) Had BD-Day 1 and BD-Day 29 Ab assessment for the analysis endpoint e) Had no major protocol deviations that impact key or critical data. The PP Immunogenicity Subset for Booster Dose analysis will serve as the population for the analysis of immunogenicity in booster dose by pre-booster SARS-CoV-2 status (negative vs. positive). The mITT1 Set for booster dose analysis consists of all participants in the FAS for booster dose who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) pre-booster dose and received one booster dose without wrong treatment, i.e., all FAS participants excluding those with pre-booster positive or missing RT-PCR test or serology test and those who received the wrong booster dose (i.e., dose received in booster dose is

not as assigned). Participants will be analysed according to their treatment group (mRNA-1273-Booster, or Placebo-mRNA-1273-Booster). The Solicited Safety Set for Booster Dose Analysis consists of all participants who received booster dose, and contribute any solicited AR data, i.e., have at least one post-booster solicited safety assessment in booster phase. The Solicited Safety Set will be used for the analyses of solicited ARs in Booster Dose analysis. The Safety Set in Booster Dose Analysis consists of all participants who received a booster dose in booster phase. The Safety Set will be used for analysis of safety except for the solicited ARs.

Objectives

Primary Safety Objective – Study P203

The primary safety objective is to evaluate the safety of the 50 µg booster dose (BD) of mRNA-1273.

Primary Immunogenicity Objective

The primary immunogenicity objective is to infer effectiveness of the 50 µg booster of mRNA-1273 by establishing non-inferiority of Ab response after the booster dose compared to the primary series of mRNA-1273. GM values of serum Ab and seroresponse rate of post-booster in Study P203 compared with primary series from young adult (18-25 years of age) recipients of mRNA-1273 in the clinical endpoint efficacy trial (Study P301).

Key Secondary Objective

The key secondary objective is to evaluate immune response elicited by the 50 µg prototype booster of mRNA-1273 against variant(s) of interest.

Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the persistence of the immune response of the BD of mRNA-1273 vaccine (50 µg) as assessed by the level of SARS-CoV-2 S2P specific bAb through 1 year after BD
- To evaluate the persistence of the immune response of the BD of mRNA-1273 vaccine (50 µg) as assessed by the level of nAb through 1 year after BD
- To evaluate the incidence of SARS-CoV-2 infection or COVID-19 after vaccination with mRNA-1273

Primary Objectives – Study P204

(1) To evaluate the safety of mRNA-1273 booster or third dose

(2) To infer effectiveness of the mRNA-1273 booster by establishing non-inferiority of Ab response after the booster dose in children in Study P204 compared with post-primary series in adult recipients of mRNA-1273 in the clinical endpoint efficacy trial (Study P301)

Secondary Objective – Study P204

(3) To evaluate the persistence of the immune response to mRNA-1273 vaccine

Exploratory Objectives – Study P204

- To evaluate immune response elicited by the booster dose of mRNA-1273 against variant(s) of interest

Outcomes/endpoints

Primary safety endpoints – Study P203

- Solicited local and systemic ARs through 7 days after BD
- Unsolicited AEs through 28 days after BD injection
- MAAEs post-booster dose through the last day of study participation
- SAEs post-booster dose through the last day of study participation
- AESIs post-booster dose through the last day of study participation AEs leading to discontinuation from study participation post-booster dose through the last day of study participation

Primary Immunogenicity Endpoints (Co-primary)

- GM of post-booster (post-Dose 3) Ab against original strain in Study P203 as compared to post-primary series (post-Dose 2) against original strain in the young adults in Study P301
- Seroresponse rate of post-booster/Dose 3 from baseline (pre-Dose 1) in Study P203 as compared to post-Dose 2 from baseline (pre-Dose 1) against original strain in the young adults 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

Key Secondary Endpoints

The key secondary objective will be evaluated by the following endpoints:

- GM of post-booster (post-Dose 3) Ab against circulating strain in Study P203 as compared to post-primary series (post-Dose 2) against circulating strain in the young adults in Study P301
- Seroresponse rate of post-booster/Dose 3 from baseline (pre-Dose 1) in Study P203 as compared to post-Dose 2 from baseline (pre-Dose 1) against circulating strain using 4 fold rise definition in the young adults in Study P301

Exploratory Endpoints

The exploratory endpoints are the following:

- The GM value of SARS-CoV-2 S2P specific bAb on BD-Day 1, BD-Day 29 (1 month after BD), BD-Day 181 (6 months after BD), and BD-Day 361 (1 year after BD)
- The GM values of SARS-CoV-2-specific nAb on BD-Day 1, BD-Day 29 (1 month after BD), BD-Day 181 (6 months after BD), and BD Day 361 (1 year after BD)
- The incidence of SARS-CoV-2 infection (symptomatic or asymptomatic infection) counted starting 14 days after BD of mRNA-1273
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) counted starting 14 days after BD in participants with negative SARS-CoV-2 at baseline or pre-booster
- The incidence of the first occurrence of symptomatic COVID-19 starting 14 days after BD of mRNA-1273

Primary Safety Endpoints – Study P204

- Solicited local and systemic Ars through 7 days after booster dose
- Unsolicited AEs through 28 days after booster dose
- 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
- AEs leading to discontinuation from study participation post-booster through the last day of study participation

Primary Immunogenicity Endpoints (Co-primary)

- The GM value of post-booster (post-third dose) Ab in Study P204 compared with post-primary series (post-Dose 2) in adults (18 to 25 years) in Study P301
- The seroresponse rate of post-booster (post-third dose) from baseline (pre-Dose 1 of primary series) compared with post-primary series (post-Dose 2) from baseline (pre-Dose 1 of primary series) in the adults (18 to 25 years) Study P301, using 4-fold rise definition
    - Seroresponse is defined as a titer change from baseline (pre-Dose 1 of primary series) below the LLOQ to ≥ 4 × LLOQ, or at least a 4 fold rise if baseline is ≥ LLOQ

Secondary Endpoints

- The GM values of SARS-CoV-2 S protein-specific bAb on Booster Dose (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 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)

Exploratory Endpoints

- GM, SRR, and GMFR of Ab against variant(s) of concern or interest

Sample size

Sample Size and Power (Study P203 Part C, Booster Dose)

All participants enrolled in Part A or Part B who meet the eligibility criteria for BD will be offered a BD of mRNA-1273 50 µg. With more than 1,000 participants expected to receive mRNA-1273 BD, the study Part C (Homologous Booster Dose) has a 90% probability to observe at least 1 participant with an AE at a true AE rate of 0.25%.

Serum samples from all participants will be collected and banked, a subset of participants will be selected, and their samples will be processed for immunogenicity testing (the Immunogenicity Subset) at specified timepoints.

Approximately 362 participants who receive mRNA-1273 BD will be selected for the Immunogenicity Subset for Part C, with a target of 289 participants receiving mRNA-1273 BD in the PP Immunogenicity Subset for Part C (adjusting for approximately 20% of participants who may be excluded from the PP

Immunogenicity Subset, as they may not have immunogenicity results due to any reason or may have protocol deviations impacting critical data).

For the primary immunogenicity objective in Part C, non-inferiority tests of two null hypotheses based on two coprimary endpoints, respectively, will be performed. The sample size calculation for each of the two non-inferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants receiving mRNA-1273 BD in the PP Immunogenicity Subset in Study P203 Part C and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) in Study P301, there will be 90% power to demonstrate non-inferiority of the immune response post-booster dose as measured by Ab GM in adolescents in Study P203 Part C compared with that in young adults (18-25 years of age) following primary series of mRNA-1273 in Study P301, at a 2-sided alpha of 0.05, assuming an underlying GMR value of 1, a non-inferiority margin of 1.5, and a point estimate minimum threshold of 0.8. The standard deviation (SD) of the log-transformed levels is assumed to be 1.5.
- With approximately 289 participants receiving mRNA-1273 BD in the PP Immunogenicity Subset in Study P203 Part C and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) in Study P301, there will be at least 90% power to demonstrate non-inferiority of the immune response post-booster dose as measured by seroresponse rate in adolescents in Study P203 Part C compared with that in young adults (18-25 years of age) following primary series of mRNA-1273 in Study P301, at a 2-sided alpha of 0.05, assuming a true seroresponse rate of 90% in young adults (18-25 years of age) following primary series of mRNA-1273 in Study P301, and a true seroresponse rate of 90% post-booster dose in adolescents in P203 Part C (i.e., true rate difference is 0 compared to young adults [18-25 years of age] in Study P301), and a non-inferiority margin of 10%.

Power and Sample Size – Study P204

A subset of Full Analysis Set (FAS) participants (Immunogenicity Subset) in each age group will be selected for measuring immunogenicity data. The immunogenicity samples of the Immunogenicity Subset will be processed, and the analysis of primary immunogenicity endpoint will be based on the PP Immunogenicity Subset.

- In Part 1 or Part 2 for the booster dose primary immunogenicity analysis in an age group, with approximately 289 participants receiving mRNA-1273 booster dose in the PP Immunogenicity Subset with pre-booster negative SARS-CoV-2 in Study P204 and 289 young adults (18 to 25 years of age) receiving mRNA-1273 100 µg primary series in Study P301, there will be a 90% power to demonstrate non-inferiority of the immune response, as measured by the antibody GM value, in children receiving a booster dose compared with that in adults (18 to 25 years of age) receiving mRNA-1273 primary series in Study P301, at a 2-sided alpha of 0.05, assuming an underlying true GMR value of 1.0 and a non-inferiority margin of 1.5. The standard deviation of the natural log-transformed GMT levels is assumed to be 1.5. Also, if the true SRRs were assumed to be 95% or higher in children receiving mRNA-1273 booster dose in Study P204 and adults receiving mRNA-1273 primary series in Study P301, with between-group true difference within 4%, there will be a > 90% power to demonstrate non-inferiority by SRR in children receiving a booster-dose compared with adults receiving primary series in Study P301, at a 2-sided alpha of 0.05.

Blinding (masking)

Study P203

Both Part B and Part C are open-label phase.

Study P204 - Optional Booster Doses:

Part 2 open-label phase, booster dose analysis, and Part 3 open-label phase are all open-label.

The CHMP considered the lack of blinding to be acceptable for the immunogenicity analyses.

Statistical methods

Study P203

Immunogenicity analyses

The GM with 95% CI will be summarised using t-distribution of the log transferred values and then back transformed to the original scale. The GMR with 95% CI to compare post-booster GM at BD-Day 29 in adolescents in Study P203 with the primary series GM at Day 57 (28 days after Dose 2) in young adults (18-25 years of age) in Study P301 will be computed based on the t-distribution of mean difference in the log transferred values and then back transformed to the original scale. The non-inferiority of immune response to mRNA-1273 as measured by GM will 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 GMR point estimate ≥ 0.8 (minimum threshold).

The number and percentage (rate) of participants achieving Ab seroresponse at BD-Day 29 will be summarised. The SRR difference with 95% CI (using Miettinen-Nurminen score method) to compare post-booster SRR at BD-Day 29 in adolescents in Study P203 with the primary series SRR at Day 57 (28 days after Dose 2) in young adults in Study P301 will be calculated. The non-inferiority in seroresponse rate of adolescents in P203 compared to adults of 18-25 years of age in P301 will be considered demonstrated if the lower bound of the 95% of the seroresponse rate difference is ≥ -10% based on the non-inferiority margin of 10%.

The primary immunogenicity objective in Part C is met if the non-inferiority is demonstrated based on both coprimary endpoints. The non-inferiority of key secondary endpoints (Ab GM and SRR against the circulating strain) will be assessed and tested using the same method as primary analysis.

Multiplicity Adjustment – P203

A sequential hypothesis testing (fixed-sequence) method will be used to adjust multiplicity to preserve the family-wise Type I error rate (alpha = 0.05). The hypothesis testing for the two coprimary endpoints (geometric mean titer [GMT] and SRR) for the primary series of mRNA-1273 in Part A was completed and statistically significant based on data snapshot dated 08 May 2021, and thus the alpha level of 0.05 can be passed to Part C hypothesis testing. In Part C, the hypothesis testing for the two coprimary endpoints (GMT and SRR against the original strain) after BD of mRNA-1273 will be tested first at alpha level of 0.05. If the testing of both the coprimary endpoints in Part C is statistically significant (meeting the non-inferiority success criteria of the coprimary endpoints), the alpha level of 0.05 will be passed to the hypothesis testing of the key secondary endpoints (GMT and SRR against circulating strain). The testing will continue through the sequence only until an endpoint is not statistically significant (did not meet specified non-inferiority success criteria), in which case the testing will stop.

Study P204

Immunogenicity Analyses

The primary analysis population for immunogenicity will be the PP Immunogenicity Subset, unless specified otherwise. Analyses of immunogenicity will be performed for each paediatric age group separately at the selected dose level based on the participants in the PP Immunogenicity Subset. Participants from Part 1 and Part 2 who receive the same mRNA-1273 dose level selected for expansion may be combined for immunogenicity analyses. For Part 1 or Part 2 booster dose primary immunogenicity analysis of -booster GM in children will 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. The estimated GMT with 95% CI and GMR with 95% CI will also be provided using t-distribution.

For Part 1 or Part 2 booster dose primary immunogenicity analysis of seroresponse in children receiving mRNA-1273 booster dose, the SRR with 95% CI (using Clopper-Pearson method) will be summarised. The SRR difference with 95% CI (using Miettinen-Nurminen score method) to compare post-booster SRR at BD-Day 29 in children in Study P204 with the primary series SRR at Day 57 (28 days after Dose 2) in adults (18 to 25 years of age) in Study P301 will be computed. The SRR 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. The non-inferiority of SRR in children receiving mRNA-1273 booster dose will be considered demonstrated if the lower bound of the 95% CI of the SRR difference is ≥ -10% based on the non-inferiority margin of 10%.

Booster dose primary immunogenicity objective for an age group in Part 2 will be considered to be met if the non-inferiority in the age group compared with the adults (18 to 25 years of age) is demonstrated based on both coprimary endpoints.

Multiplicity Adjustment

If the hypothesis testing is statistically significant for all the primary series primary immunogenicity endpoints in Part 2, the alpha 0.05 is preserved for the hypothesis testing for the booster dose primary immunogenicity endpoint in Part 1 or Part 2, starting in the oldest age group (6 years to < 12 years of age), then the middle age group (2 years to < 6 years of age), followed by the youngest age group (6 months to < 2 years of age) for booster dose in applicable age groups in Part 1 or Part 2. The testing will continue through the sequence only until an endpoint is not statistically significant (did not meet specified non-inferiority success criteria of any primary endpoint) in Part 1 or Part 2, in which case the testing will stop. If the hypothesis testing for all the booster dose primary endpoints in Part 2 is statistically significant (meeting the non-inferiority success criteria of the primary endpoints), the alpha level of 0.05 will be passed to the hypothesis testing in Part 3.

Efficacy Analysis

Exploratory analyses of incidence rates in COVID-19, SARS-CoV-2 infection, and asymptomatic infection will be performed using mITT1 Set. The mITT1 Set for the long-term analysis will be used for the incidence rate analysis in the long term including both the blinded and open-label phases; the mITT1 Set for the booster dose analysis will be used for the incidence analysis in the booster dose phase, unless otherwise specified.

The CHMP considered the defined statistical analyses to be generally in line with previous analyses used for bridging of the primary vaccination series and for the introduction of booster doses in adults. The statistical analysis methods described are therefore acceptable.

Regarding multiplicity control, the CHMP noted that the MAH argues that *"the hypothesis testing for the two coprimary endpoints (geometric mean titer [GMT] and SRR) for the primary series of mRNA-*

1273 in part 2 blinded phase was completed and statistically significant based on data snapshot dated 10 Nov 2021 for 6 -<12 years age group, and was also statistically significant based on data snapshot dated 21 Feb 2022 for 2-<6 years and 6 months -<2 years age group for pseudovirus neutralising antibody. Thus, the alpha level of 0.05 may be passed to Part 2 booster dose analysis hypothesis testing." The same argument (successful Part A) was used for Study P203.

While this argument might be true if pre-specified and pre-planned (at study initiation or at least before unblinding and agnostic of results), post-hoc it is considered problematic. If results would have turned out differently, one could have defined another T1E control approach. The dependency on previous and known results might lead to an inflation of the type 1 error. The post-hoc justification for the overall type 1 error control over the trial does not hold in the way presented. The assessment of booster doses is considered a different study part with a different hypothesis (based on an effective primary vaccination approach) and hence it is considered acceptable to use a separate significance level of 5%. Strictly speaking, however, the results should be considered as exploratory analyses. The added benefit in re-using subjects from the primary vaccination series (which provides information on Abs during primary series) is a benefit that outweighs the potential inflation of type 1 error.

Results

Immunogenicity – Study P203

Non-inferiority success criteria: Per protocol, effectiveness of a BD in adolescents is inferred based on establishing non-inferiority (NI) of nAb GMC at BD-Day 29 mRNA-1273 boosted adolescents in the PP Immunogenicity Subset – Pre-booster SAS-CoV-2 negative (PPIS-Neg) compared to those following primary series in young adults (Study Day 57; 18 to 25 years of age) in Study P301. Demonstration of NI in the difference in SRR among boosted adolescents (BD-Day 29) in the PP Immunogenicity Subset – Pre-booster SAS-CoV-2 (PPIS-Pos) compared to those post-primary series (Day 57) among young adults is also required. Non-inferiority is successfully met by showing: (i) that the lower bound of 95% CI of the GMR (P203 BD-Day 29/young adult P301 Day 57) is >0.667 (1/1.5) and (ii) that the lower bound of the 95% of the SRR difference is >-10%.

Measurement of serum nAb levels: Initial data from the P203 adolescent primary series and P301 young adult comparator group supporting the EUA for the 100 µg primary series (EUA 27073 Amendment 191, submitted 09 Jun 2021; Ali et al., 2021) were from a pseudovirus neutralisation assay (PsVNA) at Duke University laboratories. The comparison was based on nAb titers (ID50). Immunogenicity testing was subsequently transferred to PPD Laboratories to optimise assay throughput. For this submission, P203 BD samples and primary series samples from P301 young adults were tested for nAb levels at PPD Vaccine Laboratories using a validated PsVNA and are reported as nAb concentration (arbitrary unit [AU]/ml).

In a previous procedure the MAH submitted descriptions of the different assays. From these descriptions it was understood that the neutralisation assay VSDVAC62 is using a GFP-expressing reporter virus based on SARS-CoV-2. However, it was clarified that VSDVAC62 is a cell-based assay that is designed to determine the ability of anti-SARS CoV-2 Spike neutralising antibodies to inhibit the infection of 293T-ACE2 cells by SARS CoV-2 Spike Reporter Virus Particles (RVP) which express green fluorescent protein (GFP). The RVP used in VSDVAC62 are replication-incompetent pseudotyped virus particles. The SARS-CoV-2 RVPs display antigenically correct spike protein on a heterologous virus core and carry a modified genome that expresses a convenient optical reporter gene (GFP or luciferase) within 24 hours of cellular infection.

Results: In the P203 PPIS-neg (n = 257), pre-booster (BD-Day 1) nAb GMC was 400.4 (95% CI: 370.0, 433.4; Table 7); on BD-Day 29, the GMC was 7,172.0 (95% CI: 6,610.4, 7,781.4; Table 7).

Post-booster BD-Day 29 GMC increased approximately 18-fold from pre-booster GMC, demonstrating the potency of the BD to adolescents.

Antibody responses (nAb, GMC) were assessed among the subgroup of participants with evidence of previous SARS-CoV-2 infection at the BD-Day 1 visit (Table 7). Participants who were previously infected (PPIS-Pos) had, as expected, higher nAb titers measured at the BD-Day 1 visit (GMC 2,885.6, 95% CI: 1,878.2, 4,433.4) compared with participants without previous evidence of infection (GMC = 400.4, 95% CI [370.0, 433.4]). Administration of a BD nonetheless enhanced serum nAb yielding a BD-Day 29 GMC in this group (BD-Day 29 GMC = 13,456.8; 95% CI: 11,061.8, 16,370.5). Results confirm that regardless of pre-booster status, administration of a BD induces measurable increases in nAb levels relative to pre-booster levels.

Table 7: Summary of Serum nAb (PsVNA) GMC and SRR Among P203 Booster Recipients by Pre-Booster SARS-CoV-2 Status (PP Immunogenicity Subset for Part C, Booster Dose)

	Pre-booster SARS-CoV-2 Status		
	Negative N = 257	Positive N = 51	Overall N = 327
Pre-Dose 1 - Baseline GMC (95% CI)	11.3 (10.7, 12.0)	11.1 (9.5, 13.0)	11.3 (10.8, 11.9)
BD-Day 1- pre-booster GMC (95% CI)	400.4 (370.0, 433.4)	2885.6 (1878.2, 4433.4)	540.9 (479.5, 610.0)
BD-Day 29 GMC (95% CI)	7172.0 (6610.4, 7781.4)	13456.8 (11061.8, 16370.5)	7760.9 (7180.3, 8388.4)
GMFR (BD-Day 29/Pre-Dose 1) (95% CI)	633.0 (573.0, 699.4)	1213.5 (918.3, 1603.5)	685.6 (623.2, 754.3)
GMFR (BD-Day 29/BD-Day 1) (95% CI)	17.9 (16.2, 19.8)	4.7 (3.3, 6.6)	14.3 (12.9, 16.0)
SRR at BD-29 from pre-Dose 1 of primary series % (n/N) (95% CI)	100 (257/257) (98.6, 100)	100 (51/51) (93.0, 100)	100 (327/327) (98.9, 100)

Abbreviations: BD = booster dose; GMC = geometric mean concentration; GMFR = geometric mean fold rise; PsVNA = pseudovirus neutralization assay; SARs-CoV-2 Status = severe acute respiratory syndrome coronavirus 2; SRR = seroresponse rate

The *t*-distribution of the log-transformed values or the difference in the log-transformed values is used for the mean 95% CI calculation, then back-transformed to the original scale for presentation of GMC or GMFR 95% CI.

SRR at BD-Day 29 is defined as the % of participants with a change from below the lower limit of quantification (LLOQ) to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. SRR 95% CI is calculated using the Clopper-Pearson method.

Source: Table 14.2.3.1.5.1.1; Table 14.2.3.1.5.1.2

It was clarified that the Per-Protocol Immunogenicity Subset (overall N=327) includes pre-booster SARS-CoV-2 negative (N=257), positive (N=51) and missing (N=19). The pre-booster SARS CoV 2 status is defined based on both RT-PCR virology test and Elecsys serology test for bAb against SARS CoV-2 nucleocapsid at BD-Day 1:

(a) if both RT-PCR and Elecsys tests are negative, then SARS-CoV-2 status is negative

(b) if either RT-PCR or Elecsys test is positive, then SARS-CoV-2 status is positive

(c) if neither (a) nor (b), SARS-CoV-2 status is missing.

Among the 19 participants with missing pre-booster SARS-CoV-2 status, 7 had negative RT-PCR but missing Elecsys serology test data, and 12 had negative Elecsys test but missing RTPCR test data at BD Day 1. The missing RT-PCR or Elecsys test results at BD-Day 1 were due to missing samples, insufficient sample volumes for tests, or no results generated from tests.

Table 8 provides serum nAb levels at BD-Day 29 for adolescents in the PP Immunogenicity Subset pre-booster SARS-CoV-2 negative, at and after completion of the primary series (Day 57) in young adults

in Study P301 and the comparison of the two (GMR). The GMR of P203 BD-Day 29 GMC compared with young adults in Study P301, Day 57 GMC was 5.1 (95% CI: 4.5, 5.8), meeting the NI criteria (ie, lower bound of the 95% CI >0.667 (1/1.5); point estimate ≥0.8); the SRR difference was 0.7% (95% CI: -0.8, 2.4), meeting the NI criteria (lower bound of the 95% of the SRR difference >-10%).

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

Table 8: Serum nAb (PsVNA) GMC and SRR Among Recipients in Study P203 post-BD Compared with Young Adults in Study P301 Post-Primary Series: (Per-Protocol Immunogenicity Subset – Pre-Booster SARS-CoV-2 negative)

	Study P203: ≥12 to 17 Years BD-Day 29 N = 257	Study P301: ≥18 to ≤25 Years Day 57 N = 295		
Serum nAb Level (PsVNA, AU/mL)	**GMC 95% CI N1 = 257**	**GMC 95% CI N1 = 294**	**GMR Study P203 vs Study P301 95% CI**	**Met Success Criteria?**
	7172.0 6610.4, 7781.4	1400.4 1272.7, 1541.0	5.1 4.5, 5.8	Yes
Seroresponse Rate (PsVNA)	**% (n/N1) 95% CI**	**% (n/N1) 95% CI**	**Difference in Seroresponse Rate (%) 95% CI**	**Met Success Criteria?**
	100 (257/257) 98.6, 100.0	99.3 (292/294) 97.6, 99.9	0.7 -0.8, 2.4	Yes

Abbreviations: AU = arbitrary units; BD = booster dose; CI = confidence interval; GMC=geometric mean concentration; GMR = geometric mean ratio; LLOQ = lower limit of quantitation; nAb = neutralizing antibody; PsVNA = pseudovirus neutralization assay

N: the number of participants in Per-Protocol Immunogenicity Subset for booster – Pre-booster SAS-CoV-2 negative in P203 or Per-Protocol Immunogenicity Subset for primary series in P301.

N1: the number of participants who have nAb data available at the timepoint(s) for specific analysis.

The log-transformed antibody levels are analyzed using *t*-test method with the group variable (adolescents in P203 and young adults in P301), and 95% CI is calculated based on the *t*-distribution. The resulting means and 95% CIs are back-transformed to the original scale for presentation of the GMC and GMR with 95% CIs.

Seroresponse rate at BD-Day 29 from baseline (predose 1 of the primary series) is defined as the % of participants with a change from below LLOQ to equal or above 4 × LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method. Seroresponse rate difference 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.

Source: Table 14.2.1.1.3.5.1.1, Table 14.2.1.2.3.5.1.1

The CHMP considered the pre-specified success criteria for the primary immunogenicity objective in study P203 to be met. Of note, the pre-booster GMC value in the group of previously infected individuals in study P203 (GMC 2885.6 AU/mL) was substantially higher than the GMC in participants after the primary vaccination series (GMC 1400.4 AU/mL) in study P301. Nevertheless, a booster dose also elicited an increase (4.7-fold) in the GMC values in previously infected participants.

Study P204

Immunogenicity

Non-inferiority success criteria: Per protocol, effectiveness of a BD in children 6 through 11 years is inferred based on establishing NI of nAb GMC at BD-Day 29 mRNA-1273 boosted children in the Per Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status (PPIS-Neg), compared to those following primary series in young adults (Study Day 57; 18 to 25 years of age) in Study P301. Demonstration of NI in the difference in SRR among boosted children (BD-Day 29) in the PPIS-Neg participants compared to those among young adults is also required. Non-inferiority is successfully met by showing: (i) that the lower bound of 95% CI of the GMR (P204 BD-Day 29/young adult P301 Day 57) is >0.667 and (ii) that the lower bound of the 95% CI of the SRR difference is >-10%.

Measurement of serum nAb levels: Initial data supporting effectiveness of the mRNA-1273 primary series (50 µg) was derived from P204 participants 6 through 11 years and the P301 young adult comparator group (to assess NI). This data formed the basis for authorisation of the primary series under EUA (EUA 27073 Amendment 364, submitted 08 Mar 2022) where nAb levels were measured using an ancestral strain-specific PsVNA conducted at Duke University laboratories. The comparison was based on nAb titers (ID50). PsVNA testing was subsequently transferred to PPD Vaccine Laboratories to optimise assay throughput. For this submission, ancestral strain-specific nAb levels at PPD Vaccine Laboratories were measured using a validated PsVNA ("VAC62" assay). Neutralising antibody levels were measured in both the P204 Booster group and the P301 comparator group young adult primary series samples (Day 57;) using PsVNA testing at PPD, and the results from the same assay were compared to assess the effectiveness of the mRNA-1273 BD (25 µg) in P204 participants as compared to the primary series in P301 young adults.

In addition to measuring nAb levels against the ancestral strain, nAb levels against BA.1 (Omicron; "VAC122" assay) were also measured at PPD Laboratories for this age group using a validated PsVNA.

Results: As summarised in Table 9, in the P204 PPIS-Neg group (N=95), pre-booster (BD-Day 1) nAb GMC was 485.6 (95% CI: 423.1, 557.3); on BD-Day 29 the GMC was 5,847.5 (95% CI: 5,212.3, 6,560.1). Post-boost GMC increased approximately 12-fold from pre-booster GMC, demonstrating the ability of the BD to recall memory responses in children 6 through 11 years when administered 6 months or more post-completion of the primary series.

Antibody responses (nAb, GMC) were also assessed among the subgroup of participants with evidence of prior SARS-CoV-2 infection at the pre-booster visit (Table 9; N=27). Previously infected participants, as expected, had higher nAb titers measured at the pre-booster visit (GMC 4,513.3, 95% CI [2,979.3, 6,837.1]) compared to participants without prior evidence of infection (GMC 485.6, 95% CI [423.1, 557.3]). Administration of the BD nonetheless enhanced serum nAb levels (BD-Day 29 GMC = 8903.7, 95% CI [6736.9, 11767.6]). Results confirm that regardless of pre-booster SARS-CoV-2 status, administration of a BD induces measurable increases in nAb levels relative to pre-booster levels.

Table 9: Serum nAb Levels against Ancestral SARS-CoV-2 (D614G PsVNA, VAC62 assay) by Pre-booster SARS-CoV-2 Status in the P204 (6 through 11 years) PPIS

P204, 6 through 11 years, boosted	Pre-booster SARS-CoV-2 Status		
Timepoint/Parameter	Negative N = 95	Positive N=27	Overall N=129
Pre-Dose 1 Baseline GMC (95% CI)	N1=88 7.9 (7.2, 8.7)	N1=25 7.3 (6.2, 8.7)	N1=120 7.6 (7.1, 8.3)
BD-Day 1 (pre-booster) GMC (95% CI)	N1=95 485.6 (423.1, 557.3)	N1=27 4513.3 (2979.3, 6837.1)	N1=129 780.3 (635.5, 958.2)
BD-Day 29 GMC	N1=95	N1=27	N1=129

P204, 6 through 11 years, boosted	Pre-booster SARS-CoV-2 Status		
Timepoint/Parameter	Negative N = 95	Positive N=27	Overall N=129
(95% CI)	5847.5 (5212.3, 6560.1)	8903.7 (6736.9, 11767.6)	6586.1 (5906.6, 7343.8)
GM fold-rise[a] (BD-Day 29/BD-Day 1) (95% CI)	N1=95 12.0 (10.3, 14.1)	N1=27 2.0 (1.4, 2.8)	N1=129 8.4 (7.0, 10.2)
Seroresponse Rate at BD-Day 29 from pre-Dose 1 of primary series % (n/N1) (95% CI)	100% (88/88) (90.5, 100.0)	100% (25/25) (86.3, 100.0)	100% (120/120) (97.0, 100.0)

Abbreviations: BD = booster dose; CI = confidence interval; GMC = geometric mean concentration of nAb (D64G PsVNA, "VAC62" assay); LLOQ = lower limit of quantification; nAb = neutralizing antibody; PPIS = Per-Protocol Immunogenicity Subset for booster.
[a] GM fold-rise refers to the fold rise in GMC at the two defined timepoints
N: the number of participants in PPIS – pre-booster SARS-CoV-2 negative, positive or overall.
N1: the number of participants who have nAb data available at the time point(s) for specific analysis.
The t-distribution of the log-transformed values or the difference in the log-transformed values is used for the mean 95% CI calculation, then back transformed to the original scale for presentation of GMC or GM fold-rise 95% CI.
Seroresponse rate at BD-Day 29 from pre-Dose 1 of primary series is defined as the % of participants with a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.
Source: Table 14.2.3.1.3.1.1.2, Table 14.2.3.1.3.1.2.2

Results supporting the NI analysis are summarised inTable 10. Serum nAb levels (measured by PsVNA) for children 6 through 11 years in the PPIS-Neg and the comparison with those from young adults (18 to 25 years of age) in Study P301 are displayed. The GMR of P204 BD-Day 29 GMC compared to P301 young adults Day 57 GMC was 4.2 (95% CI [3.5, 5.0]), meeting the NI criteria (ie, lower bound of the 95% CI > 0.667); the SRR difference was 0.7% (95% CI: -3.5, 2.4), meeting the NI criteria (lower bound of the 95% of the SRR difference >-10%).

Table 10: Serum nAb against Ancestral Strain (PsVNA, VAC62) GMC and SRR among

P204 (6 through 11 years) Booster Recipients Post-BD Compared to P301 Young Adults Post-primary Series: (PPIS-Neg)

	Study P204: ≥6 through 11 Years BD-Day 29 N=95	Study P301: ≥18 to ≤25 Years Day 57 N=295		
Serum nAb level (PsVNA, AU/ml)	GMC 95%LS CI N1=95	GMC 95% CI N1=294	GMR Study P204 vs. Study P301 95% CI	Met Success Criteria[a]?
	5847.5 4999.6, 6839.1	1400.4 1281.1, 1530.8	4.2 3.5, 5.0	Yes
Seroresponse Rate (SRR) (PsVNA)	% (n/N1) 95% CI	% (n/N1) 95% CI	Difference in Seroresponse Rate (%) 95% CI	Met Success Criteria[b]?
	100% (88/88) 95.9, 100.0	99.3% (292/294) 97.6, 99.9	0.7% -3.5, 2.4	Yes

Abbreviations: ANCOVA = analysis of covariance; AU = arbitrary units; BD = booster dose; CI = confidence interval; GMC=geometric mean concentration; GMR = geometric mean ratio; LLOQ = lower limit of quantification; LS = least squares; nAb = neutralizing antibody; PPIS-neg = Per-Protocol Immunogenicity Subset with pre-booster SARS-CoV-2 negative status.
[a] The lower bound of GMR 95% confidence interval is > 0.667.
[b] The lower bound of SRR difference 95% confidence interval is > -10%.
N: the number of participants in PPIS-neg in P204, or Per-Protocol Immunogenicity Subset for primary series in P301.
N1: the number of participants who have nAb data available at the time point(s) for specific analysis.
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 resulting LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation of GMC and GMR with 95% CIs.
SRR = Seroresponse rate at BD-Day 29 from baseline (pre-dose 1 of the primary series) is defined as the % of participants with a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse rate 95% CI is calculated using the Clopper-Pearson method. Seroresponse rate difference 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits.
Source: Table 14.2.1.1.4.1.1.2, Table 14.2.1.2.5.1.1.2

The pre-specified success criteria for the primary immunogenicity objective were met, thus enabling the inference of BD vaccine effectiveness. The brisk recall response evident within 4 weeks of BD is evidence of the robust priming induced by the mRNA-1273 primary series.

Neutralising antibody levels against an Omicron variant of SARS-CoV-2 (BA.1, VAC122 assay) were assessed among booster recipients as well (Table 11). In the P204 PPIS-Neg participants, BD administration resulted in a rise of GMC from 53.0 (95% CI 45.3, 61.9) at BD-Day 1 to 632.6 (95% CI 546.7, 731.9) at BD-Day 29, a GM fold-rise of 12.1, (95% CI 9.7, 15.0). Among the Pre-Booster SARS CoV-2 positive group, higher nAb titers measured at the BD-Day 1 visit (1360.6, 95% CI 939.5, 1970.4) were observed. Confirmation of the infecting strain of SARS-CoV-2 was not possible in this study but given that boosting occurred during the Omicron wave in the US, participants may have had an Omicron infection. Importantly, even in children with immunity both from mRNA-1273 priming as well as SARS CoV-2 infection (hybrid immunity), Omicron nAb responses were further boosted (GMC 2362.9, 95% CI 1778.0, 3140.4) at BD-Day 29, with geometric mean fold rise 1.7 (95% CI, (1.3, 2.3) from administration of the BD. This again emphasises that responses primed by mRNA-1273 can be boosted regardless of baseline SARS-CoV-2 status.

Table 11: Serum nAb levels against Omicron SARS-CoV-2 (BA.1 PsVNA, "VAC122" assay) by Pre-booster SARS-CoV-2 Status among P204 (6 through 11 years) Booster Recipients in PPIS

P204, 6 through 11 years, boosted	Pre-booster SARS-CoV-2 Status		
Timepoint/Parameter	Negative N=95	Positive N=27	Overall N=129
Pre-Dose 1 Baseline GMC[a] (95% CI)	N1=50 8.6 (7.7, 9.6)	N1=19 7.2 (5.7, 9.1)	N1=70 8.2 (7.4, 9.1)
BD-Day 1 (pre-booster) GMC (95% CI)	N1=92 53.0 (45.3, 61.9)	N1=27 1360.6 (939.5, 1970.4)	N1=124 108.5 (82.4, 143.0)
BD-Day 29 GMC (95% CI)	N1=95 632.6 (546.7, 731.9)	N1=27 2362.9 (1778.0, 3140.4)	N1=129 860.6 (737.0, 1004.9)
GM fold-rise[b] (BD-Day 29/BD-Day 1) (95% CI)	N1=92 12.1 (9.7, 15.0)	N1=27 1.7 (1.3, 2.3)	N1=124 8.1 (6.5, 10.1)
Seroresponse rate (SRR) at BD-29 from pre-Dose 1 of primary series % (n/N1) (95% CI)	100% (50/50) (92.9, 100.0)	100% (19/19) (82.4, 100.0)	100% (70/70) (94.9, 100.0)

BD = booster dose; CI = confidence interval GMC = Geometric mean concentration of nAb (BA.1 PsVNA, "VAC122" assay); nAb = neutralizing antibody; PPIS = Per-Protocol Immunogenicity Subset for booster.
[a] Pre-dose Day 1 samples have been used previously for dose selection testing or primary analysis testing. Samples from those participants with available pre-dose 1 serum aliquots still remaining at the time of this Omicron testing were utilized.
[b] GM fold-rise refers to the fold rise in GMC at the two defined timepoints.
N: the number of participants in PPIS – pre-booster SARS-CoV-2 negative, positive or overall.
N1: the number of participants who have nAb data available at the time point(s) for specific analysis.
The t-distribution of the log-transformed values or the difference in the log-transformed values is used for the mean 95% CI calculation, then back transformed to the original scale for presentation of GMC or GM fold-rise 95% CI.
SRR = Seroresponse rate at BD-Day 29 from pre-Dose 1 of primary series is defined as the % of participants with a change from below LLOQ to equal or above 4 x LLOQ, or at least a 4-fold rise if baseline is equal to or above LLOQ. Seroresponse 95% CI is calculated using the Clopper-Pearson method.
Source: Table 14.2.3.1.4.1.1.2; Table 14.2.3.1.4.1.2.2

The CHMP considered the pre-specified success criteria for the primary immunogenicity objective in Study P204 to be met.

GMC values in the group of Negative participants 6 – 11 years of age, i.e. with no evidence of prior SARS-CoV-2 infection, were comparable to the group of Negative participants 12 – 17 years of age. A booster dose elicited an increase in the GMC values to 5,847.5 AU/mL which is lower than the value in the group 12 – 17 years of age (GMC 7172.0 AU/mL).

The GMC value in the group of Positive, i.e. participants with evidence of previous SARS-CoV-2 infection prior to booster dose, was higher in the age group 6 – 11 years of age (GMC 4,513.3 AU/mL)

as compared to the group of Positive 12 – 17 years of age (GMC 2,885.6 AU/mL). In the group of Positive participants in both studies, P203 and P204, there is no information on the interval between SARS-CoV-2 infection and booster dose. The differences in the GMC values prior to booster dose might be influenced by more recent or less recent infections.
A booster dose elicited an increase in nABs in the group of Positive participants in both age groups, however, in the younger group 6 – 11 years of age the GMC was increased to 8903.7 AU/mL whereas the GMC was increased in the group of Positive participants 12 – 17 years of age to 13,456.8 AU/mL. The lower GMC values in the younger age group (6 – 11 yoa) as compared to adolescent 12 – 17 years of age might reflect the lower dose of 25 µg as compared to 50 µg.

No nAB titers against VOCs have been analysed in adolescent. In children nABs against SARS-CoV-2 Omicron BA.1 have been analysed. A booster dose with mRNA-1273 increased nAB titers against Omicron BA.1 in both, the group of Negative and Positive participants. Of note, the GMC value in the group of Negative on day 29 after the booster dose (GMC 632.6 AU/mL) was substantially lower than the GMC in the group of Positive participants prior to booster dose (GMC 1360.6 AU/mL) and after the booster dose (GMC 2362.9 AU/mL). As this study was conducted during the Omicron wave the group of Positive participants is likely to have had infections with SARS-CoV-2 Omicron variant that elicited an immune-response with substantially higher nAB GMCs as compared to a booster vaccination with mRNA-1273 in previously non-infected participants. In absence of clinical data particular nAB GMC values against SARS-CoV-2 Omicron BA.1 after vaccination with mRNA-1273.214 remain a matter of speculation but would generally be expected to be higher as compared to BD with mRNA-1273 as previously shown in adults 18 years of age and older.

COVID-19 Incidence Rate - Study P203

Incidence Rate Assessment: As noted previously, RT-PCR confirmed COVID-19 case monitoring continued beyond unblinding. After unblinding, however, the reference group of the placebo comparator was lost, limiting the interpretation of the incidence rate. Monthly incidence rates of COVID-19 starting in May 2021 (end of Blinded Phase), in participants prior to the receipt of a BD, through 31 Jan 2022, were previously submitted to the Agency (EUA 27073 Amendment 373, submitted 24 March 2022). Administration of BD initiated in Dec 2021 and monthly incidence rates of COVID-19 after receipt of a BD are provided here from 01 Jan 2022 through the data cut-off. Examining the incidence rates of COVID-19 in Jan 2022 allowed the comparison of the incidence of COVID-19, pre- and post-booster. For this comparison of rates of RT-PCR confirmed COVID-19 cases, the "P301 case definition" was employed. This time period (January 2022) also represented the Omicron surge – which provides a unique opportunity to assess the influence of the mRNA-1273 BD on COVID-19 incidence (compared to primary series alone).

Results: In adolescents boosted with a 50 µg BD, the COVID-19 incidence rate was 4.676 cases/1000 person-months from Jan 2022 to May 2022. In Jan 2022, the COVID-19 incidence rate was 88.9 cases/1000 person-months among P203 participants completing the primary series, but not yet boosted (1696 participants at risk; data cut-off 31 Jan 2022, data snapshot of 02 Mar 2022; EUA 27073 Amendment 373, submitted 24 March 2022). In contrast, during this same month of observation, the COVID-19 incidence rate in adolescents boosted with a 50 µg BD was 9.778 cases/1000 person-months (1 case out of 353 participants at risk). Although highly dependent on the force of infection in the community, the incidence rates post-booster were lower than those among adolescents receiving only primary series. None of the COVID-19 cases following BD were assessed by the Investigator to be severe.

Table 12: Analysis of Incidence Rate of COVID-19 Starting 14 Days After Booster Dose by Calendar Month mITT1 Set (Part C, Booster Dose)

	mRNA-1273-Booster N = 653
From 01 January 2022 through 31 May 2022	
Number of participants at risk (N1)	639
Number of participants with COVID-19, n (%)[1]	10 (1.6)
Person-months[2]	2138.6
Incidence rate per 1000 person-months (95% CI)[3]	4.676 (2.242, 8.599)
In January 2022	
Number of participants at risk (N1)	353
Number of participants with COVID-19, n (%)[1]	1 (0.3)
Person-months[2]	102.3
Incidence rate per 1000 person-months (95% CI)[3]	9.778 (0.248, 54.477)
In February 2022	
Number of participants at risk (N1)	577
Number of participants with COVID-19, n (%)[1]	1 (0.2)
Person-months[2]	469.3
Incidence rate per 1000 person-months (95% CI)[3]	2.131 (0.054, 11.873)
In March 2022	
Number of participants at risk (N1)	625
Number of participants with COVID-19, n (%)[1]	4 (0.6)
Person-months[2]	619.7
Incidence rate per 1000 person-months (95% CI)[3]	6.465 (1.762, 16.553)
In April 2022	
Number of participants at risk (N1)	632
Number of participants with COVID-19, n (%)[1]	4 (0.6)
Person-months[2]	618.7
Incidence rate per 1000 person-months (95% CI)[3]	6.465 (1.762, 16.553)
In May 2022	
Number of participants at risk (N1)	628
Number of participants with COVID-19, n (%)[1]	2 (0.3)
Person-months[2]	328.6
Incidence rate per 1000 person-months (95% CI)[3]	6.086 (0.737, 21.984)

Abbreviations: CI = confidence interval; mITT1 = modified-intent-to-treat-1.
[1] Percentages are based on N1.
[2] Person-months for each time period is defined as the total months from the earlier date of the start of each time period or 14 days after BD to the earliest date of the first occurrence of COVID-19, the end of each time period, study discontinuation, non-study COVID-19 vaccination or data cutoff.
[3] Incidence rate for each time period is defined as the number of subjects with an event during the time period divided by the number of subjects at risk during the time period and adjusted by person-months (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-months.
1 month = 30.4375 days.
Source: Table 14.2.7.7.2

In adults, mRNA-1273 BD administration enhanced effectiveness against Omicron infection compared with the effectiveness measured after a two-dose primary series, with >99% effectiveness against Omicron-related hospitalisation (Tseng et al., 2022). With demonstration of NI of the mRNA-1273 BD compared to mRNA-1273 primary series in adults, similar clinical effectiveness benefits are anticipated among boosted adolescents.

Incidence of COVID-19 Cases – Study P204

As part of ongoing monitoring, COVID-19 case occurrence was captured. At the time of the data cut-off date for this submission (23 May 2022), the median time of follow-up from BD was 32 and 29 days (Parts 1 and 2, respectively) – too limited a period to yield meaningful insights. Hence, no incidence rates were calculated.

The CHMP noted that for study P203, incidence rates are provided for a period of 5 months. During this period, 12 SARS-CoV-2 infections were detected out of 639 participants at risk. For study P204 no incidence rates have been calculated as the follow-up period was too short.

Incidence rates for study P203 cannot be interpreted as there is no comparator group available. Hence, there is no information on efficacy available for adolescent and children, however, the CHMP considered that efficacy can be inferred by comparison of the immunogenicity results in these age groups with young adults in study P301 in which efficacy has been demonstrated.

Summary of main studies

The below Table 13 summarise the efficacy results from the main study mRNA-1273-P204 supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13: Summary of Efficacy for trial mRNA-1273-P204

<table>
<tr><td colspan="4">Title:
A Phase 2/3, Three-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</td></tr>
<tr><td>Study identifier</td><td colspan="3">mRNA-1273-P204</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Administration of booster dose with 25 µg mRNA-1273 after primary series with 50 µg mRNA-1273 in children 6 – 11 yoa.</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>29 Days
not applicable
not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Non-inferiority</td></tr>
<tr><td rowspan="3">Treatments groups</td><td colspan="2">Children 6 – 11 years of age</td><td>Booster dose 25 µg mRNA-1273</td></tr>
<tr><td colspan="2">group descriptor</td><td>n/a for this submission</td></tr>
<tr><td colspan="2">group descriptor</td><td>n/a for this submission</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Co-Primary endpoint</td><td>Non-inferiority</td><td>*GMR after booster dose compared to primary vaccination series in young adults 18-25 yoa in study P301.
*difference in seroresponse rate after booster dose compared to primary vaccination series in young adults 18-25 yoa in study P301.</td></tr>
<tr><td>Secondary endpoint</td><td>To evaluate the incidence of SARS-CoV-2 infection after vaccination with mRNA-1273</td><td>*serology and/or RT-PCR
*bAb-levels against SARS-CoV-2 nucleocapsid protein
*symptomatic COVID-19 postbaseline</td></tr>
<tr><td>Database lock</td><td colspan="3">16 May 2022</td></tr>
</table>

Results and Analysis				
Analysis description	**Interim Analysis**			
Analysis population and time point description	Per-protocol-Immunogenicity-Subset-Negative (PPIS-Neg); Pre-booster Day1, post-booster Day 29			
Descriptive statistics and estimate variability	Treatment group	PPIS-Negative	PPIS-Positive	PPIS-Overall
	Number of subjects	N=95	N=27	N=129
	Pre-Dose 1 Baseline GMC	7.9	7.3	7.6
	95% CI	7.2, 8.7	6.2, 8.7	7.1, 8.3
	BD-Day 1 (pre-booster) GMC	485.6	4513.3	780.3
	95% CI	423.1, 557.3	2979.3, 6837.1	635.5, 958.2
	BD-Day 29 GMC	5847.5	8903.7	6586.1
	95% CI	5212.3, 6560.1	6736.9, 11767.6	5906.6, 7343.8
Effect estimate per comparison	Co-Primary endpoint	Comparison groups	Young adults 18-25 yoa (P301)	
		GMR	4.2	
		95% CI	3.5, 5.0	
		P-value		
	Co-Primary	Comparison groups	Young adults 18-25 yoa (P301)	
		SRR difference	0.7%	
		95% CI	-3.5, 2.4	
		P-value		
Notes	No clinical data are available after booster vaccination with mRNA-1273.214 (Spikevax bivalent (Original/Omicron BA.1)) in children 6-11 yoa. Indication for booster vaccination with mRNA-1273.214 in children 6–11 yoa is sought based on (1) immunobridging of immunogenicity results after booster dose with mRNA-1273 in children 6-11 yoa to immunogenicity results after primary vaccination series in young adults 18-25 yoa (non-inferiority) and (2) inference of superiority of mRNA-1273.214 in eliciting nAB GMTs against SARS-CoV-2 Omicron BA.1 as demonstrated in adults to the age group 6-11 yoa.			
Analysis description	**Interim Analysis**			

2.3.2.1. Discussion on clinical efficacy

The pre-specified success criteria for the primary immunogenicity objectives in studies P203 and P204 were met, i.e. the nAB GMC values after a booster dose with mRNA-1273 were non-inferior to the nAB GMC value after a primary vaccination series, and the SRR differences were also non-inferior.

GMC values prior to booster dose in the group of negative participants at the age of 6 – 11 years of age, i.e. with no evidence of prior SARS-CoV-2 infection, were comparable to the group of Negative participants at the age of 12 – 17 years of age. A booster dose elicited an increase in the GMC values

to 5,847.5 AU/mL which is lower than the value in the age group 12 – 17 years of age (GMC 7,172.0 AU/mL).

The GMC value in the group of positive participants, i.e. participants with evidence of previous SARS-CoV-2 infection prior to booster dose, was higher in the age group 6 – 11 years of age (GMC 4,513.3 AU/mL) as compared to the group of Positive at the age of 12 – 17 years of age (GMC 2,885.6 AU/mL). In the group of Positive participants in both studies, P203 and P204, there is no information on the interval between SARS-CoV-2 infection and booster dose. The differences in the GMC values prior to booster dose might be influenced by more recent or less recent infections.

The pre-booster GMC values in the group of previously infected individuals in both studies, P203 (GMC 2,885.6 AU/mL) and P204 (GMC 4,513.3 AU/mL) were substantially higher than the GMC value in participants after the primary vaccination series (GMC 1,400.4 AU/mL) in study P301. Nevertheless, a booster dose also elicited an increase (4.7-fold and 2.0-fold, respectively) in the GMC values in previously infected participants in both age groups, however, in the younger age group 6 – 11 years of age the GMC was increased to 8,903.7 AU/mL whereas the GMC was increased in the group of positive participants in the age group 12 – 17 years of age to 13 456.8 AU/mL. The lower GMC values in the younger age group (6 – 11 yoa) as compared to adolescent 12 – 17 years of age might reflect the lower dose of 25 µg as compared to 50 µg mRNA-1273.

No nAB titers against VOCs have been analysed in adolescent. In children nABs against SARS-CoV-2 Omicron BA.1 have been analysed. A booster dose with mRNA-1273 increased nAB titers against Omicron BA.1 in both, the group of Negative and Positive participants. Of note, the GMC value in the group of Negative on day 29 after the booster dose (GMC 632.6 AU/mL) was substantially lower than the GMC in the group of Positive participants prior to booster dose (GMC 1,360.6 AU/mL) and after the booster dose (GMC 2,362.9 AU/mL). As this study was conducted during the Omicron wave the group of Positive participants might have had infections with SARS-CoV-2 Omicron variant that elicited a variant adapted immune-response. This supports the use of variant adapted vaccines.

For study P203 incidence rates are provided for a period of 5 months. During this period 12 SARS-CoV-2 infections have been detected out of 639 participants at risk. For study P204 no incidence rates have been calculated as the follow-up period was too short.

Incidence rates for study P203 cannot be interpreted as there is no comparator group available. Hence, there is no information on efficacy available for adolescent and children, however, efficacy can be inferred by comparison of the immunogenicity results in these age groups with young adults in study P301 in which efficacy has been demonstrated.

2.3.2.2. Conclusions on the clinical efficacy

The MAH presented immunogenicity results after a booster dose with mRNA-1273 from studies in adolescent and children (12 – 17 years of age and 6 – 11 years of age) as compared to immunogenicity results from young adults 18 – 25 years of age from study P301 in which efficacy has been demonstrated. Studies P203 and P204 demonstrate that immunogenicity results against the ancestral SARS-CoV-2 D614G after a booster dose in adolescent and children are non-inferior to immunogenicity results after primary vaccination based on GMR values and seroresponse rates.

Spikevax (mRNA-1273) is approved as a booster dose in adolescent and adults 12 years of age and older. The MAH is now seeking the indication for a booster dose with Spikevax bivalent Original/Omicron BA.1 (mRNA-1273.214) in children 6 through 11 years of age. Spikevax bivalent Original/Omicron BA.1 is approved as a booster dose in adolescent and adults 12 years of age and older based on immunobridging of nAB GMTs against SARS-CoV-2 Omicron BA.1 and BA.4-5, as

determined in adults 18 years of age and older. Immunogenicity results against SARS-CoV-2 Omicron BA.1 could demonstrate superiority of a booster dose with mRNA-1273.214 as compared to mRNA-1273 based on GMRs in study P205. The MAH is now presenting immunogenicity results after a booster dose in adolescent that support the indication of a booster dose with Spikevax bivalent Original/Omicron BA.1 as well as immunogenicity results after a booster dose in children 6 through 11 years of age.

In summary, non-inferiority of a booster dose with mRNA-1273 in adolescent and children could be demonstrated in studies P203 and P204, and superiority of a booster dose with mRNA-1273.214 vs. mRNA-1273 against SARS-CoV-2 Omicron BA.1 has been demonstrated earlier in study P205. Therefore, efficacy can be inferred by immunobridging of immunogenicity results with mRNA-1273 as a booster dose in children 6 through 11 years of age. Based on previous experience there is reason to assume that a booster dose with mRNA-1273.214 would elicit nABs against SARS-CoV-2 Omicron BA.1 and BA.4-5 to a level that is superior as compared to a booster dose with mRNA-1273 in children 6 through 11 years of age, supporting the use of mRNA-1273.214 as a booster dose in children 6 through 11 years of age. The data also supports the indication of a booster dose with Spikevax in the same age group.

2.3.3. Clinical safety

Currently, the use of Spikevax (mRNA-1273) for booster vaccination is authorised for individuals ≥12 years of age. The MAH submitted an application to request an amendment of this indication, to expand booster vaccination to individuals aged 6 through 11 years of age. The ongoing paediatric mRNA-1273 study (P204) has indicated an acceptable safety profile and immunogenicity of a primary series of two injections of 50 µg of mRNA-1273 in children 6 through 11 years.

Although the primary series demonstrated good vaccine efficacy within a few months of completing the primary series, it has been demonstrated in adults that vaccine efficacy has waned over time, in particular, after the emergence of the Omicron variant. The enhanced effectiveness of mRNA-1273 after booster dose administration in individuals ≥18 years of age during the Omicron surge prompted the amendment of the P204 protocol to evaluate the safety and immunogenicity of a booster dose of mRNA- 1273 (25 µg) in children 6 through 11 years who previously completed the primary vaccination series ("booster group"). The intention is to extrapolate the reactogenicity and the safety profile of a 25 µg booster dose of mRNA-1273.214 given to children 6 through 11 years of age from a booster dose of 25 µg of mRNA-1273 given to children of this age group and from the known safety profile of a booster dose of 50 µg of mRNA-1273.214 in the adult population. In addition, the MAH submitted clinical data to underpin the administration of a booster dose for adolescents 12 to 18 years of age that has already been implemented in the SmPC. Initial EUA and Marketing Authorisation Application (MAA) filings for use of a booster dose of mRNA-1273 in adolescents were based on extrapolation of immunogenicity and safety data from adult booster dose studies. The submitted data allows the assessment of a single booster dose of 50 µg mRNA-1273 for adolescents from 12 through 17 years of age who previously completed a primary vaccination series of two 100 µg doses administered approximately 1 month apart.

Booster dose of 25 µg of mRNA-1273 in children 6 through 11 years of age

Safety sets

Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomised and received any study injection, and contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set was to be used for the analyses of solicited ARs. Participants were to be included in the vaccination group corresponding to the study injection they actually received rather than the vaccination group to which the subject was randomised.

Safety Set

The Safety Set consists of all randomised participants who received any study injection. The Safety Set was to be used for analysis of safety except for the solicited ARs. Participants were to be included in the vaccination group corresponding to the vaccination they actually received.

Participant exposure and follow up

This submitted data describe the reactogenicity, safety, and immunogenicity of a 25 µg booster dose of mRNA-1273 administered to children 6 through 11 years of age enrolled in study P204 (data cut-off date of 23 May 2022). Participants had received a primary series of 50 µg mRNA-1273 (from Part 1, open-label, or Part 2, randomised) and subsequently received a 25 µg booster dose at least 6 months after Dose 2 ("Booster group"). Data for participants who received placebo during the randomised blinded phase of the study and subsequently received a booster dose following cross-over vaccination ("placebo-mRNA-1273-Booster") are included in the tables and listings accompanying this submission. Additionally, post-booster dose data from children in Part 1 who received the 100 µg primary series (as part of the Part 1 dose-finding phase) are included in the tables and listings but not discussed in the submission.

Overall, 1,294 participants 6 through 11 years of age received a 25 µg mRNA-1273 booster dose after 2 doses of 50 µg mRNA-1273 within the primary vaccination course. All subjects (1,294/1,294) included in the safety set had received 2 doses of the primary schedule before the booster dose of 25 µg of mRNA-1273 (100%). One participant discontinued the study due to withdrawal of consent. Withdrawal for this participant was not related to AEs.

176 subjects received a 25 µg booster dose of mRNA-1273 after priming with 50 µg mRNA-1273 in part 1 and 1,115 subjects in part 2. As mentioned above, 3 subjects in the previous placebo group ("placebo-mRNA-1273-Booster") subsequently received a 25 µg booster following cross-over vaccination with 2 doses of 50 µg primary vaccination with mRNA-1273. The solicited safety set includes 1,280 subjects (part 1 and part 2 and 2 former placebo subjects). The safety set includes 1,294 subjects (part 1 and part 2 together, and 3 former placebo subjects). The patient exposure for the full analysis set and the 2 safety sets for part 1 and part 2 are shown in Table 14 to Table 16.

Table 14: P204 Subject Disposition After Booster Dose Full Analysis Set (6 through 11 years)

Age Group: >=6 and <12 Years

	Part 2			Part 1 + Part 2
	Placebo - mRNA-1273 50 µg - Booster (N=3) n (%)	mRNA-1273 50 µg - Booster (N=1115) n (%)	Total (N=1118) n (%)	mRNA-1273 50 µg Primary Series - Booster (N=1294) n (%)
Received Booster Injection	3 (100)	1115 (100)	1118 (100)	1294 (100)
Completed Study [1]	0	0	0	0
Discontinued from Study	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Reason for Discontinuation of Study				
Adverse Event	0	0	0	0
COVID-19 Infection	0	0	0	0
SAR/Reactogenicity Event	0	0	0	0
Other	0	0	0	0
Death	0	0	0	0
Lost to Follow-up	0	0	0	0
Physician Decision	0	0	0	0
Pregnancy	0	0	0	0
Protocol Deviation	0	0	0	0
Study Terminated by Sponsor	0	0	0	0
Subject Received Another COVID-19 Vaccine Under EUA	0	0	0	0
Withdrawal of Consent by Participant	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
COVID-19 Non-Infection Related	0	0	0	0
Other	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Other	0	0	0	0

Table 15: Number of Subjects in Each Analysis Set of Part 1 in Booster Dose Analysis by Age Group and Dose Level in Part 1 Full Analysis Set (Booster Dose Analysis)

Age Group: >=6 and <12 Years

	mRNA-1273 50 µg - Booster	mRNA-1273 100 µg - Booster	Total
Full Analysis Set [1]	176	184	360
Modified Intent-to-Treat-1 (mITT1) Set, n (%) [1]	105 (59.7)	100 (54.3)	205 (56.9)
Safety Set [2]	176	184	360
Solicited Safety Set, n (%) [2]	176 (100)	184 (100)	360 (100)

Table 16: Number of Subjects in Each Analysis Set of Part 2 in Booster Dose Analysis by Age Group Full Analysis Set (Booster Dose Analysis)

Age Group: >=6 and <12 Years

	Part 2			Part 1 + Part 2
	Placebo - mRNA-1273 50 µg - Booster	mRNA-1273 50 µg - Booster	Total	mRNA-1273 50 µg Primary Series - Booster
Full Analysis Set [1]	3	1115	1118	1294
Modified Intent-to-Treat-1 (mITT1) Set, n (%) [1]	1 (33.3)	634 (56.9)	635 (56.8)	740 (57.2)
Safety Set [2]	3	1115	1118	1294
Solicited Safety Set, n (%) [2]	2 (66.7)	1102 (98.8)	1104 (98.7)	1280 (98.9)

Follow-up

The median follow-up time after booster dose is 29 days (Part 1 and Part 2). Until the time of data cut-off 577 subjects (44.6%) in Part 1 and Part 2 together had a follow up of less than 28 days; a safety follow-up of ≥ 28 days is available for approximately 717 (55.4%) children; 694 children (53.6) were followed for >= 28 and < 56 Days (Part 1 and Part 2 together). Additional safety data for a 6-month

safety follow-up on at least 1000 boosted participants 6-11 years of age is anticipated to be available at the end of 2023, but booster vaccinations in the trial are still ongoing. The median time interval from primary dose 2 to booster dose in Part 1 and Part 2 together is 225.0 days. The follow-up period after booster dose and the time interval between dose 2 and booster dose is displayed in Table 17: and Table 18.

Table 17: Summary of Time on Study by Age Group Safety Set (Booster Dose Analysis)

Age Group: >=6 and <12 Years

	Part 2			Part 1 + Part 2
	Placebo - mRNA-1273 50 µg - Booster (N=3)	mRNA-1273 50 µg - Booster (N=1115)	Total (N=1118)	mRNA-1273 50 µg Primary Series - Booster (N=1294)
Follow-Up Time on Study After Booster (Days)				
n	3	1115	1118	1294
Mean (SD)	24.7 (10.21)	28.6 (13.82)	28.6 (13.81)	29.0 (13.68)
Median	29.0	29.0	29.0	29.0
Q1, Q3	13.0, 32.0	18.0, 39.0	18.0, 39.0	18.0, 40.0
Min, Max	13, 32	1, 57	1, 57	1, 57
< 28 Days	1 (33.3)	512 (45.9)	513 (45.9)	577 (44.6)
>= 28 Days	2 (66.7)	603 (54.1)	605 (54.1)	717 (55.4)
>= 28 and < 56 Days	2 (66.7)	582 (52.2)	584 (52.2)	694 (53.6)
>= 56 Days	0	21 (1.9)	21 (1.9)	23 (1.8)
Person-years from Booster [2]	0.20	87.37	87.57	102.74
Time on Study from Dose 1 of mRNA-1273 (Days)				
n	3	1115	1118	1294

Table 18: Table 18 Summary of Time on Study by Age Group Safety Set (Booster Dose Analysis)

Age Group: >=6 and <12 Years

	Part 2			Part 1 + Part 2
	Placebo - mRNA-1273 50 µg - Booster (N=3)	mRNA-1273 50 µg - Booster (N=1115)	Total (N=1118)	mRNA-1273 50 µg Primary Series - Booster (N=1294)
Time Since Primary Series Dose 2 to Booster (Days) [1]				
n	3	1115	1118	1294
Mean (SD)	136.3 (14.98)	221.9 (14.92)	221.7 (15.56)	235.0 (37.63)
Median	132.0	221.0	221.0	225.0
Q1, Q3	124.0, 153.0	211.0, 232.0	211.0, 232.0	213.0, 239.0
Min, Max	124, 153	182, 256	124, 256	124, 378
< 168 Days Since Primary Series	3 (100)	0	3 (0.3)	3 (0.2)
>= 168 and < 196 Days	0	48 (4.3)	48 (4.3)	48 (3.7)
>= 196 and < 224 Days	0	566 (50.8)	566 (50.6)	566 (43.7)
>= 224 and < 252 Days	0	480 (43.0)	480 (42.9)	480 (37.1)
>= 252 and < 280 Days	0	21 (1.9)	21 (1.9)	21 (1.6)
>= 280 and < 308 Days	0	0	0	72 (5.6)
>= 308 and < 336 Days	0	0	0	66 (5.1)
>= 336 and < 364 Days	0	0	0	26 (2.0)
>= 364 Days	0	0	0	12 (0.9)

The MAH clarified that additional booster data can be expected in May 2023 for Study P203, including a 6-months safety follow-up of at least 1,000 boosted participants, and at the end of 2023 for a booster dose in 6 to 11 year old children from Study P204 (6 months of safety follow-up on at least 1,000 boosted participants). As participants in P204 are still being boosted currently, the proposed timing is tentative for P204.

Demography

The demographics and baseline characteristics of participants in the Safety Set of study P204 are presented in Table 19. The mean age is 8.5 years. The proportion of males and females is balanced with only slightly more males than females included (51.9% versus 48.1%). Approximately 33% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Table 19: P204 Participant Demographics and Baseline Characteristics Safety Set (6 through 11 years)

	mRNA-1273 25 µg – Booster N=1294 n (%)
Age (Years)	
n	1294
Mean (SD)	8.5 (1.62)
Median	8.0
Min, Max	6, 11
Sex, n (%)	
Male	672 (51.9)
Female	622 (48.1)
Race, n (%)	
White	850 (65.7)
Black	142 (11.0)
Asian	101 (7.8)
American Indian or Alaska Native	6 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)
Multiracial	153 (11.8)
Other	24 (1.9)
Not Reported	14 (1.1)
Unknown	3 (0.2)
Ethnicity, n (%)	
Hispanic or Latino	202 (15.6)
Not Hispanic or Latino	1079 (83.4)
Not Reported	10 (0.8)
Unknown	3 (0.2)
Race and Ethnicity Groupa, n (%)	
White non-Hispanic	699 (54.0)
Communities of Color	593 (45.8)
Missing	2 (0.2)
Weight (kg)	

Study population

Children in good health and with stable chronic diseases (e.g., asthma, diabetes mellitus, cystic fibrosis, and human immunodeficiency virus [HIV] infection) were allowed to participate in trial P204. Stable diseases were defined as 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. A change in medication for dose optimisation (e.g., insulin dose changes), change within class of medication, or reduction in dose were not considered signs of instability. Receipt of 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) is an exclusion criterion.

Adverse events

Safety assessment included monitoring of:

- Solicited local and systemic adverse reactions (ARs) that occurred during the 7 days following BD, recorded daily using an eDiary.

- Unsolicited AEs observed or reported during the 28 days following BD (i.e., the day of injection and 27 subsequent days).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 of BD through the last day of study participation.
- SAEs and MAAEs from BD on Day 1 through the entire study period.
- AESI from booster dose on Day 1 through the entire study period, including: acute myocarditis or pericarditis and MIS-C. A complete list of AESI has been provided in the CTP for P204 (Section 2).
- Symptoms suggestive of potential myocarditis or pericarditis were sought from participants during safety calls (7 days following each injection and subsequent safety calls).

Solicited adverse reactions

Local solicited adverse reactions (ARs) included pain, erythema, swelling, and axillary swelling or tenderness. Systemic ARs included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills.

93.2% of children 6 through 11 years of age reported any solicited AR after a 25 µg booster dose of mRNA-1273. The majority of solicited ARs in children 6 through 11 years of age was mild (45.9% of subjects) to moderate (39.4% of subjects). 7.9% of subjects reported any severe solicited AR of Grade 3 and 1 subject reported a Grade 4 solicited AR of fever (104.5°F). Fatigue was the most common Grade 3 solicited AR after booster (3.7% of participants), followed by pain (1.9%), and headache (1.7%).

Any solicited local AR was reported by 91.1% of participants. Pain was the most reported solicited local AR (90.1% of participants), followed by Axillary (or Groin) Swelling or Tenderness (27.8%) and erythema (10.7%) and swelling/hardness (10.9%). Any systemic solicited AR was reported by 64.3% of participants. The most frequently reported systemic solicited AR was fatigue (48.9%), followed by headache (38.2%) and myalgia (21.0%). Chills, nausea, and arthralgia were reported by comparable proportions of subjects, i.e. by 14.0%, 13.1%, and 12.5%, respectively. Fever was reported by 8.5% of subjects.

Solicited ARs had a median onset within 1 day after vaccination and a median duration of 3 days. Solicited local ARs persisting beyond 7 days after booster dose administration were reported in 1.3% of participants. The most common events were axillary (or groin) swelling or tenderness (0.7%) and pain (0.5%). Solicited systemic ARs persisting beyond 7 days after booster vaccination were reported in 2.0% of participants. The most common events were fatigue (1.3%) and headache (1.0%).

Comparison of solicited ARs after 25 µg booster dose to after any 50 µg primary series dose

Solicited ARs after a booster dose with 25 µg mRNA-1273 were compared to solicited ARs after receipt of any dose of a primary series of 50 µg mRNA-1273. With one exception, the incidence of each specified solicited AR (local and systemic) was notably higher after receipt of any dose of the primary series compared to after the booster dose. In addition to the higher dose that is used in the primary series this observation is likely driven by a notable higher reactogenicity post-dose 2 compared with post-dose 1 of the primary series vaccination. The corresponding reactogenicity data by dose were submitted within procedure EMEA/H/C/005791/II/0041, the procedure that led to the extension of the Spikevax (mRNA-1273) indication to include children 6-11 years of age.

The incidence of any solicited AR after any dose of the priming series is 99.2% compared with 93.2% after the booster dose. The incidence of any solicited local AR is 98.4% versus 91.1% respectively and the incidence of any solicited systemic AR is also higher after any dose of the priming series compared to after the booster dose (86.1% versus 64.3% of subjects). With regard to specific solicited ARs the incidence was notably higher for all pre specified solicited ARs (local and systemic) after receipt of a primary series dose except for Axillary (or Groin) Swelling or Tenderness for which the incidence was comparable, i.e. 27.8% of subjects after the booster dose compared with 26.1% after any dose of the primary series.

Solicited ARs after the 25 µg booster dose of mRNA-1273 and after any dose of the 2-dose 50 µg primary series are summarised in Table 20.

Table 20: Summary Solicited ARs After 25 µg Booster or 50 µg Primary Series (any injection), Solicited Safety Set by Grade (6 through 11 years)

Solicited Adverse Reaction Category Grade	mRNA-1273 25 µg – Booster N=1280 n (%)	mRNA-1273 50 µg Primary Series N=3386 n (%)
Solicited Adverse Reactions – N1	1280	3386
Any solicited Adverse Reactions	1193 (93.2)	3358 (99.2)
95% CI [a]	91.7, 94.5	98.8, 99.4
Grade 1	587 (45.9)	902 (26.6)
Grade 2	504 (39.4)	1888 (55.8)
Grade 3	101 (7.9)	568 (16.8)
Grade 4	1 (<0.1)	0
Solicited Local Adverse Reaction – N1	1279	3386
Any Solicited Local Adverse Reactions	1165 (91.1)	3333 (98.4)
95% CI [a]	89.4, 92.6	98.0, 98.8
Grade 1	722 (56.5)	1510 (44.6)
Grade 2	410 (32.1)	1642 (48.5)
Grade 3	33 (2.6)	181 (5.3)
Grade 4	0	0
Pain[b] – N1	1279	3386
Any	1152 (90.1)	3325 (98.2)
Grade 1	778 (60.8)	1777 (52.5)

Grade 2	350 (27.4)	1437 (42.4)
Grade 3	24 (1.9)	111 (3.3)
Grade 4	0	0
Erythema (Redness) – N1 [c]	1279	3386
Any	137 (10.7)	818 (24.2)
Grade 1	67 (5.2)	410 (12.1)
Grade 2	66 (5.2)	355 (10.5)
Grade 3	4 (0.3)	53 (1.6)
Grade 4	0	0
Swelling (Hardness) - N1 [c]	1279	3386
Any	139 (10.9)	767 (22.7)
Grade 1	83 (6.5)	469 (13.9)
Grade 2	52 (4.1)	256 (7.6)
Grade 3	4 (0.3)	42 (1.2)
Grade 4	0	0
Axillary (or Groin) Swelling or Tenderness – N1 [d]	1279	3386
Any	355 (27.8)	883 (26.1)
Grade 1	245 (19.2)	693 (20.5)
Grade 2	106 (8.3)	184 (5.4)
Grade 3	4 (0.3)	6 (0.2)
Grade 4	0	0
Solicited Systemic Adverse Reactions – N1[e]	1280	3386
Any Solicited Systemic Adverse Reactions	823 (64.3)	2917 (86.1)
95% CI [a]	61.6, 66.9	84.9, 87.3
Grade 1	414 (32.3)	1005 (29.7)
Grade 2	331 (25.9)	1464 (43.2)

Solicited Adverse Reaction Category Grade	mRNA-1273 25 µg – Booster N=1280 n (%)	mRNA-1273 50 µg Primary Series N=3386 n (%)
Grade 3	77 (6.0)	448 (13.2)
Grade 4	1 (<0.1)	0
Fever – N1 [f]	1276	3386
Any	108 (8.5)	861 (25.4)
Grade 1	59 (4.6)	451 (13.3)
Grade 2	32 (2.5)	271 (8.0)
Grade 3	16 (1.3)	139 (4.1)
Grade 4	1 (<0.1)	0
Headache - N1	1280	3384
Any	489 (38.2)	2094 (61.9)
Grade 1	275 (21.5)	989 (29.2)
Grade 2	192 (15.0)	957 (28.3)
Grade 3	22 (1.7)	148 (4.4)
Grade 4	0	0
Fatigue – N1	1279	3384
Any	625 (48.9)	2458 (72.6)
Grade 1	340 (26.6)	1011 (29.9)
Grade 2	238 (18.6)	1201 (35.5)
Grade 3	47 (3.7)	246 (7.3)
Grade 4	0	0
Myalgia – N1	1280	3384
Any	269 (21.0)	1168 (34.5)
Grade 1	147 (11.5)	628 (18.6)
Grade 2	103 (8.0)	451 (13.3)
Grade 3	19 (1.5)	89 (2.6)
Grade 4	0	0
Arthralgia – N1	1279	3384
Any	160 (12.5)	700 (20.7)
Grade 1	102 (8.0)	468 (13.8)

Solicited Adverse Reaction Category Grade	mRNA-1273 25 µg – Booster N=1280 n (%)	mRNA-1273 50 µg Primary Series N=3386 n (%)
Grade 2	46 (3.6)	202 (6.0)
Grade 3	12 (0.9)	30 (0.9)
Grade 4	0	0
Nausea/Vomiting – N1	1279	3384
Any	168 (13.1)	979 (28.9)
Grade 1	126 (9.9)	736 (21.7)
Grade 2	36 (2.8)	217 (6.4)
Grade 3	6 (0.5)	26 (0.8)
Grade 4	0	0
Chills – N1	1279	3384
Any	179 (14.0)	1136 (33.6)
Grade 1	118 (9.2)	649 (19.2)
Grade 2	57 (4.5)	464 (13.7)
Grade 3	4 (0.3)	23 (0.7)
Grade 4	0	0

Abbreviations: CI = Confidence intervals; G = Severity grade; N1 = Number of exposed participants who submitted any data for the event. Any = Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Data cut-off for BD data = 23 May 2022. Data cut-off for primary series data = 10 Nov 2021.
[a] 95% CI is calculated using the Clopper-Pearson method.
[b] Pain for participants age 6 through 11 years is injection site pain or tenderness/injection site pain.
[c] Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participants age 37 months to <12 years is defined as: G1 = 25 - 50 mm; G2 = 51 - 100 mm; G3>100 mm; G4 = Necrosis or exfoliative dermatitis.
[d] Toxicity grade for Groin or underarm swelling or tenderness for Axillary swelling or tenderness for participants age 37 months to < 12 years is defined as: G1 = No interference with activity; G2 = Some interference with activity; G3 = Prevents daily activity; G4 = Emergency room visit or hospitalization.
[e] Toxicity grades for systemic adverse reactions other than Fever are defined as: G1 = no interference with activity; G2 = Some interference with activity; G3 = Prevents daily activity; G4 = Emergency room visit or hospitalization.
[f] Toxicity grade for Fever for participants age 37 months to <12 years is defined as: G1 = 38 - 38.4°C; G2 = 38.5 - 38.9°C; G3 = 39 - 40 °C; G4 = >40°C.
Source: Study P204 Table 14.3.1.3.7.1.2, Study P204 EUA 10 Nov 2021 Table 14.3.1.1.3.2.1

Solicited adverse events by SARS-CoV-2 baseline serostatus

The incidence of any solicited ARs was higher among participants who were SARS-CoV-2 negative at baseline, i.e. prior to booster dose administration (95.8% of 757 participants) compared with participants who were SARS-CoV-2 positive at baseline (89.5% of 428 participants).

Reactogenicity comparison of a booster dose of mRNA-1273 given to children 6-11 years, adolescents 12-18 years of age, and adults and a booster dose of mRNA-1273.214 given to adults

A reactogenicity comparison was provided between a booster dose of either 25 µg or 50 µg mRNA-1273 given to children 6-11 years (25 µg in study P204), to adolescents 12 to below 18 years (50 µg in study P203), and to adults ≥18 to below 55 years (50 µg in study P201 B) or a second booster dose of 50 µg of mRNA.1273.214 given to adults ≥18 to below 65 years of age (study P205G).

The submitted safety data indicate some variability with regard to reactogenicity in the 4 vaccine groups, but no clear trend or pattern can be seen that suggests a clinical meaningful difference between a booster dose in children, adolescents and adults as well as between a booster dose of mRNA-1273 and mRNA-1273.214 in adults. Only minor differences are noted for the overall incidences and the severity of solicited local and systemic ARs without any clear pattern or trend towards one of the vaccine groups. The incidence of any solicited local adverse reaction ranged from 87.3% in the mRNA-1273 vaccine group ≥18 to <55 years to 91.1% in the mRNA-1273 vaccine group ≥6 to below 12 years of age. The incidence was 89.4% in the mRNA-1273.214 vaccine group ≥18 to below 65 years of age and 92.1% in the mRNA-1273 vaccine group 12 to below 18 years of age. Grade 3 solicited local adverse reactions ranged from 5.1% in the mRNA-1273 vaccine group ≥18 to <55 years to 2.6% in the mRNA-1273 vaccine group ≥6 to below 12 years of age. Grade 4 solicited local AR were not reported in any group. The incidence of any solicited systemic AR ranged from 64.3% in the P204 vaccine group (children 6 to below 12 years of age) to 74.7% percent each in the adult vaccine groups P201 (mRNA-1273, 18 to below 55 years of age) and P205 (mRNA-1273.214, 18 to below 65 years of age). None of the systemic solicited ARs had a higher incidence in children except for fever. Any fever was reported by 8.5% of children in the P204 group, followed by 7.6% in the adult population of P201 (mRNA-1273), by 6.1% of adolescent subjects in P203, and by 3.4% of adult subjects in P205 (mRNA-1273.214).

The incidence of common (≥1% of Participants) unsolicited AEs is comparable across age groups with the exception of the P201group where event rates were lower than the other 3 groups. The incidence of any unsolicited AEs was 13.1% in the P204 vaccine group, 14.2% in the P203, 7.3% in the P201 Part B, and 18.5% in the P205 Part G vaccine group.

It should be noted, that the submitted comparison has its limitations. The age range (18 years of age and older) that has been selected for comparison is considered less adequate than the age range of young adults. However, the sample size of subjects 18-25 years of age would have been too small to draw any conclusion (8 subjects 18-25 years of age each in study P201 and P205). The variable sample size with a notable lower number of participants in the P201 Part B vaccine group must be considered when interpreting the results. Though the reactogenicity profile does not show any clinical meaningful difference, differences with regard to the safety profile in children and adults cannot be excluded as can be seen e.g. for the different prevalence of myocarditis in the different age groups or the event of MIS-C which is an AESI for children for children but not for adults. However, provided, that BA.1 vaccine will be administered to children rare events or events specific for the paediatric population need to be monitored anyway. They cannot be detected in a pre-licensure study due to the sample size. The comparison is moreover not suitable to detect differences with regard to safety profile concerning uncommon or rare AEs. The results for solicited and unsolicited adverse events are displayed in Table 21 to Table 23 below.

Table 21: Solicited local ARs

Frequency of Solicited Local Adverse Reactions within 7 Days after Booster Dose by Maximum Severity, Participants ≥6 to <12 years, 12 to <18 years, 18 to <55 years after mRNA-1273 booster dose and 18 to <65 years after mRNA-1273.214 booster dose

Event	Study P204	Study P203	P201 (B)	P205 (G)
	≥6 to <12 years mRNA-1273 50 µg Primary Series – 25 µg Booster (N=1280) n (%)	12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%)	≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 n (%)	≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%)
Solicited Local Adverse Reaction	N1=1279	N1=1312	N1=79	N1=263
Any solicited local adverse reactions	1165 (91.1)	1208 (92.1)	69 (87.3)	235 (89.4)
Grade 1	722 (56.5)	835 (63.6)	48 (60.8)	193 (73.4)
Grade 2	410 (32.1)	316 (24.1)	17 (21.5)	32 (12.2)
Grade 3	33 (2.6)	57 (4.3)	4 (5.1)	10 (3.8)
Grade 4	0	0	0	0
Pain	N1=1279	N1=1312	N1=79	N1=263
Any	1152 (90.1)	1196 (91.2)	68 (86.1)	231 (87.8)
Grade 1	778 (60.8)	900 (68.6)	50 (63.3)	202 (76.8)
Grade 2	350 (27.4)	257 (19.6)	15 (19.0)	27 (10.3)
Grade 3	24 (1.9)	39 (3.0)	3 (3.8)	2 (0.8)
Grade 4	0	0	0	0
Erythema (redness)	N1= 1279	N1=1311	N1=79	N1=263
Any	137 (10.7)	120 (9.2)	5 (6.3)	20 (7.6)
Grade 1	67 (5.2)	59 (4.4)	2 (2.5)	10 (3.8)
Grade 2	66 (5.2)	53 (4.0)	2 (2.5)	3 (1.1)
Grade 3	4 (0.3)	9 (0.7)	1 (1.3)	7 (2.7)
Grade 4	0	0	0	0
Swelling (hardness)	N1= 1279	1311	N1=79	N1=263
Any	139 (10.9)	176 (13.4)	5 (6.3)	22 (8.4)
Grade 1	83 (6.5)	98 (7.5)	3 (3.8)	12 (4.6)
Grade 2	52 (4.1)	69 (5.3)	2 (2.5)	6 (2.3)
Grade 3	4 (0.3)	9 (0.7)	0	4 (1.5)
Grade 4	0	0	0	0
Axillary (or groin) swelling or tenderness	N1= 1279	N1=1311	N1=79	N1=263
Any	355 (27.8)	367 (28.0)	22 (27.8)	56 (21.3)
Grade 1	245 (19.2)	310 (23.6)	18 (22.8)	53 (20.2)
Grade 2	106 (8.3)	53 (4.0)	3 (3.8)	3 (1.1)
Grade 3	4 (0.3)	4 (0.3)	1 (1.3)	0
Grade 4	0	0	0	0

Abbreviation: AR=adverse reaction; n=number of exposed participants who reported the event on any day within 7 days of the booster dose; N1=Number of exposed participants who submitted any data for the event.

Note: Any=Grade 1 or higher. Part 1 + Part 2 mRNA-1273 primary series - booster group includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. 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=25-50 mm; Grade 2=51-100 mm; Grade 3=>100 mm; Grade 4=necrosis or exfoliative dermatitis. Toxicity grade 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. The Solicited Safety Set consists of all participants in the Safety Set who contributed any solicited AR data (ie, had at least 1 post-baseline solicited safety assessment).

Source: P204: Table 14.3.1.3.7.1.2; P203: Table 14.3.1.1.1.5.1; P201: Table 14.3.1.1.4.1; P205: Table 14.3.1.1.1.8

Table 22: Solicited systemic ARs

Frequency of Solicited Systemic Adverse Reactions within 7 Days after Booster Dose by Maximum Severity, Participants ≥6 to <12 years, 12 to <18 years, 18 to <55 years after mRNA-1273 booster dose and 18 to <65 years after mRNA-1273.214 booster dose

Solicited Adverse reaction Category Grade	P204 ≥6 to <12 years mRNA-1273 50 µg Primary Series– 25 µg Booster N=1280 n (%)	P203 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%)	P201 (B) ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 N (%)	P205 (G) ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%)
Solicited adverse reaction	N1=1280	N1=1311	N1=79	N1=263
Any Solicited Systemic Adverse Reactions	823 (64.3)	1004 (76.6)	59 (74.7)	197 (74.9)
Grade 1	414 (32.3)	463 (35.3)	23 (29.1)	102 (38.8)
Grade 2	331 (25.9)	433 (33.0)	29 (36.7)	78 (29.7)
Grade 3	77 (6.0)	108 (8.2)	6 (7.6)	17 (6.5)
Grade 4	1 (<0.1)	0	0	0

Solicited Adverse reaction Category Grade	P204 ≥6 to <12 years mRNA-1273 50 µg Primary Series– 25 µg Booster N=1280 n (%)	P203 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%)	P201 (B) ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 N (%)	P205 (G) ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%)
Fever	N1=1276	N1=1297	N1=79	N1=262
Any	108 (8.5)	79 (6.1)	6 (7.6)	9 (3.4)
Grade 1	59 (4.6)	45 (3.5)	4 (5.1)	6 (2.3)
Grade 2	32 (2.5)	26 (2.0)	1 (1.3)	2 (0.8)
Grade 3	16 (1.3)	8 (0.6)	1 (1.3)	1 (0.4)
Grade 4	1 (<0.1)	0	00	0
Headache	N1=1280	N1=1311	N1=79	N1=263
Any	489 (38.2)	748 (57.1)	45 (57.0)	129 (49.0)
Grade 1	275 (21.5)	492 (37.5)	28 (35.4)	96 (36.5)
Grade 2	192 (15.0)	228 (17.4)	16 (20.3)	29 (11.0)
Grade 3	22 (1.7)	28 (2.1)	1 (1.3)	4 (1.5)
Grade 4	0	0	0	0
Fatigue	N1=1279	N1=1311	N1=79	N1=263
Any	625 (48.9)	769 (58.7)	46 (58.2)	154 (58.6)
Grade 1	340 (26.6)	364 (27.8)	18 (22.8)	75 (28.5)
Grade 2	238 (18.6)	352 (26.8)	25 (31.6)	69 (26.2)
Grade 3	47 (3.7)	53 (4.0)	3 (3.8)	10 (3.8)
Grade 4	0	0	0	0
Myalgia	N1=1280	N1=1311	N1=79	N1=263
Any	269 (21.0)	529 (40.4)	37 (46.8)	114 (43.3)
Grade 1	147 (11.5)	274 (20.9)	19 (24.1)	64 (24.3)
Grade 2	103 (8.0)	208 (15.9)	15 (19.0)	41 (15.6)
Grade 3	19 (1.5)	47 (3.6)	3 (3.8)	9 (3.4)
Grade 4	0	0	0	0
Arthralgia	N1=1279	N1=1311	N1=79	N1=263
Any	160 (12.5)	316 (24.1)	34 (43.0)	87 (33.1)
Grade 1	102 (8.0)	184 (14.0)	20 (25.3)	56 (21.3)
Grade 2	46 (3.6)	115 (8.8)	12 (15.2)	28 (10.6)
Grade 3	12 (0.9)	17 (1.3)	2 (2.5)	3(1.1)
Grade 4	0	0	0	0
Nausea/vomiting	N1=1279	N1=1311	N1=79	N1=263
Any	168 (13.1)	234 (17.8)	12 (15.2)	35 (13.3)
Grade 1	126 (9.9)	180 (13.7)	12 (15.2)	31 (11.8)
Grade 2	36 (2.8)	52 (4.0)	0	4 (1.5)
Grade 3	6 (0.5)	2 (0.2)	0	0
Grade 4	0	0	0	0
Chills	N1=1279	N1=1311	N1=79	N1=263
Any	179 (14.0)	399 (30.4)	30 (38.0)	64 (24.3)

Solicited Adverse reaction Category Grade	P204 ≥6 to <12 years mRNA-1273 50 µg Primary Series– 25 µg Booster N=1280 n (%)	P203 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1312) n (%)	P201 (B) ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster N=79 N (%)	P205 (G) ≥18 to <65 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=263 n (%)
Grade 1	118 (9.2)	251 (19.1)	20 (25.3)	38 (14.4)
Grade 2	57 (4.5)	141 (10.8)	10 (12.7)	25 (9.5)
Grade 3	4 (0.3)	7 (0.5)	0	1 (0.4)
Grade 4	0	0	0	0

Abbreviation: AR=adverse reaction; n=number of exposed participants who reported the event on any day within 7 days of the booster dose; N1 = Number of exposed participants who submitted any data for the event.

Study P204 Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants in the safety set who contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. Part 1 + Part 2 mRNA-1273 primary series - booster group includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. Pain for participant age 37 months to <12 years is injection site pain. Toxicity grade for Injection site erythema (redness) or swelling (hardness) for participant age 37 months to < 12 years is defined as: G1 = 25 — 50 mm; G2 = 51 — 100 mm; G3 = > 100 mm; G4 = Necrosis or exfoliative dermatitis. Toxicity grade for Axillary swelling or tenderness for participant age 37 months to < 12 years is defined as: G1 = No interference with activity; G2 = Some interference with activity; G3 = Prevents daily activity; G4 = Emergency room visit or hospitalization. Toxicity grade for Fever for participant age 37 months to < 12 years is defined as: G1 = 38 — 38.4 °C; G2 = 38.5 — 38.9 °C; G3 = 39 — 40 °C; G4 = > 40 °C.

Study P203 Notes: Any = Grade 1 or higher. Percentages are based on the number of exposed participants who submitted any data for the event (N1). The Solicited Safety Set consists of all participants who received BD in Part C, and contribute any solicited AR data (ie, had at least 1 post-booster solicited safety assessment in Part C).

[a] Toxicity grade for erythema (redness) is defined as: G1 = 25 - 50 mm; G2 = 51 - 100 mm; G3 = > 100 mm.

Study P205 Notes: Toxicity grade for Erythema (Redness) is defined as: G1 = 25 — 50 mm; G2 = 51 — 100 mm; G3 = > 100 mm. Toxicity grade for Fever is defined as: G1 = 38 — 38.4 C; G2 = 38.5 — 38.9 C; G3 = 39 — 40 C; G4 = > 40 C. This interim analysis includes Part F Cohort 2 mRNA-1273 and Part G subjects immunogenicity data up to Day 29 visit. The data cutoff date for safety and SARS-CoV-2 infection is 27APR2022.

Source: P204: Table 14.3.1.3.7.1.2, Table 14.1.8.3.2; P203: Table 14.3.1.1.1.5.1, Table 14.1.5.3.5; P201: Table 14.3.1.1.4.1; P205: Table 14.3.1.1.1.8

Table 23: Common (≥1%) unsolicited TEAEs

Frequency of Unsolicited TEAEs with Occurrence in ≥ 1% of Participants in Any Treatment Group up to 28 Days After Injection Classified by MedDRA System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	P204 mRNA-1273 50 µg Primary Series – 25 µg Booster N=1294 n (%)		P203 12 to <18 Years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=1346) n (%)		P201 ≥18 to <55 years mRNA-1273 100 µg Primary Series – 50 µg Booster (N=82) n (%)		P205 (G) ≥18 years mRNA-1273 100 µg Primary Series – 50 µg Booster - mRNA-1273.214 50 µg Booster N=437 n (%)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Number of participants reporting unsolicited adverse events	169 (13.1)	7 (0.5)	191 (14.2)	3 (0.2)	6 (7.3)	0	81 (18.5)	4 (0.9)
Number of unsolicited adverse events	238	13	263	3	8	0	114	5
Infections and infestations	80 (6.2)	0	102 (7.6)	0	2 (2.4)	0	29 (6.6)	0
COVID-19	25 (1.9)	0	41 (3.0)	0	2 (2.4)	0	5 (1.1)	0
Asymptomatic COVID-19	6 (0.5)	0	17 (1.3)	0	0	0	2 (0.5)	0
Upper respiratory tract infection	17 (1.3)	0	16 (1.2)	0	0	0	5 (1.1)	0
Urinary tract infection	0	0	0	0	1 (1.2)	0	1 (0.2)	0
Immune System Disorder	5 (0.4)	0	1 (<0.1)	1 (<0.1)	1 (1.2)	0	0	0
Allergy to arthropod bite	0	0	0	0	1 (1.2)	0	0	0
Psychiatric disorders	3 (0.2)	0	6 (0.4)	0	1 (1.2)	0	0	0
Anxiety	0	0	2 (0.1)	0	1 (1.2)	0	0	0
Nervous system disorders	15 (1.2)	1 (<0.1)	26 (1.9)	0	2 (2.4)	0	8 (1.8)	0
Headache	15 (1.2)	1 (<0.1)	26 (1.9)	0	2 (2.4)	0	7 (1.6)	0
Respiratory, thoracic, and mediastinal disorders	23 (1.8)	0	11 (0.8)	0	0	0	5 (1.1)	0
Skin and subcutaneous tissue disorders	13 (1.0)	0	12 (0.9)	0	0	0	4 (0.9)	0
Musculoskeletal and connective tissue disorders	9 (0.7)	2 (0.2)	13 (1.0)	0	0	0	14 (3.2)	0
Myalgia	3 (0.2)	2 (0.2)	7 (0.5)	0	0	0	5 (1.1)	0
Arthralgia	4 (0.3)	0	5 (0.4)	0	0	0	7 (1.6)	0
General disorders and administration site conditions	34 (2.6)	5 (0.4)	43 (3.2)	1 (<0.1)	1 (1.2)	0	21 (4.8)	1 (0.2)
Fatigue	13 (1.0)	3 (0.2)	23 (1.7)	1 (<0.1)	1 (1.2)	0	11 (2.5)	1 (0.2)
Injury, poisoning and procedural complications	8 (0.6)	0	14 (1.0)	0	0	0	9 (2.1)	1 (0.2)

Abbreviations: COVID-19=coronavirus disease 2019; MedDRA=Medical Dictionary for Regulatory Activities; n=number of exposed participants who reported the event on any day within 28 days of the booster dose; TEAE=treatment-emergent adverse event.

Note: Data from P204 includes Part 1 mRNA-1273 selected dose, Part 2 mRNA-1273 and Part 2 Placebo-mRNA-1273 participants who received booster dose. A TEAE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages are based on the number of safety participants (N) in booster dose analysis.

Note: Data from P203 includes mRNA-1273-booster group. Percentages are based on the number of safety participants in Part C.

Note: Data from P301 is the Total of mRNA-1273-booster + placebo-mRNA-1273-booster. Percentages are based on the number of Part C safety subjects between 18-25 years of age.

Note: Data from P205 Part G interim analysis includes immunogenicity data up to Day 29 visit.

The CHMP considered that the submitted safety data indicates that the reactogenicity after receipt of a 25 µg booster dose of mRNA-1273 is lower than after receipt of any 50 µg dose within the primary vaccination series that comprises 2 doses of 50 µg given 28 days apart. This observation is, beside the lower dose concentration of the booster dose, likely driven by a notable higher reactogenicity after

dose 2 compared with dose 1 in the primary series vaccination. The reactogenicity data by dose for the primary vaccination series were provided within procedure EMEA/H/C/005791/II/0041, the procedure that led to the extension of the Spikevax indication to include children 6-11 years of age. A direct comparison of the 25 µg booster dose to the first and the second dose of the primary vaccination series has not been provided, only a comparison to any dose of the primary vaccination schedule. The submitted reactogenicity data in summary do not indicate a higher reactogenicity of the booster dose compared with the higher dose administered within the primary vaccination course and do not raise any concern with regard to the administration of a 25 µg booster dose of mRNA-1273 in children 6-11 years of age.

Comparison between age groups and variant vaccines:

The MAH submitted clinical data from P204 for mRNA-1273 but for mRNA-1273.214, the variant BA.1 vaccine for which no clinical safety data are available for the age group 6-11 years of age. The intended approach is to support the administration of a 25 µg booster dose of mRNA-1273.214 based on the safety and reactogenicity profile after administration of 25 µg of mRNA-1273 and to extrapolate from the known safety profile of a booster dose of mRNA-1273.214 given to adults.

To support this extrapolation approach, the MAH submitted a comparison of booster dose between children, adolescents, and adults 18 years of age and older, and for a booster dose of mRNA-1273 and mRNA-1273.214 given to adults 18 years of age and older. The submitted comparison has its limitations, but does not suggest any clear trend or pattern of different reactogenicity across age and vaccine groups. Differences with regard to the safety profile and the prevalence of rare events can only be detected post-authorisation (as seen for myocarditis).

The MAH claims an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine. The interval of the mRNA-1273 booster in P204 however is at least 6 months. The CHMP was of the view that a reduction of the interval to 3 months is acceptable based on extrapolation.

Unsolicited adverse events

The incidence of unsolicited adverse events up to 28 days after booster dose irrespective of causality was 13.1% (169 of 1,294 subjects) and the incidence of unsolicited adverse events considered to be vaccine-related by the investigator was 4.0% (52 out of 1,294 subjects). This is lower compared to the incidence of unsolicited adverse events reported after any dose of the primary vaccination series in Part 2 of study P204. The incidence of unsolicited adverse events irrespective of causality in part 2 after any dose of the 50 µg primary series vaccination was 29.6% (891 of 3,007 participants) and the incidence of unsolicited adverse events considered to be vaccine-related by the investigator was 10.6% (319 of 3,007 participants). When taking part 1 and part 2 together, the respective incidence after any 50 µg dose in the primary series was 29.8% (1,010 of 3,387 subjects) and 10.7% (363 of 3,387 subjects). No unsolicited AEs caused discontinuation from study participation.

The most common SOCs represented by unsolicited AEs were of Infections and infestations (n=80, 6.2%), General disorders and administration site conditions (n=34, 2.6%), and Respiratory, thoracic and mediastinal disorders (n=23, 1.8%). The most commonly reported unsolicited AE PT was COVID-19 (25 participants, 1.9%), followed by Upper respiratory tract infection (17 participants, 1.3%).

Unsolicited AEs by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) reported for >1 participant up to 28 days after booster dose administration are presented in Table 24.

Table 24: Unsolicited AE by System Organ Class and Preferred Term (>1 participant) up to 28 Days after 25 µg BD Safety Set (6 through 11 years)

MedDRA version 23.0 **System Organ Class** **Preferred Term**	**mRNA-1273 25 µg - Booster** **N=1294** **n (%)**
Number of participants reporting unsolicited adverse events	169 (13.1)
Number of events	238
Infections and Infestations	80 (6.2)
COVID-19	25 (1.9)
Upper respiratory tract infection	17 (1.3)
Asymptomatic COVID-19	6 (0.5)
Respiratory tract infection viral	5 (0.4)
Ear infection	4 (0.3)
Influenza	4 (0.3)
Gastroenteritis	3 (0.2)
Otitis media	3 (0.2)
Gastroenteritis viral	2 (0.2)
Nasopharyngitis	2 (0.2)
Viral infection	2 (0.2)
Immune System Disorder	5 (0.4)
Seasonal allergy	3 (0.2)
Metabolism and nutrition disorder	2 (0.2)
Decreased appetite	2 (0.2)
Psychiatric disorders	5 (0.4)
Attention deficit hyperactivity disorder	3 (0.2)
Nervous System Disorder	15 (1.2)
Headache	15 (1.2)
Respiratory, thoracic and mediastinal disorders	23 (1.8)
Cough	6 (0.5)
Oropharyngeal pain	6 (0.5)
Rhinorrhoea	6 (0.5)

MedDRA version 23.0 System Organ Class Preferred Term	mRNA-1273 25 µg - Booster N=1294 n (%)
Nasal congestion	5 (0.4)
Gastrointestinal disorders	12 (0.9)
Vomiting	8 (0.6)
Abdominal pain	2 (0.2)
Abdominal pain upper	2 (0.2)
Skin and subcutaneous tissue disorders	13 (1.0)
Urticaria	7 (0.5)
Mechanical urticaria	2 (0.2)
Musculoskeletal and connective tissue disorders	9 (0.7)
Arthralgia	4 (0.3)
Myalgia	3 (0.2)
General disorders and administration site conditions	34 (2.6)
Fatigue	13 (1.0)
Pyrexia	10 (0.8)
Injection site lymphadenopathy	9 (0.7)
Injection site pain	5 (0.4)
Chills	2 (0.2)
Injection site erythema	2 (0.2)
Injury, poisoning, and procedural complications	8 (0.6)
Ligament sprain	3 (0.2)
Arthropod bite	2 (0.2)

Abbreviations: AE = adverse event; BD = booster dose; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities.
An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.
Percentages are based on the number of safety participants in BD analysis.
Source: Study P204 Table 14.3.1.10.3.2

Seven (0.5%) participants reported 13 severe (Grade 3 or higher) unsolicited AEs. The events included headache, vomiting, abdominal pain, myalgia, injection site pain, fatigue, pyrexia, and chills. 6 of the reported events were considered to be vaccine-related by the investigator. All severe unsolicited AEs are already listed in section 4.8 of the SmPC. This is comparable to what has been reported after the primary vaccination series where 12 of 3007 participants (0.4%) reported severe events. 9 (0.3%) of them reported severe unsolicited AEs that were considered related by the Investigator.

Unsolicited AEs considered to be vaccine-related

Nature and incidence of unsolicited AEs considered to be vaccine-related by the investigator including severe AEs for part 1 and part 2 are presented in Table 25 and Table 26 below.

Table 25 Part 1: Subject Incidence of Unsolicited Treatment-Related TEAE by Age Group, Dose Level, System Organ Class and Preferred Term up to 28 Days After Booster Dose in Part 1, Safety Set (Booster Dose Analysis)

Age Group: >=6 and <12 Years

System Organ Class Preferred Term	mRNA-1273 50 µg - Booster (N=176) n (%)		mRNA-1273 100 µg - Booster (N=184) n (%)		Total (N=360) n (%)	
	Any	Severe	Any	Severe	Any	Severe
Number of Subjects Reporting Unsolicited Adverse Events	10 (5.7)	0	2 (1.1)	0	12 (3.3)	0
Number of Unsolicited Adverse Events	17	0	2	0	19	0
Infections and infestations	2 (1.1)	0	0	0	2 (0.6)	0
COVID-19	2 (1.1)	0	0	0	2 (0.6)	0
Nervous system disorders	3 (1.7)	0	0	0	3 (0.8)	0
Headache	3 (1.7)	0	0	0	3 (0.8)	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0	0	0	1 (0.3)	0
Dyspnoea	1 (0.6)	0	0	0	1 (0.3)	0
Gastrointestinal disorders	2 (1.1)	0	0	0	2 (0.6)	0
Abdominal pain upper	2 (1.1)	0	0	0	2 (0.6)	0
Musculoskeletal and connective tissue disorders	1 (0.6)	0	0	0	1 (0.3)	0
Arthralgia	1 (0.6)	0	0	0	1 (0.3)	0
General disorders and administration site conditions	4 (2.3)	0	2 (1.1)	0	6 (1.7)	0
Fatigue	3 (1.7)	0	1 (0.5)	0	4 (1.1)	0
Chest pain	1 (0.6)	0	0	0	1 (0.3)	0
Injection site erythema	0	0	1 (0.5)	0	1 (0.3)	0
Pyrexia	1 (0.6)	0	0	0	1 (0.3)	0
Injury, poisoning and procedural complications	1 (0.6)	0	0	0	1 (0.3)	0
Ligament sprain	1 (0.6)	0	0	0	1 (0.3)	0

Table 26: Part 2: Subject Incidence of Unsolicited Treatment-Related TEAE by Age Group, System Organ Class and Preferred Term up to 28 Days After Booster Dose Safety Set (Booster Dose Analysis)

Age Group: >=6 and <12 Years

System Organ Class Preferred Term	Part 2 Placebo - mRNA-1273 50 µg - Booster (N=3) n (%)		Part 2 mRNA-1273 50 µg - Booster (N=1115) n (%)		Total (N=1118) n (%)		Part 1 + Part 2 mRNA-1273 50 µg Primary Series - Booster (N=1294) n (%)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Number of Subjects Reporting Unsolicited Adverse Events	0	0	42 (3.8)	6 (0.5)	42 (3.8)	6 (0.5)	52 (4.0)	6 (0.5)
Number of Unsolicited Adverse Events	0	0	58	12	58	12	75	12
Infections and infestations	0	0	2 (0.2)	0	2 (0.2)	0	4 (0.3)	0
COVID-19	0	0	2 (0.2)	0	2 (0.2)	0	4 (0.3)	0
Immune system disorders	0	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Serum sickness-like reaction	0	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Psychiatric disorders	0	0	2 (0.2)	0	2 (0.2)	0	2 (0.2)	0
Aggression	0	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0

System Organ Class Preferred Term	Placebo - mRNA-1273 50 µg - Booster (N=3) n (%)		Part 2 mRNA-1273 50 µg - Booster (N=1115) n (%)		Total (N=1118) n (%)		Part 1 + Part 2 mRNA-1273 50 µg Primary Series - Booster (N=1294) n (%)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Psychiatric disorders (Cont.)								
Insomnia	0	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Nervous system disorders	0	0	9 (0.8)	1 (<0.1)	9 (0.8)	1 (<0.1)	12 (0.9)	1 (<0.1)
Headache	0	0	9 (0.8)	1 (<0.1)	9 (0.8)	1 (<0.1)	12 (0.9)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	1 (<0.1)	0
Dyspnoea	0	0	0	0	0	0	1 (<0.1)	0
Gastrointestinal disorders	0	0	5 (0.4)	2 (0.2)	5 (0.4)	2 (0.2)	7 (0.5)	2 (0.2)
Vomiting	0	0	4 (0.4)	2 (0.2)	4 (0.4)	2 (0.2)	4 (0.3)	2 (0.2)
Abdominal pain upper	0	0	0	0	0	0	2 (0.2)	0
Abdominal pain	0	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0

System Organ Class Preferred Term	Placebo - mRNA-1273 50 µg - Booster (N=3) n (%)		Part 2 mRNA-1273 50 µg - Booster (N=1115) n (%)		Total (N=1118) n (%)		Part 1 + Part 2 mRNA-1273 50 µg Primary Series - Booster (N=1294) n (%)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
Skin and subcutaneous tissue disorders	0	0	2 (0.2)	0	2 (0.2)	0	2 (0.2)	0
Urticaria	0	0	2 (0.2)	0	2 (0.2)	0	2 (0.2)	0
Musculoskeletal and connective tissue disorders	0	0	3 (0.3)	2 (0.2)	3 (0.3)	2 (0.2)	4 (0.3)	2 (0.2)
Myalgia	0	0	3 (0.3)	2 (0.2)	3 (0.3)	2 (0.2)	3 (0.2)	2 (0.2)
Arthralgia	0	0	0	0	0	0	1 (<0.1)	0
General disorders and administration site conditions	0	0	26 (2.3)	5 (0.4)	26 (2.3)	5 (0.4)	30 (2.3)	5 (0.4)
Fatigue	0	0	10 (0.9)	3 (0.3)	10 (0.9)	3 (0.3)	13 (1.0)	3 (0.2)
Injection site lymphadenopathy	0	0	9 (0.8)	0	9 (0.8)	0	9 (0.7)	0
Injection site pain	0	0	5 (0.4)	1 (<0.1)	5 (0.4)	1 (<0.1)	5 (0.4)	1 (<0.1)

System Organ Class Preferred Term	Placebo - mRNA-1273 50 µg - Booster (N=3) n (%)		Part 2 mRNA-1273 50 µg - Booster (N=1115) n (%)		Total (N=1118) n (%)		Part 1 + Part 2 mRNA-1273 50 µg Primary Series - Booster (N=1294) n (%)	
	Any	Severe	Any	Severe	Any	Severe	Any	Severe
General disorders and administration site conditions (Cont.)								
Pyrexia	0	0	4 (0.4)	1 (<0.1)	4 (0.4)	1 (<0.1)	5 (0.4)	1 (<0.1)
Chills	0	0	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)
Injection site erythema	0	0	2 (0.2)	0	2 (0.2)	0	2 (0.2)	0
Chest pain	0	0	0	0	0	0	1 (<0.1)	0
Injection site induration	0	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Injection site swelling	0	0	1 (<0.1)	0	1 (<0.1)	0	1 (<0.1)	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1 (<0.1)	0
Ligament sprain	0	0	0	0	0	0	1 (<0.1)	0

The majority of unsolicited AEs considered to be vaccine-related is indicative of expected reactogenicity reactions. All unsolicited AEs considered to be vaccine-related are already covered in the SmPC, except for the events of dyspnoea, chest pain, serum-sickness-like reaction, aggression, and insomnia.

The AEs of aggression and insomnia are likely unspecific reactions related to the general reactogenicity of mRNA-1273 or to the vaccination procedure. The event of aggression e.g., occurred in a participant with previous history of aggression and was accompanied with concurrent vaccine-related

reactogenicity (Grade 1 chills and Grade 2 injection site pain and fatigue). It can be agreed not to include these 2 single unspecific events into the SmPC.

The case of mild self-limiting chest pain was report for a participant, with medical history of bronchial hyperreactivity 2 days after booster dose. A cardiac workup was completed. Results did not indicate a cardiac event. Causality cannot finally be confirmed because of the medical history of bronchial hyperreactivity.

The event of dyspnoea that occurred in a participant is unlikely vaccine-related because of the late onset of 27 days after booster dose. Another case of dyspnoea was reported for a participant in study P203 on the day of booster dose and was considered to be vaccine-related by the investigator because of temporal relationship. The participant has a medical history of ADHD and anxiety. Concurrent events of fatigue, myalgia, arthralgia, nausea/vomiting, and chills were recorded. 2 other cases of dyspnoea occurred in the adolescent population in study P204 after dose 2. The 2 events of dyspnoea were also considered to be vaccine-related by the investigator due to temporal relationship but are confounded either by a medical history of anxiety and depression or by concurrent symptoms like fever, fatigue, headache, chills and sore throat. Dyspnoea is an unspecific symptom. From the 3 discussed cases it is not possible to establish causality to a specific property of mRNA-1273. Dyspnoea as an unspecific reaction to the vaccination procedure or to the general reactogenicity of mRNA-1273 per se is possible. In summary, it is based on the submitted clinical information, the confounding factors, and the singularity of cases deemed justified to not include the AE of dyspnoea into section 4.8 of the SmPC.

The CHMP considered that the majority of unsolicited AEs considered to be vaccine-related are already listed in the SmPC. Only the following AEs considered to be vaccine-related are not yet listed in the SmPC:

1 case of mild Dyspnoea starting on day 27 and 1 case of mild chest pain starting on day 3 in part 1.

1 case of Serum sickness-like reaction starting on day 10 and ongoing, 1 case of mild aggression starting on day 3, and 1 case of mild insomnia starting on day 1 in part 2.

Narratives were submitted for the cases of dyspnoea, chest pain, and serum-sickness like reaction and are discussed here.

The case of dyspnoea was reported for a participant, with no relevant medical history, who was randomly assigned to 50 µg mRNA-1273 in Part 1 of the study on Day 1. The participant received the booster dose of 25 µg mRNA-1273 in the right arm on Study Day 346/Booster Dose Day 1. On Study Day 372, 27 days post-booster dose, the participant experienced a non-serious mild AE of dyspnoea (difficulty breathing). Other non-serious AEs reported by the participant included: fatigue, cough pyrexia, sinusitis, throat irritation, tonsillitis, and respiratory tract congestion (chest congestion). All events were reported prior to the event of dyspnoea, but the time to onset of the events is not specified. No concurrent AEs are mentioned in the listing of AEs submitted for this procedure. No concomitant medication or concomitant procedures were ongoing at the time of the event of dyspnoea. No action was taken in regard to the IP. The event of dyspnoea was considered to be resolved on Study Day 372. The investigator assessed the event of dyspnoea to be related to the IP.

The CHMP considered that the time to onset of dyspnoea after booster dose (27 days post-booster dose) is rather late to indicate relatedness to vaccination. Several other events that are indicative of a viral respiratory infection were reported prior to the dyspnoea event and could explain the dyspnoea. However, the exact time points of onset of the symptoms of respiratory infection are not specified and the listing does not mention any concurrent AE. The narrative does not indicate any cardiac related cause of dyspnoea. Overall, vaccine-relatedness is rather unlikely. Clinical information for 3 other cases of dyspnoea considered to be vaccine-related was also reviewed. 1 case occurred after booster

dose in study P203 and 2 in study P204 after dose 2. The 3 events of dyspnoea considered to be vaccine-related by the investigator due to temporal relationship are confounded either by a medical history of anxiety and depression or by concurrent symptoms like fever, fatigue, headache, chills and sore throat. Dyspnoea is an unspecific symptom. From the 3 discussed cases it is not possible to establish causality to a specific property of mRNA-1273. A concurrent reaction to the vaccination procedure or to the general reactogenicity of mRNA-1273 per se is possible. The CHMP therefore considers it justified to not include "dyspnoea" into section 4.8 of the SmPC.

The case of mild chest pain was report for a participant, with medical history of eczema, seasonal allergies, bronchial hyperreactivity, food allergies, and erythema. The participant received the first dose of 50 µg mRNA-1273 in the left arm on Study Day 1 and the second dose of 50 µg mRNA-1273 in the left arm on Study Day 30. The participant received the booster dose of 25 µg mRNA-1273 in the left arm on Study Day 350/Booster Dose Day 1. 2 days after booster dose on Study Day 352, the participant experienced a non-serious mild AE of chest pain. A cardiac workup was completed including an electrocardiogram, which was normal, as well as normal values for high sensitivity troponin 1, erythrocyte sedimentation rate, and C-reactive protein. Given these results, the event was considered to be non-cardiac chest pain of unknown aetiology by the Investigator. The chest pain resolved within the same day. Other non-serious AEs reported by the participant included: two events of bronchial hyperreactivity (exacerbation of reactive airway disease), fatigue, arthropod bite, decreased appetite, respiratory tract infection viral, rhinovirus infection, oropharyngeal pain (sore throat), and sunburn. All these events were reported prior to the event of chest pain, without further specification of the time to onset. No concurrent AE is recorded in the AE listing submitted within this procedure. Concomitant medication or concomitant procedures ongoing at the time of the event of chest pain included: salbutamol (reactive airways), allergens NOS (seasonal allergies), and loratadine (seasonal allergies). Because of the temporal relationship the event was considered to be vaccine-related by the investigator.

The CHMP considered that the known history of bronchial hyperreactivity could explain the event of chest pain. The narrative does not indicate any cardiac relationship. Overall, causality cannot clearly be established based on the submitted clinical information and taking the medical history of bronchial hyperreactivity into account.

The case of serum-sickness-like reaction was reported for a participant, with no relevant medical history. The participant received the first dose of 50 µg mRNA-1273 in the left arm on Study Day 1 and the second dose of 50 µg mRNA-1273 in the left arm on Study Day 29. The participant received the booster dose of 25 µg mRNA-1273 in the left arm on Study Day 256/Booster Dose Day 1. 10 days after booster dose the participant experienced a non-serious mild AE of serum sickness (serum sickness-like reaction). Symptoms related to the event of serum sickness-like reaction are not specified or described in the narrative, but are provided in the clinical overview. Symptoms included generalised pruritis that progressed to urticaria on trunk and bilateral thighs as well as arthralgia, myalgia, chills, and nausea. There was no fever or upper respiratory infection symptoms. There were no new medications or change in food/soap, lotion or detergents and no family members with similar symptoms. Medical treatment included acetaminophen, ibuprofen, topical and oral antihistamines, and prednisone. According to the summary in the clinical overview, no concurrent AEs were reported. The event was ongoing but recovering/resolving at the time of the data cut-off (23May2022). Events reported prior to the event include upper respiratory tract infection and viral infection (not related to COVID-19 or flu). Time points to onset for these events are not specified. No concurrent AEs were reported according to the summary in the overview and according to the submitted listing.

The CHMP noted that serum sickness is a delayed type III immune-complex mediated hypersensitivity reaction that could occur after exposure to foreign antigens including vaccine antigens. Particularly

medication and antitoxins including animal serum protein are associated with serum sickness and serum sickness-like reactions. The clinical information on the case of serum sickness-like reaction indicates development of chronic hives. The individual has no medical history of allergy, had no allergic reactions after the 2 primary vaccination doses of mRNA-1273, nonetheless, it cannot be excluded that the event of chronic urticaria was triggered by the 3rd mRNA-1273 vaccination. The diagnostic for chronic urticaria is not yet finalised. Based on the singularity of the case of serum-sickness-like reaction and chronic urticaria temporarily associated with mRNA-1273 vaccination it is considered justified to not include serum sickness-like reaction and "chronic urticaria", into section 4.8 for the time being. Urticaria have recently been included in the SmPC of Spikevax. The event could be considered covered by the AE "Hypersensitivity" that is already included in the SmPC, section 4.8.

Unsolicited Medically Attended Adverse Events (MAAE)

Overall, 96 participants (7.4%) experienced an MAAE within 28 days after the mRNA-1273 booster dose as stated on page 29 in the clinical overview. According to the clinical overview, 116 of 1,294 (9.0 %) participants experienced at least one MAAE after booster dose. It is understood that the latter data are for the data-cut off period, i.e., beyond day 28. Two participants (0.2%) reported 4 MAAEs that were considered severe: abdominal pain (n=1, <0.1%), myalgia (n=1, <0.1%), chills (n=1, <0.1%), and fatigue (n=1, <0.1%). Ten (0.8%) participants had MAAEs considered to be vaccine-related by the investigator. 3 cases of attention deficit hyperactive disorder with time to onset on day 8, day 14, and day 22 were reported, all are not resolved at the time of data cut.

MAAEs considered vaccine-related

After booster dose, 15 MAAEs considered vaccine-related were reported in 10 participants,

4 participants in Part 1 and 6 in Part 2. All participants reported one event except for one participant in Part 1 who had 3 events and one participant in Part 2 who had 4 events. 3 MAAEs were severe (chills, fatigue, and myalgia), all other events were either mild (6) or moderate (6). The outcome of 4 of the 15 MAAEs (mild symptomatic COVID-19, fatigue, headache, fever) was not reported and is therefore unknown. Except for 2 events (mild non-cardiac chest pain and mild serum sickness-like reaction) all events are either not considered to be vaccine-related (4 cases of mild COVID-19) or are not unexpected and explained by vaccine reactogenicity (1 case of severe chills, moderate and severe fatigue, moderate headache, severe myalgia, moderate fever, and 2 cases of moderate urticaria). The event of non-cardiac chest pain occurred in a participant two days after receiving 25 µg mRNA-1273 booster dose. The event is also discussed in the safety section of this AR ("Unsolicited AEs considered to be vaccine-related"). Very limited clinical information is available. The event is based on the submitted information not consistent with a cardiac event like myocarditis or pericarditis. Causality has been based by the investigator in temporal relationship. The assessment of causality is however impeded by a medical history of bronchial hyperreactivity, which does not allow confirm causality to the product.

The clinical information on the case of serum sickness-like reaction indicates development of chronic hives. The individual has no medical history of allergy, and had no allergic reactions after the 2 primary vaccination doses of mRNA-1273, nonetheless, it cannot be excluded that the event of chronic urticaria was triggered by the 3rd mRNA-1273 vaccination. The diagnostic for chronic urticaria is not yet finalised. Based on the singularity of the case of serum-sickness-like reaction and chronic urticaria temporarily associated with mRNA-1273 vaccination it is deemed justifiable to not including serum sickness-like reaction and "chronic urticaria", into section 4.8. Urticaria have recently been included in the SmPC of Spikevax. The event is also discussed in the safety section of this AR ("Unsolicited AEs considered to be vaccine-related").

The MAAEs considered vaccine-related are displayed in Table 27 below.

Table 27: MAAEs considered vaccine-related after booster dose, P203

Subject	Preferred Term	Verbatim	Relative Start Day from BD	Relative End Day from BD	Severity	Outcome
1	Non-cardiac chest pain	Chest pain	3	3	Mild	R/R
2	Chills	Chills	5	8	Severe	R/R
3	COVID-19	Symptomatic COVID-19	19	29	Mild	R/R
4	COVID-19	Symptomatic COVID-19	1		Mild	R/R
5	COVID-19	Symptomatic COVID-19	3	10	Mild	R/R
6	COVID-19	Symptomatic positive COVID-19 test	9		Mild	NR/NR
7	Fatigue	Fatigue	7		Moderate	NR/NR
8	Fatigue	Fatigue	5	13	Severe	R/R
9	Headache	Headache	7		Moderate	NR/NR
10	Myalgia	Myalgia (muscle aches all over body)	5	8	Severe	R/R
11	Pyrexia	Fever	8		Moderate	NR/NR
12	Pyrexia	Fever	5	9	Moderate	R/R
13	Serum sickness-like reaction	Serum sickness-like reaction	10		Mild	R/R
14	Urticaria	Urticarial rash, non-papular	11		Moderate	NR/NR
15	Urticaria	Generalized urticarial rash	15		Moderate	NR/NR

BD=booster dose, R/R=Recovering/resolving, NR/NR=not recovered, not resolved (as of data cut-off 23 May 2022)
Table 14.3.1.7.4.1.2 and Listing 16.2.7.1.6.2

The MAH submitted a list of MAAE considered to be vaccine-related. 15 MAAEs considered vaccine-related were reported in 10 participants, 4 of the participants were vaccinated in in Part 1 and 6 in Part 2. 3 events were severe (chills, fatigue, and myalgia), all other events were either mild (6) or moderate (6). The outcome of 4 of the 15 MAAEs (mild symptomatic COVID-19, fatigue, headache, fever) was not reported and is therefore unknown. Except for 2 events (mild non-cardiac chest pain and mild serum sickness-like reaction) all events are either not considered to be vaccine-related (4 cases of mild COVID-19) or are not unexpected and explained by vaccine reactogenicity (1 case of severe chills, moderate and severe fatigue, moderate headache, severe myalgia, moderate fever, and 2 cases of moderate urticaria).

Serum sickness-like reaction

Clinical information on the case of serum sickness-like reaction had already been submitted in the dossier but were now supplemented with follow up information after cut-off date. The additional submitted clinical information indicate development of chronic hives. The participant has no medical history of allergy, and had no allergic reactions after the 2 primary vaccination doses of mRNA-1273, nonetheless, it cannot be excluded that the event of chronic urticaria was triggered by the 3rd mRNA-1273 vaccination. The diagnostic for chronic urticaria is not yet finalised. Based on the singularity of the case of serum-sickness-like reaction and chronic urticaria temporarily associated with mRNA-1273 vaccination it is deemed justifiable to not including serum sickness-like reaction and "chronic urticaria", into section 4.8. Urticaria have recently been included in the SmPC of Spikevax.

Non-cardiac chest pain

The event of non-cardiac chest pain occurred in a participant two days after receiving 25 µg mRNA-1273 booster dose. Clinical information about this case of chest pain have previously been submitted by the MAH in the dossier. The event is discussed in the safety section of this AR ("Unsolicited AEs considered to be vaccine-related"). Very limited clinical information is available. The event is based on the submitted information not consistent with a cardiac event like myocarditis or pericarditis. Causality has been based by the investigator in temporal relationship. The assessment of causality is impeded by a medical history of bronchial hyperreactivity. This is the only case of chest pain considered to be vaccine-related in study P204. Of note, 2 more cases of non-cardiac chest pain considered to be vaccine-related occurred in study P203. Another case of chest pain considered vaccine-related is reported for a subject in P203 after dose 2. This event occurred in a participant with a medical history of depression, anxiety and seasonal allergy on the day after booster vaccination. The event of cardiac chest pain was accompanied by palpitations and wheezing. Concurrently the participant experienced moderate headache and vomiting/nausea. The participant was seen by a cardiologist in the ER. CTG was normal. No further information on the cardiac workup is available. All symptoms are reported as resolved. It is difficult to draw a final conclusion on the relatedness of chest-pain, based on the single events in study P203 and P204 which are accompanied either by concomitant AEs or by a medical history that could precludes final assessment. Moreover, it is not possible to determine whether the event of chest pain is induced by a specific property of the vaccine or if it is a more unspecific reaction to the procedure of vaccination and the reactogenicity in general. For the time being causality cannot conclusively be confirmed.

Serious adverse event/deaths/other significant events

Serious adverse events (SAE)

No SAE considered to be vaccine-related has been reported.

One SAE not considered to be vaccine-related has been reported for a participant. The event had an onset 16 days after the 25 µg booster dose. The participant developed severe abdominal pain and vomiting. Magnetic resonance imaging and abdominal ultrasound ruled out appendicitis, hernia, and bowel obstruction, and a COVID-19 test was negative. The participant was admitted to hospital and started on intravenous fluid therapy and anti-emetic medications. By the next day the participant was tolerating oral intake and discharged from the hospital. No definitive diagnosis was determined; the event was recorded as "stomach inflammation". The event of abdominal pain was considered to be resolved on Study Day 252.

Deaths

No fatal AEs were reported until data cut-of.

Analyses of Adverse Events of Special Interest (AESI)

AESI are pre-specified in Appendix 4 of the CTP and are to be followed for the entire study period, i.e. from Day 1 through the final visit (Day 514).

MIS-C

No events of MIS-C were reported.

Anaphylaxis/hypersensitivity

Twenty-four (1.9%) participants reported hypersensitivity events after 25 µg of mRNA-1273 booster dose according to the narrow and broad standardised MedDRA Query (SMQ) of hypersensitivity.

The most commonly reported event was urticaria, occurring in 8 (0.6%) participants. The only other events occurring in more than one participant were mechanical urticaria (n=2, 0.2%) and seasonal allergy (n=3, 0.2%). Three participants experienced events that were considered related to study vaccination by the Investigator, including one event of serum sickness-like reaction and 2 events of urticaria. The event of serum sickness-like reaction is described and discussed in the section "Unsolicited AEs considered to be vaccine-related" in this AR.

AESI categorised by the investigator

One AE has been categorised by the investigator as an AESI although it did not meet protocol-defined definition of an AESI. This was an event in a participant who experienced mild chest pain on day 3 after having received the 25 µg booster dose. The event was considered to be vaccine-related by the investigator because of temporal relationship to vaccination. The case is described and discussed in the section "Unsolicited AEs considered to be vaccine-related" in this AR.

Cases of Clinical Interest Based on MedDRA Cardiomyopathy SMQs

As a supplemental measure to search for unrecognised myocarditis/pericarditis cases, the safety dataset was interrogated for AEs compatible with signs, symptoms, laboratory investigations or procedural findings that might indicate unrecognised cases. Since these event terms are not specific for myocarditis and pericarditis, each of the identified cases was evaluated. Events were filtered for those occurring within 28 days of the most recent vaccine dose. Two overlapping approaches were used to interrogate all AEs using:

- The narrow and broad cardiomyopathy SMQs
- An algorithm generated using MedDRA terms v23.0 included in the CDC working case definitions for acute myocarditis and acute pericarditis (Gargano JW 2021)

There were 2 events in the cardiomyopathy in the standard Medical Dictionary for Regulatory Activities queries (SMQ). One was the event of mild chest pain that was categorised as an AESI by the investigator. The other event a mild episode of dyspnoea. Both events are described and discussed in the section "Unsolicited AEs considered to be vaccine-related" in this AR.

Other Events of Clinical Interest

Autoimmune mediated AE

One AE of juvenile rheumatoid arthritis (JRA) has been reported. It should be noted, that the event of JRA was already known and occurred for the first time reported as post-viral transient synovitis of bilateral hips 4 months and 5 days after Dose 2 of the primary series. The family history includes multiple members with autoimmune disorders. The participant received his 25 µg booster dose on Booster Dose Day 1. On Booster Dose Day 8 an AE of JRA (hips and hands predominant, non-serious, moderate) was recorded. Of note, there was no change in clinical status, just confirmation of the diagnosis from the ongoing work-up.

The full narrative is summarised as follows: A participant with a medical history of asthma and seasonal allergies, experienced an SAE of post-viral transient synovitis of bilateral hips 4 months and 5 days after Dose 2 of the primary series. The participant developed bilateral hip pain after active exercise which was treated with ibuprofen. Overnight the participant awoke with severe pain, and was admitted to the hospital. Magnetic resonance imaging showed fluid accumulation around both hip joints. Family history includes autoimmune disorders.. A COVID-19 test taken at the time was negative and all laboratory studies were reported as normal. Although the participant had not been ill or diagnosed with a viral infection recently, the diagnosis of post-viral transient synovitis was assigned given the negative work-up. The participant was treated with intravenous ketorolac tromethamine and

sent home with ibuprofen and a referral for physical therapy. The event was reported as resolved 20 days after hospital admission. At a regularly scheduled 3-month follow-up appointment following discharge from the hospital, the practitioner noted on the participant's physical exam that the fingers on both hands were swollen, and the participant had decreased grip strength bilaterally. Given the family history of autoimmune disorders and the recent hip pain hospital admission, the provider checked autoimmune laboratory studies again, which then came back elevated. The participant was then seen by Rheumatology and received the diagnosis of JRA. The participant was prescribed Humira injections biweekly and has been doing well since. Prior to the diagnosis of JRA, the participant was asymptomatic. The participant's hip pain had resolved and there had been no complaints of finger pain.

The CHMP noted that this report of JRA is not an AE associated with the booster dose, but was known prior to booster vaccination. The first event of JRA occurred 4 months and 5 days after Dose 2 of the primary series. Initially due to a negative work-out the event was erroneously categorised as post-viral transient synovitis (without history of viral infection). The participant's family history includes immune disorders. The time to onset from 2nd dose to the event was 4 months. It cannot be excluded, that vaccination triggered the autoimmune disease in this individual with a family history of autoimmune disease. Of note, other triggers cannot be excluded either in this individual with a high risk of developing an autoimmune disorder.

Laboratory findings

No laboratory evaluation has been performed in the trial.

Safety in special populations

No special population has been included in the trial.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions and other interactions are not scope of this trial.

Discontinuation due to adverse events

One participant discontinued the study due to withdrawal of consent. Withdrawal for this participant was not related to AEs. No unsolicited AEs caused discontinuation from study participation.

Booster dose of 50 µg of mRNA-1273 in adolescents 12 through 17 years of age

Data presented here summarise the tolerability, safety, and immunogenicity of a 50 µg booster dose of mRNA-1273 to adolescents who previously completed a primary vaccination series of two 100 µg doses administered approximately 1 month apart. The booster dose could be given at least 5 months after completion of the mRNA-1273 primary series. The data cut-off date for this submission is 16 May 2022.

The executive summary focuses on participants originally randomised to mRNA-1273 primary series and subsequently boosted, hereafter referred to as mRNA-1273 Booster group. Some participants originally randomised to placebo were subsequently crossed over to receive an mRNA-1273 primary

series and then received the mRNA-1273 booster dose. This group is referred to as "placebo-mRNA-1273-Booster". The sample size of the placebo-mRNA-1273-Booster group is small (n=18) and the majority had less than 28 days of follow-up).

Safety sets

The safety sets are the same as in trial P204

Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomised and received any study injection, and contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set was to be used for the analyses of solicited ARs. Participants were to be included in the vaccination group corresponding to the study injection they actually received rather than the vaccination group to which the subject was randomised.

Safety Set

The Safety Set consists of all randomised participants who received any study injection. The Safety Set was to be used for analysis of safety except for the solicited ARs. Participants were to be included in the vaccination group corresponding to the vaccination they actually received.

Participant exposure and follow up

A total of 1346 participants 12 to 17 years of age who completed the 100 µg mRNA-1273 primary series in Study P203 Part 1A, received a 50 µg mRNA-1273 booster dose (mRNA-1273 –Booster group).

The safety set includes 1346 subjects (100% of the FAS), the solicited safety set 1294 (96.1% of the FAS). The participant disposition after booster dose (full analysis set) is summarised in Table 28 below.

Table 28: Participant Disposition After Booster Dose Full Analysis Set (Booster Dose)

	mRNA-1273-Booster N = 1346 n (%)
Received booster injection	1346 (100)
Completed study[1]	1 (<0.1)
Discontinued from study	11 (0.8)
Reason for discontinuation from study	
Lost to follow up	4 (0.3)
Withdrawal of consent by participant	6 (0.4)
COVID-19 non-infection related[2]	1 (<0.1)
Other	5 (0.4)
Other	1 (<0.1)
Adverse event	0
Protocol deviation	0

Abbreviations: BD = booster dose

[1] Study completion is defined as a participant who completed 12 months of follow up after the BD. A total of 1334 participants are still in the 12-month follow-up period.

[2] "COVID-19 non-infection related" refers to situations related to pandemic conditions (eg, reluctance to attend study site visits because of concerns regarding SARS-CoV-2 transmissibility) rather than to SARS-CoV-2 infection or COVID-19 in the study participant.

Percentages are based on the number of participants (N) in Full Analysis Set for Part C.

Source: Table 14.1.1.1.5.

Follow-up

After administration of the booster dose, participants in the mRNA-1273-booster group were followed for a median of 117 days (range: 2 to 141 days). Almost all subjects, i.e. 1327 (98.6%) had a follow-up of ≥ 28 days; 95.8% of subjects (1,289/1,346) were followed up for ≥56 days (Table 29). The median time interval from Dose 2 of the primary series to booster dose was 316 days (range: 274 to 422 days).

Table 29: Summary of Time on Study by Age Group Safety Set (Part C, Booster Dose)

	Placebo-mRNA-1273 -Booster (N=18)	mRNA-1273-Booster (N=1346)	Total (N=1364)
Follow-Up Time on Study After Booster (Days)			
Mean (SD)	21.3 (13.05)	109.2 (23.08)	108.0 (25.07)
Median	21.0	117.0	116.0
Q1, Q3	18.0, 22.0	98.0, 125.0	96.0, 125.0
Min, Max	4, 64	2, 141	2, 141
< 28 Days	16 (88.9)	19 (1.4)	35 (2.6)
>= 28 Days	2 (11.1)	1327 (98.6)	1329 (97.4)
>= 28 and < 56 Days	1 (5.6)	38 (2.8)	39 (2.9)
>= 56 Days	1 (5.6)	1289 (95.8)	1290 (94.6)
>= 84 Days	0	1174 (87.2)	1174 (86.1)
>= 112 Days	0	736 (54.7)	736 (54.0)
>= 140 Days	0	4 (0.3)	4 (0.3)
Person-years from Booster [2]	1.1	402.3	403.4

Demography

The demographics and baseline characteristics of participants in the Safety Set of study P203 are presented in Table 30. The median age is 14.0 years. The majority of participants in the mRNA-1273-Booster group, i.e. 80.2% (1079/1346) are in the age range ≥ 12 to <16 years, 267 participants are ≥ 16 to < 18 years (19.8%). The proportion of males and females is balanced with only slightly more males than females included (51.3% versus 48.7%). SARS-CoV-2 status was evaluated by serology and RT-PCR before receipt of the booster dose on BD-Day 1. A total of 536 participants (39.8%) were positive for SARS-CoV-2 status on BD-Day 1 (before receipt of booster dose). Approximately 39.8% of participants had evidence of prior SARS-CoV-2 infection at the time of boosting.

Table 30: Participant Demographics and Baseline Characteristics by Age Group (Safety Set – Booster Dose)

	mRNA-1273-Booster N = 1346 n (%)
Age group	
≥ 12 to < 16 years	1079 (80.2)
≥ 16 to < 18 years	267 (19.8)
Sex	
Male	691 (51.3)
Female	655 (48.7)
Race	
White	1140 (84.7)
Black	43 (3.2)
Asian	66 (4.9)
American Indian or Alaska Native	7 (0.5)
Native Hawaiian or Other Pacific Islander	1 (<0.1)
Multiracial	71 (5.3)
Other	10 (0.7)
Not Reported	4 (0.3)
Unknown	4 (0.3)
Ethnicity	
Hispanic or Latino	171 (12.7)
Not Hispanic or Latino	1164 (86.5)
Not reported	11 (0.8)
Unknown	0
Race and ethnicity group[a]	
White non-Hispanic	999 (74.2)
Communities of color[a]	346 (25.7)
Missing	1 (<0.1)
Body mass index ≥ 30 kg/m^2	104 (7.7)
Obesity[b]	265 (19.7)
Positive Pre-Booster SARS-CoV-2 status[c]	536 (39.8)
Positive pre-booster Elecsys anti-SARS-CoV-2	471 (35.0)
Positive pre-booster baseline RT-PCR	101 (7.5)

Abbreviations: BD = booster dose; COVID-19 = coronavirus disease 2019; RT-PCR = reverse-transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; WHO = World Health Organization

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

[b] Obesity is defined as body mass index $\geq 95^{th}$ percentile in the WHO growth reference data.

[c] Pre-booster 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 BD-Day 1 in Part C. Negative is defined as negative RT-PCR test and negative Elecsys result at BD-Day 1 in Part C.

Percentages are based on the number of safety participants for Part C (N).

Source: Table 14.1.3.14.1.

The CHMP understands that a positive Pre-booster SARS-CoV-2 Status was confirmed on booster day 1 not only via serology but also via SARS-CoV-2 PCR, which could be in case of a positive result indicative of an acute SARS-CoV-2 infection. In study P204 a known history of SARS-CoV-2 infection within 2 weeks prior to administration of IP or even known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to administration of IP is an exclusion criterion.

Solicited adverse reactions

Local and systemic ARs were solicited in the 7 days after booster dose. Assessed local ARs included pain, erythema, swelling, and axillary swelling or tenderness. Systemic ARs included fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, and chills.

Solicited ARs were reported by 95.1% of participants in the mRNA-1273 –Booster group. The majority of solicited ARs was mild or moderate. 11.0% of subjects reported a Grade 3 solicited AR and none reported a Grade 4 solicited AR. Most solicited ARs occurred within 1 to 2 days after booster vaccination and generally persisted for a median of 3 days. 0.5% of subjects reported solicited ARs with onset after Day 7.

Solicited local ARs were reported by 92.0% of participants in the mRNA-1273-Booster group. Pain was the most reported solicited local AR (91.1% of participants); followed by Axillary Swelling or Tenderness (28.1% of subjects), swelling//hardness (13.5%), and erythema/redness (9.2%). The majority of solicited local ARs was mild to moderate. Only 4.3% of subjects reported Grade 3 local ARs. The solicited local AR with the highest incidence was pain (2.9%). The Grade 3 incidence of the other solicited local ARs was a maximum of 0.7%. Most solicited local ARs occurred within 1 to 2 days after booster and generally persisted for a median of 3 days.

Solicited systemic AR were reported for 76.7% of subjects. Headache and fatigue were the most reported solicited systemic ARS (57.2% and 58.7% of participants, respectively), followed by myalgia (40.4%), chills (30.6%), arthralgia (24.1%), and nausea/vomiting (17.9%). Fever was reported for 6.1% of subjects. Most solicited systemic ARs occurred within 1 to 2 days after booster dose and generally persisted for a median of 2 days. The majority of solicited systemic ARs were mild to moderate. Grade 3 ARs were reported by 8.1% of subjects. No grade 4 solicited systemic AR was reported. The most frequently reported grade 3 solicited systemic AR was fatigue (4.0%), followed by myalgia (3.4%), and headache (2.2%).

Comparison of solicited ARs after 50 µg booster dose to after any 100 µg primary series dose

Solicited ARs after a booster dose with 50 µg mRNA-1273 were compared to solicited ARs after receipt of any dose of a primary series of 2 doses of 100 µg mRNA-1273.

The reactogenicity was lower after booster dose compared to after any dose of the primary vaccination course. This was observed for all solicited ARs (local and systemic). The difference was notable particularly for the local solicited ARs, including fewer Grade 3 events (11.0% and 25.2% post-booster and post-Dose 2, respectively) and no Grade 4 events. This is consistent to what has been observed for children 6-11 years of age.

Solicited ARs within 7 days after the 50 µg mRNA-1273 booster dose and any dose of the 2-dose 100 µg primary vaccination are displayed in Table 31.

Table 31: Summary of P203 Participants with Solicited Adverse Reactions within 7 Days After Booster and Primary Series – Solicited Safety Set (Part C, Booster Dose)

	mRNA-1273-Booster N = 1294 n (%)	Primary Series mRNA-1273 after any injection N = 2485 n (%)
Solicited Adverse Reactions – N1	1294	2485
Any solicited adverse reactions	1231 (95.1)	2466 (99.2)
Grade 3	142 (11.0)	626 (25.2)
Grade 4	0	3 (0.1)
Solicited Local Adverse Reactions – N1	1294	2485
Any solicited local adverse reactions	1191 (92.0)	2431 (97.8)
Grade 3	55 (4.3)	344 (13.8)
Grade 4	0	0
Pain – N1	1294	2485
Any	1179 (91.1)	2415 (97.2)
Grade 3	38 (2.9)	227 (9.1)
Grade 4	0	0
Erythema (Redness) – N1	1293	2485
Any	119 (9.2)	641 (25.8)
Grade 3	9 (0.7)	86 (3.5)
Grade 4	0	0
Swelling (Hardness) – N1	1293	2485
Any	174 (13.5)	688 (27.7)
Grade 3	9 (0.7)	80 (3.2)
Grade 4	0	0
Axillary Swelling or Tenderness – N1	1293	2484
Any	363 (28.1)	859 (34.6)
Grade 3	3 (0.2)	16 (0.6)
Grade 4	0	0
Solicited Systemic Adverse Reactions – N1	1293	2485
Any	990 (76.6)	2284 (91.9)
Grade 3	105 (8.1)	411 (16.5)
Grade 4		3 (0.1)
Fever – N1	1279	2484
Any	78 (6.1)	340 (13.7)
Grade 3	8 (0.6)	54 (2.2)
Grade 4	0	1 (< 0.1)
Headache – N1	1293	2485
Any	739 (57.2)	1947 (78.4)
Grade 3	28 (2.2)	160 (6.4)
Grade 4	0	1 (< 0.1)
Fatigue – N1	1293	2485
Any	759 (58.7)	1868 (75.2)
Grade 3	52 (4.0)	210 (8.5)
Grade 4	0	0
Myalgia – N1	1293	2484
Any	523 (40.4)	1349 (54.3)
Grade 3	44 (3.4)	143 (5.8)

	mRNA-1273-Booster N = 1294 n (%)	Primary Series mRNA-1273 after any injection N = 2485 n (%)
Grade 4	0	0
Arthralgia – N1	1293	2484
Any	311 (24.1)	859 (34.6)
Grade 3	17 (1.3)	66 (2.7)
Grade 4	0	0
Nausea/Vomiting – N1	1293	2484
Any	231 (17.9)	728 (29.3)
Grade 3	2 (0.2)	4 (0.2)
Grade 4	0	1 (<0.1)
Chills – N1	1293	2484
Any	396 (30.6)	1219 (49.1)
Grade 3	7 (0.5)	13 (0.5)
Grade 4	0	0

Abbreviations: N1 = Number of exposed participants who submitted any data for the event.
Any = Grade 1 or higher.
Percentages are based on the number of exposed participants who submitted any data for the event (N1).
Toxicity grade for erythema (redness) is defined as: Grade 1 = 25–50 mm; Grade 2 = 51–100 mm; Grade 3 ≥100 mm. Toxicity grade for fever is defined as Grade 1 = 38–38.4 C; Grade 2 = 38.5–38.9 C; Grade 3 = 39–40 C; Grade 4 = ≥40 C.
Source: Table 14.3.1.1.1.5.1 and Table 3.1.1.3, EUA Primary Series, Data Cutoff 08 May 2021

Unsolicited adverse events (AEs)

Unsolicited adverse events up to 28 days after booster vaccination were reported by 14.2% of subjects (191/1,346) in the mRNA-1273 booster Group. Unsolicited AEs considered to be vaccine-related by the investigator were reported by 4.1% of subjects (55/1,346). These event rates were lower than those in the primary series (after any injection) where unsolicited AEs occurred in 510/2,486 participants (20.5%) and 312/2,486 participants (12.6%) reported unsolicited AEs that were considered vaccine-related. The highest incidence of unsolicited AEs is observed within the SOC of Infections and infestation (7.6%/102 subjects), General disorders and administration site conditions (3.2%/43 subjects), and nervous system disorders (1.9%/26 subjects, all events related to the PT of headache). The most frequently reported PTs in the SOC of Infections and infestation was COVID-19 (3.0%/41 subjects), asymptomatic COVID-19 (1.3%/17 subjects), and upper respiratory tract infection (1.2%16 subjects). This is followed by Nasopharyngitis (0.5%/7 subjects), pharyngitis (0.4%/6 subjects), viral infection (0.3%4 subjects), and influenza (0.2%/3 subjects). All other PTs were only reported by singular subjects. The leading PT in the SOC of General disorders and administration site conditions was fatigue (1.7%/23 subjects), followed by injection site pain (1.7%/23 subjects), and pyrexia (0.4%/5 subjects). One case of non-cardiac chest pain considered to be vaccine-related was reported in this SOC. Unsolicited AEs irrespective of causality up to 28 days after booster dose are displayed in Table 32.

Table 32: Overall Unsolicited TEAE by MedDRA System Organ Class and Preferred Term (≥2 participants) up to 28 Days After Booster Dose Safety Set

System Organ Class Preferred Term	mRNA-1273-Booster N = 1294 n (%)
Number of participants reporting unsolicited adverse events	191 (14.2)

System Organ Class Preferred Term	mRNA-1273-Booster N = 1294 n (%)
Number of unsolicited adverse events	263
Infections and infestations	102 (7.6)
COVID-19	41 (3.0)
Asymptomatic COVID-19	17 (1.3)
Upper respiratory tract infection	16 (1.2)
Nasopharyngitis	7 (0.5)
Pharyngitis	6 (0.4)
Viral infection	4 (0.3)
Influenza	3 (0.2)
Psychiatric Disorders	6 (0.4)
Anxiety	2 (0.1)
Nervous system disorders	26 (1.9)
Headache	26 (1.9)
Respiratory, thoracic, and mediastinal disorders	11 (0.8)
Nasal congestion	3 (0.2)
Cough	2 (0.1)
Dyspnoea	2 (0.1)
Oropharyngeal pain	2 (0.1)
Rhinorrhea	2 (0.1)
Gastrointestinal disorders	10 (0.7)
Vomiting	3 (0.2)
Abdominal pain	3 (0.2)
Skin and subcutaneous tissue disorders	12 (0.9)
Acne	4 (0.3)
Urticaria	4 (0.3)
Musculoskeletal and connective tissue disorders	13 (1.0)

System Organ Class Preferred Term	mRNA-1273-Booster N = 1294 n (%)
Myalgia	7 (0.5)
Arthralgia	5 (0.4)
General disorders and administration site conditions	43 (3.2)
Fatigue	23 (1.7)
Injection site pain	9 (0.7)
Pyrexia	5 (0.4)
Injection site induration	4 (0.3)
Chills	3 (0.2)
Injection site lymphadenopathy	2 (0.1)
Pain	2 (0.1)
Injury, poisoning, and procedural complications	14 (1.0)
Ligament sprain	5 (0.4)
Hand fracture	2 (0.1)

Abbreviations: MedDRA = Medical Dictionary of Regulatory Activities
A treatment-emergent adverse event was defined as any event not present before exposure to study injection or any event already present that worsens in intensity or frequency after exposure.
Percentages are based on the number of safety participants in Part 1C-1 (N).
MedDRA version 23.0
Source: Table 14.3.1.8.5.1.1

The CHMP was of the view that unsolicited AEs including those reported for singular subjects do not reveal any safety signal. The majority is either indicative of known reactogenicity related to the vaccine or commonly observed in the population of adolescents. In comparison to the primary series, the incidence of unsolicited AEs (related and unrelated to vaccination) was lower after the booster dose.

Unsolicited AEs considered to be vaccine-related

Unsolicited AEs reported within 28 days after booster dose and considered to be vaccine-related are displayed in Table 33. The majority of unsolicited AEs considered to be vaccine-related are expected reactogenicity events that are already covered in the SmPC. Unsolicited AEs considered to be vaccine-related and not covered in the SmPC are

- non-cardiac chest pain (starting and resolving on day 2)
- dyspnoea (starting on day 1, resolved on day 2)
- intermittent constipation (starting on day 1, ongoing during data cut)
- pharyngitis (starting on day 9, resolved on day 12).

2 severe unsolicited AEs considered to be vaccine-related were reported (vomiting, diagnosed as viral gastroenteritis and fatigue).

The event of dyspnoea considered to be vaccine-related was reported for a participant, with a medical history of ADHD, anxiety, post-traumatic stress disorder, and depression. On the day of the booster dose, the participant experienced a non-serious mild AE of dyspnoea (shortness of breath). No other relevant concurrent AEs were reported by the participant. The symptom of dyspnoea is unspecific and could be a related to the vaccine procedure or a reaction to the reactogenicity of mRNA-1273 per se.

Causality for the dyspnoea event cannot finally be excluded because no concurrent AEs indication reactogenicity are reported. Considering the medical history of anxiety and depression, it is difficult to determine whether the symptom of dyspnoea is related to specific reactogenicity associated with mRNA-1273 or a stress reaction to the procedure of vaccination.

The case of non-cardiac chest pain occurred in participant with a medical history of depression, anxiety and seasonal allergy on the day after booster vaccination. The event of cardiac chest pain was accompanied by palpitations and wheezing. Concurrently the participant experienced moderate headache and vomiting/nausea. The participant was seen by a cardiologist in the ER. CTG was normal. No further information on the cardiac workup is available. All symptoms are reported as resolved. From this single case and the complexity of symptoms together with the medical history, it is not possible to confirm vaccine-relatedness. A stress reaction to the vaccine procedure cannot be excluded.

Table 33: Subject Incidence of Unsolicited Treatment-Related TEAE by Age Group, System Organ Class and Preferred Term up to 28 Days After Booster Dose Safety Set (Part C, Booster Dose)

Age Group: Overall

System Organ Class Preferred Term	Placebo-mRNA-1273-Booster (N=18) n (%)		mRNA-1273-Booster (N=1346) n (%)		Total (N=1364) n (%)	
	Any	Severe	Any	Severe	Any	Severe
Number of Subjects Reporting Unsolicited Adverse Events	2 (11.1)	1 (5.6)	55 (4.1)	2 (0.1)	57 (4.2)	3 (0.2)
Number of Unsolicited Adverse Events	5	1	79	2	84	3
Infections and infestations	0	0	1 (<0.1)	0	1 (<0.1)	0
Pharyngitis	0	0	1 (<0.1)	0	1 (<0.1)	0
Blood and lymphatic system disorders	0	0	1 (<0.1)	0	1 (<0.1)	0
Lymphadenopathy	0	0	1 (<0.1)	0	1 (<0.1)	0
Nervous system disorders	1 (5.6)	0	22 (1.6)	0	23 (1.7)	0
Headache	1 (5.6)	0	22 (1.6)	0	23 (1.7)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (<0.1)	0	1 (<0.1)	0
Dyspnoea	0	0	1 (<0.1)	0	1 (<0.1)	0
Gastrointestinal disorders	0	0	4 (0.3)	1 (<0.1)	4 (0.3)	1 (<0.1)

System Organ Class Preferred Term	Placebo-mRNA-1273-Booster (N=18) n (%)		mRNA-1273-Booster (N=1346) n (%)		Total (N=1364) n (%)	
	Any	Severe	Any	Severe	Any	Severe
Gastrointestinal disorders (Cont.)						
Vomiting	0	0	2 (0.1)	1 (<0.1)	2 (0.1)	1 (<0.1)
Abdominal pain	0	0	1 (<0.1)	0	1 (<0.1)	0
Constipation	0	0	1 (<0.1)	0	1 (<0.1)	0
Skin and subcutaneous tissue disorders	0	0	2 (0.1)	0	2 (0.1)	0
Urticaria	0	0	2 (0.1)	0	2 (0.1)	0
Musculoskeletal and connective tissue disorders	0	0	4 (0.3)	0	4 (0.3)	0
Myalgia	0	0	4 (0.3)	0	4 (0.3)	0
Arthralgia	0	0	3 (0.2)	0	3 (0.2)	0
General disorders and administration site conditions	2 (11.1)	1 (5.6)	33 (2.5)	1 (<0.1)	35 (2.6)	2 (0.1)
Fatigue	1 (5.6)	1 (5.6)	20 (1.5)	1 (<0.1)	21 (1.5)	2 (0.1)
Injection site pain	1 (5.6)	0	8 (0.6)	0	9 (0.7)	0
Injection site induration	0	0	4 (0.3)	0	4 (0.3)	0
Chills	0	0	3 (0.2)	0	3 (0.2)	0
Injection site lymphadenopathy	2 (11.1)	0	2 (0.1)	0	4 (0.3)	0

System Organ Class Preferred Term	Placebo-mRNA-1273-Booster (N=18) n (%)		mRNA-1273-Booster (N=1346) n (%)		Total (N=1364) n (%)	
	Any	Severe	Any	Severe	Any	Severe
General disorders and administration site conditions (Cont.)						
Pyrexia	0	0	2 (0.1)	0	2 (0.1)	0
Injection site swelling	0	0	1 (<0.1)	0	1 (<0.1)	0
Non-cardiac chest pain	0	0	1 (<0.1)	0	1 (<0.1)	0

The narrative of the AE of dyspnoea is summarised as follows: The event of dyspnoea considered to be vaccine-related was reported for a participant, with a medical history of ADHD, anxiety, post-traumatic stress disorder, and depression. The participant received the booster dose of 50 µg mRNA-1273 in the right arm on Study Day 360)/Booster Dose Day 1. On the day of the booster dose, the participant experienced a non-serious mild AE of dyspnoea (shortness of breath). No other relevant concurrent AEs were reported by the participant.

Assessment of the AE of dyspnoea: Generally, the symptom of dyspnoea is unspecific and could also be related to the vaccine procedure than a reaction to the specific reactogenicity of mRNA-1273. Causality for the dyspnoea event cannot finally be excluded because no concurrent AEs indication reactogenicity are reported. Considering the medical history of anxiety and depression, it is difficult to determine whether the symptom of dyspnoea is related to specific reactogenicity associated with mRNA-1273 or an unspecific reaction to the procedure of vaccination. The submitted clinical information so far do not allow to confirm causality to the product, and a change in the SmPC to include this AE is not requested for the time being. The AE of dyspnoea is discussed in more detail in the AR section for children 6-11 years of age.

The case of non-cardiac chest pain occurred in participant with a medical history of depression, anxiety and seasonal allergy on the day after booster vaccination. The event of cardiac chest pain was accompanied by palpitations and wheezing. Concurrently the participant experienced moderate headache and vomiting/nausea. The participant was seen by a cardiologist in the ER. CTG was normal. No further information on the cardiac workup is available. All symptoms are reported as resolved. From this single case and the complexity of symptoms together with the medical history, it is not possible to confirm vaccine-relatedness. An update of section 4.8 to include the AEs of chest pain, palpitation or wheezing is not considered warranted.

Unsolicited Medically Attended Adverse Events (MAAE)

At least 1 MAAE was reported by 12.2% of Booster group participants (164/1,346 subjects) throughout the duration of the safety follow up. The most reported AEs were in the infections and infestations SOC (9.4%); within the SOC, COVID-19 was the most reported event (68 participants, 5.1%), followed by Upper respiratory tract infection (1.4%/19 subjects). One case of arrhythmia was reported in the mRNA-1273-Booster group. This event was not considered to be vaccine-related. The narrative was submitted and is discussed in the section "Cases of Clinical Interest Based on MedDRA Cardiomyopathy SMQs" below.

Serious adverse event/deaths/other significant events

Serious adverse events (SAE)

No SAEs were reported after booster dose.

Analyses of Adverse Events of Special Interest (AESI)

A priority list of AESIs that may be related to COVID-19 was developed by the Brighton Collaboration (Law 2020) and incorporated into Study P203. No AESI (including multisystem inflammatory syndrome in children [MIS-C]) were reported within 28 days after BD.

Anaphylaxis/Hypersensitivity

The events of urticaria were considered treatment-related events following administration of mRNA-1273-booster.

• A participant experienced mild urticaria (verbatim urticaria on bilateral posterior hands) 2 days after receiving the booster dose. Relevant medical history included seasonal allergies. The event was resolved the following day. No medical treatment or other concurrent AEs were reported. The participant had no previous events of urticaria or hypersensitivity reactions with the previous vaccinations. The Investigator considered the event related to mRNA-1273-booster.

• A participant experienced mild urticaria 15 days after receiving BD. There was no contributory medical history and no prior or concurrent AEs. The participant was treated with cetirizine as needed for the event. The event was ongoing (recovering/resolving) as of the cut-off date (16 May 2022). The Investigator considered the event related to mRNA-1273-booster.

Cases of Clinical Interest Based on MedDRA Cardiomyopathy SMQs

There were 4 participants in total in the mRNA-1273-Booster group who reported events included within the cardiomyopathy SMQ, both narrow and broad. Three events of dyspnoea (only one considered to be vaccine-related) and 1 event of arrhythmia (not considered to be vaccine-related) were reported. None of the cases are associated with myocarditis or pericarditis.

Arrhythmia

• A participant experienced mild cardiac arrythmia 101 days after receiving the booster dose. The participant had an ongoing medical condition of environmental allergy and asthma at the time of study entry and was being treated with loratadine and Symbicort. A concurrent AE of COVID-19 was reported. The participant received the first dose of 100 µg mRNA-1273 on Study Day 1 and the second dose of 100 µg mRNA-1273 on Study Day 29. The participant received the booster dose of 50 µg mRNA-1273 in the left arm on Study Day 330. The participant experienced a non-serious mild AE of arrhythmia (cardiac arrhythmia) 101 days post-booster dose. Other non-serious AEs reported by the participant included a mild AE of COVID-19 (asymptomatic COVID-19; started prior to the event of arrhythmia). No work-up was conducted and no specific follow-up planned.

The event was ongoing as of the cut-off date (16 May 2022). On the next follow-up visit (Study Day 520), the rhythm was noted by the investigator to be regular, and the AE was considered resolved. The Investigator considered the events not related to mRNA-1273-booster. This can be agreed.

Three events of dyspnoea, all non-serious, occurred in 3 participants, only one was assessed as related to the vaccine, none was associated with myocarditis or pericarditis.

A participant experienced mild dyspnoea starting on the day of the booster dose. Potentially relevant medical history included depression, anxiety, post-traumatic stress disorder and attention deficient and hyperactivity disorder. The site reported that the participant experienced mild shortness of breath on the day of the BD and the day after which resolved without medical intervention or medication. There was no associated chest pain and no other concurrent AEs reported. The event was considered resolved the day following BD. The Investigator considered the event related to mRNA-1273-booster.

A participant experienced mild dyspnoea (shortness of breath) 26 days after receiving the booster dose. A concurrent AE of COVID-19 was reported. According to the Investigator, the event of dyspnoea was associated with a confirmed diagnosis of symptomatic COVID-19. The event was ongoing as of the cut-off date (16 May 2022). The Investigator considered the event not related to mRNA-1273-booster.

A participant experienced mild dyspnoea (shortness of breath) 101 days after receiving the booster dose. Potential contributory medical history included anxiety. No other AEs were reported concurrently, and no further details were available.

The event was ongoing as of the cut-off date (16 May 2022) and was considered resolved shortly after. The Investigator considered the event not related to mRNA-1273-booster, which is supported because of the late onset of 101 days after booster dose.

In summary, the search for unrecognised myocarditis/pericarditis cases did not reveal any case of myocarditis or pericarditis.

Laboratory findings

No laboratory evaluation has been performed in the trial.

Safety in special populations

No special population has been included in the trial.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions and other interactions are not scope of this trial.

Discontinuation due to adverse events

No AE leading to discontinuation from study vaccine or study participation was reported after booster dose.

Post-marketing experience

Approximately 700 million doses of the Spikevax have been administered to individuals in more than 100 countries, with approximately 240 million individuals fully vaccinated (CDC 2022a; Moderna Bimonthly Safety Summary Report 2022). The post-marketing experience is regularly updated.

2.3.3.1. Discussion on clinical safety

Currently, the use of Spikevax for booster vaccinations for the prevention of coronavirus disease 2019 (COVID-19) caused by SARS-CoV2 is authorised for individuals ≥ 12 years of age. The MAH submitted an application to request an amendment of this indication, to expand booster vaccination to individuals aged 6 through 11 years of age, using the modified variant vaccine Spikevax bivalent Original / Omicron BA.1. For this variant vaccine no clinical data in this age group are available. Instead, the MAH submitted clinical safety data from the use of a 25 µg booster dose of mRNA-1273 (original) to support the use of the variant-modified bivalent mRNA-1273.214 (Original + Omicron BA.1) vaccine in children 6-11 years of age. The intention is to extrapolate the reactogenicity and the safety profile of a 25 µg booster dose of mRNA-1273.214 given to children 6 through 11 years of age from a booster

dose of 25 µg of mRNA-1273 given to children of this age group and from the known safety profile of a booster dose of 50 µg of mRNA-1273.214 in the adult population. In addition, the MAH submitted clinical data to underpin the administration of a booster dose for adolescents 12 to 18 years of age that has already been implemented in the SmPC.

A head-to-head comparison of the reactogenicity of a 25 µg booster dose given to children 6-11 years to any dose of a 50 µg primary schedule revealed a lower reactogenicity after the booster dose. Solicited ARs after a booster dose with 25 µg mRNA-1273 were compared to solicited ARs after receipt of any dose of a primary series of 2 doses of 50 µg mRNA-1273 in the same age group. With one exception, the incidence of each specified solicited AR (local and systemic) was notably higher after receipt of any dose of the primary series compared to after the booster dose. In addition to the higher dose that is used in the primary series this observation is likely driven by a notable higher reactogenicity post-dose 2 compared with post-dose 1 of the primary series vaccination.

Overall, the review of the submitted safety data collected in trial P204 after a 25 µg booster dose of mRNA-1273 in children between 6 through 11 years of age did not identify any new safety concerns. There are therefore no proposed changes with regard to the safety concerns specified in the RMP. A head-to-head comparison for the safety and reactogenicity of mRNA-1273 booster dose given to children, adolescents, and adults 18 years of age and older, as well as a comparison of a booster dose of mRNA-1273 to the safety and reactogenicity of a second booster dose of mRNA-1273.214 given to adults 18 years of age and older has been performed. The comparison has methodological limitations. i.e. a variable sample size in the different age and vaccine groups and an adult population which includes adults older than 25 years of age. The reactogenicity comparison however did not reveal any pattern or trend of clinical meaningful difference in reactogenicity in any of the age or vaccine groups. Differences with regard to the safety profile and the prevalence of rare events in the paediatric population after a booster dose can only be detected post-authorisation (as seen e.g. for myocarditis).

2.3.3.2. Conclusions on clinical safety

The review of the submitted safety data collected in trial P204 after a 25 µg booster dose of mRNA-1273 given at least 6 months after the last dose of the primary schedule to children between 6 through 11 years of age did not identify any new safety concerns for the use of mRNA-1273. There are therefore no proposed changes with regard to the safety concerns specified in the RMP. The submitted data moreover indicate that reactogenicity is lower than after any dose of 50 µg given within the 32-dose primary schedule. The reported unsolicited AEs are already covered in the SmPC. Clinical safety data for use of mRNA-1273.214 are not available and the safety profile is intended to be extrapolated from the available safety data from mRNA-1273.214 available from the adult population. A head-to-head-comparison of reactogenicity between the children, adolescent and adults 18 years of age and older and between a booster dose of mRNA-1273 and a second booster dose of mRNA-1273.214 given to adults 18 years of age and older has methodological limitations, but does not suggest any clear trend or pattern of clinical meaningful different reactogenicity across age and vaccine groups. Differences with regard to the safety profile and the prevalence of rare events in the paediatric population after a booster dose can only be detected post-authorisation (as seen e.g. for myocarditis).

The MAH claims an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine. The interval of the mRNA-1273 booster in P204 however is at least 6 months. The CHMP was of the view that a reduction of the interval to 3 months is acceptable based on extrapolation.

2.3.4. 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.

2.4. 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 6.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 6.3 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	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				
None				
Category 3 – Required pharmacovigilance activities				
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) Myocarditis Pericarditis Long-term safety	Interim CSR	15 Oct 2021
			Long-term follow-up Part B & C Interim CSR	31 Dec 2022
			Final CSR	30 Jun 2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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 Spikevax. Assess safety and immunogenicity of mRNA-1273.222	Myocarditis Pericarditis Long-term safety	Interim long-term safety CSR for Part A & B	31 Oct 2022
			Final CSR	15 Jul 2025
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	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
Study mRNA-1273-P205 Phase 2/3 Study to Evaluate the Immunogenicity and Safety of mRNA Vaccine Boosters for SARS-CoV-2 Variants Study status: Ongoing	Evaluate the immunogenicity, safety, and reactogenicity of mRNA vaccine boosters for SARS CoV-2 variants including mRNA-1273.211, Spikevax, mRNA-1273.617.2, mRNA-1273.213, mRNA-1273.529, mRNA-1273.214 (Spikevax bivalent Original/Omicron BA.1), and mRNA-1273.222 (Spikevax bivalent Original/Omicron BA.4-5).	Long-term safety	Study start	28 May 2021
			Interim report:	30 Jun 2022
			Final CSR	31 Dec 2023
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 elasomeran. Immunogenicity: neutralizing and binding antibody titres as surrogate endpoints expected to predict clinical benefit.	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	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	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced	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 Jan 2023

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study status: Ongoing	-Self-controlled risk interval analyses for adverse events that meet specific threshold criteria	respiratory disease (VAERD) Long-term safety AESI and emerging validated safety signals	Final study report	30 Jun 2023
Study mRNA-1273-P904 Post-Authorization Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of the mRNA-1273 Vaccine in the EU Study status: Ongoing*	The overarching research question of this study: Is the occurrence of each adverse event of special interest (AESI) among persons vaccinated with Spikevax in Europe higher than the occurrence of that AESI that would have been expected in the same population in the absence of Spikevax? Primary objective: - To assess whether vaccination with Spikevax (by dose number where feasible and for any dose) is associated with increased rates of the AESI compared with the expected rates overall and stratified by country, sex, and age group. Secondary objective: - To assess whether vaccination with Spikevax is associated with 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	Myocarditis Pericarditis Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) Use in subjects with autoimmune or inflammatory disorders	Protocol submission	30 Jun 2021
			Interim Updates	30 Sep 2021, 31 Mar 2022, 30 Sep 2022 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: Ongoing*	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-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 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	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 Interim updates Final study report	01 Mar 2021 14 Sept 2021; 14 Dec 2021; 14 Mar 2022; 30 Jun 2022; 31 Jul 2022; 14 Dec 2022; 14 Jun 2023; 14 Dec 2023 14 Apr 2025

Study Number, Title, and Categories Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	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 Natural history and clinical outcomes of vaccine associated myocarditis Study status: Planned*	Characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults	Myocarditis	Protocol submission	26 Apr 2022
			Interim report	30 Aug 2022 31 Jan 2023 30 Jun 2023 31Jan 2024 30 Jun 2024 31 Jan 2025
			Final study report	30 Jun 2025
mRNA-1273-P911 Long-term outcomes of myocarditis following administration of SPIKEVAX (COVID-19 vaccine mRNA) Study status: Planned	The overarching goal of this study is to characterize long-term outcomes of myocarditis temporally associated with administration of elasomeran (SPIKEVAX).	Myocarditis	Protocol submission	30 Apr 2022
			Interim report	31 Oct 2022 31 Oct 2023 31 Oct 2024 31 Oct 2025 31 Oct 2026 31 Oct 2027
			Final study report	31 Oct 2028
mRNA-1273-P919 An observational study to assess maternal and infant outcomes following exposure to Spikevax during pregnancy Study status: Planned	To assess whether the rate of pregnancy complications, adverse pregnancy outcomes, or adverse neonatal outcomes is associated with prenatal exposure to Spikevax.	Use in pregnancy	Protocol submission	28 Oct 2022
			Study completion	30 Sep 2023
			Final study report	31 Mar 2024

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myocarditis	Routine risk minimisation measures: SmPC Sections 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects PL Section 2 and 4 Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. (SmPC section 4.4). Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur. (PL Section 2). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow up questionnaire to collect structured clinical details of myocarditis or myopericarditis in individuals who have received Spikevax. Additional pharmacovigilance activities (final CSR due date): Study mRNA-1273-P903 (final CSR: 30 Jun 2023) Study mRNA-1273-P904 (final CSR: 31 Dec 2023) Study mRNA-1273-P204 (final CSR; 31 Mar 2024) Study mRNA-1273-P301 (final CSR: 30 Jun 2023) Study mRNA-1273-P304 (final CSR: 31 Jan 2024) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P910 (final CSR: 28 Feb 2025) Study mRNA-1273-P911 (final CSR: 31 Oct 2028)
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: 30 Jun 2023) Study mRNA-1273-P304 (final CSR: 31 Jan 2024) Study mRNA-1273-P203 (final CSR: 31 Jul 2024)
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):

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		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: 30 Jun 2023)
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-P919 (final CSR: 31 Mar 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: 30 Jun 2023) Study mRNA-1273-P203 (final CSR: 31 Jul 2024) Study mRNA-1273-P205 (final CSR: 31 Dec 2023)
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)

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)

2.5. Update of the Product information

As a consequence of this new indication, sections 2, 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC are updated. The Labelling and the Package Leaflet have been updated accordingly.

2.5.1. 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.

2.6. Therapeutic Context

2.6.1. Available therapies and unmet medical need

While the efficacy of COVID-19 vaccine encoding the ancestral strain is maintained against severe disease the efficacy against COVID-19 of any severity wanes over time. Moreover, SARS-CoV-2 epidemiology changed rapidly over time and new SARS-CoV-2 strains emerged. The Spikevax bivalent variant mRNA vaccine containing the ancestral strain together with the Omicron BA.1 strain has been authorised for individuals 12 years of age and older, subsequently followed by a licensure for Spikevax Original/Omicron BA.4-5 for the same age. Currently Spikevax variant vaccines are not authorised for the paediatric population below 12 years of age. In the adult clinical development program, two doses of 100 µg mRNA-1273 demonstrated 93.2% (95% CI: 91.0%, 94.8%; $p < 0.0001$) efficacy against COVID-19 in more than 30,000 participants over a median observation period of over 5.3 months. Effectiveness against Omicron related COVID-19 declined after time, but could be enhanced after a 50 µg booster dose. Successful immunobridging of booster responses in children 6 through 11 years to those of P301 young adults post-primary series provides confidence that the booster benefit afforded to adults will also be afforded to children.

2.6.2. Main clinical studies

Study mRNA-1273-P203

mRNA-1273 is being studied in adolescents 12 to < 18 years of age in the US in Study mRNA-1273-P203 (hereafter Study P203), a Phase 2/3, randomised, observer-blind, placebo-controlled study that evaluates the safety, reactogenicity, and effectiveness of the mRNA-1273 vaccine in healthy adolescents. The goal of the study was to support an indication for use of mRNA-1273 (100 µg IM, given as 2 doses, 28 days apart) in the 12 to < 18 years of age group. The blinded study started in Nov 2020 and enrolled 3,732 participants.

In May 2021, upon emergency authorisation of a non-study COVID-19 vaccine for use in adolescents, Study P203 transitioned to an open-label phase. This allowed unblinding of study participants and crossover of those participants randomised to placebo to receive the mRNA-1273 primary series. In November 2021, Protocol Amendment 3 was implemented to evaluate administration of a 50 µg mRNA-1273 booster dose to ongoing study participants in Part 1A and Part 1B. A booster dose was administered at least 5 months after completion of the mRNA-1273 primary series in Booster Phase (Part 1C-1).

Study mRNA-1273 P204

Study mRNA-1273 P204 is an ongoing Phase 2/3, 3-part, dose-escalation (open-label), age de-escalation and randomised, observer-blind, placebo-controlled expansion study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in children 6 months to 11 years.

The study population was evaluated in 3 discrete age groups (6 years through 11 years, 2 years to <6 years, and 6 months to <2 years), assessing up to 3 dosage levels (25, 50, and 100 µg) of mRNA-1273 in the primary series. For each of the three age groups, an open-label dose-finding (Part 1) phase preceded a blinded, placebo-controlled (Part 2) phase which evaluated the selected dose of mRNA-1273 in a placebo-controlled fashion. Data regarding the mRNA-1273 primary series for all age groups in P204 has been previously submitted and primary series of 50 µg is currently authorised for use in children from 6 through 11 years. In a subsequent amendment, the protocol was revised to offer the mRNA-1273 primary series to P204 participants randomised to placebo once vaccination against COVID-19 was authorised in the respective age group. Following evidence of enhanced effectiveness of the adult booster dose, study P204 was amended to offer a booster dose of 25 µg mRNA-1273 to all children enrolled in the 6 through 11 years age group, which could be administered starting 6 months post-dose 2 of the primary series.

2.7. Favourable effects

In the absence of a correlate of protection neutralising Ab titers lay the basis for protection against SARS-CoV-2 infection and/or COVID-19 disease.

The MAH is presenting immunogenicity results after a booster dose with mRNA-1273 from studies in adolescent and children (12–17 years of age and 6–11 years of age) as compared to immunogenicity results from young adults 18–25 years of age from study P301 in which efficacy has been demonstrated. Studies P203 and P204 demonstrate that immunogenicity results against the ancestral SARS-CoV-2 D614G after a booster dose with mRNA-1273 in adolescent and children are non-inferior to immunogenicity results after primary vaccination based on GMR values and seroresponse rates.

mRNA-1273 (Spikevax) is approved as a booster dose in adolescent and adults 12 years of age and older. The MAH is now seeking the indication for a booster dose with mRNA-1273.214 (Spikevax bivalent [Original/Omicron BA.1]) in children 6–11 years of age. Spikevax bivalent (Original/Omicron

BA.1) is approved as a booster dose in adolescent and adults 12 years of age and older based on immunobridging of nAB GMTs against SARS-CoV-2 Omicron BA.1 and BA.4-5 as determined in adults 18 years of age and older. Immunogenicity results against SARS-CoV-2 Omicron BA.1 could demonstrate superiority of a booster dose with mRNA-1273.214 as compared to mRNA-1273 based on GMRs in study P205. The MAH is now presenting immunogenicity results after a booster dose with mRNA-1273 in adolescent that support the indication of a booster dose with Spikevax bivalent (Original/Omicron BA.1) as well as immunogenicity results after a booster dose with mRNA-1273 in children 6–11 years of age.

In summary, non-inferiority of a booster dose with mRNA-1273 in adolescent and children could be demonstrated in studies P203 and P204, and superiority of a booster dose with mRNA-1273.214 vs. mRNA-1273 against SARS-CoV-2 Omicron BA.1 has been demonstrated earlier in study P205. Therefore, efficacy can be inferred by immunobridging of immunogenicity results with mRNA-1273 as a booster dose in children 6–11 years of age. Based on previous experience there is reason to assume that a booster dose with mRNA-1273.214 would elicit nABs against SARS-CoV-2 Omicron BA.1 to a level that is superior as compared to a booster dose with mRNA-1273 in children 6–11 years of age, supporting the use of mRNA-1273.214 as a booster dose in children 6–11 years of age. Based on the data submitted, the booster vaccination indication in children 6-11 years of age is also extended to the Spikevax (mRNA-1273) 0.1 mg/mL formulation, while noting that the administration of a 25 µg dose with the Spikevax (mRNA-1273) 0.2 mg/mL formulation is however not feasible.

2.8. Uncertainties and limitations about favourable effects

No clinical results have been provided for the sought indication of a booster dose with mRNA-1273.214 in children 6-11 years of age. No (immune) correlate of protection has been identified to date. A decision on the sought indication needs to be based on immunobridging from young adults 18-25 years of age from study P301 in which efficacy has been demonstrated, in combination with demonstrated superiority of a booster dose of mRNA-1273.214 against BA.1 in adults 18 years of age and older.

No efficacy results are available in children 6-11 years of age after a booster dose with mRNA-1273. Available incidence rates in adolescent 12-17 years of age cannot be interpreted without a comparator group. Therefore, efficacy needs to be inferred by immunobridging.

The impact on transmission is currently unknown.

2.9. Unfavourable effects

After receipt of a 25 µg booster dose of mRNA-1273 at least 6 months after the primary vaccination, 93.2% of children 6 through 11 years of age reported any solicited AR after a 25 µg booster dose of mRNA-1273. Any solicited local AR was reported by 91.1% of participants. Pain was the most reported solicited local AR (90.1% of participants), followed by Axillary (or Groin) Swelling or Tenderness (27.8%) and erythema (10.7%) and swelling/hardness (10.9%). Any systemic solicited AR was reported by 64.3% of participants. The most frequently reported systemic solicited AR was fatigue (48.9%), followed by headache (38.2%) and myalgia (21.0%). Chills, nausea, and arthralgia were reported by comparable proportions of subjects, i.e. by 14.0%, 13.1%, and 12.5%, respectively. Fever was reported by 8.5% of subjects.

Solicited ARs had a median onset within 1 day after vaccination and a median duration of 3 days. Solicited local ARs persisting beyond 7 days after booster dose administration were reported in 1.3% of participants. The most common events were axillary (or groin) swelling or tenderness (0.7%) and pain

(0.5%). Solicited systemic ARs persisting beyond 7 days after booster vaccination were reported in 2.0% of participants. The most common events were fatigue (1.3%) and headache (1.0%).

The incidence of any solicited ARs was higher among participants who were SARS-CoV-2 negative at baseline, i.e. prior to booster dose administration (95.8% of 757 participants) compared with participants who were SARS-CoV-2 positive at baseline (89.5% of 428 participants).

The incidence of unsolicited adverse events up to 28 days after booster dose irrespective of causality was 13.1% (169 of 1294 subjects) and the incidence of unsolicited adverse events considered to be vaccine-related by the investigator was 4.0% (52 out of 1294 subjects). The majority of unsolicited AEs considered to be vaccine-related are expected symptoms associated with the reactogenicity of the vaccine.

Three participants experienced hypersensitivity events that were considered related to study vaccination by the Investigator, including one event of serum sickness-like reaction and 2 events of urticaria.

No SAEs considered to be vaccine-related were reported.

2.10. Uncertainties and limitations about unfavourable effects

Overall, 1,294 participants 6 through 11 years of age received a 25 µg mRNA-1273 booster dose at least 6 months after the primary vaccination course. The cut-off date for the safety assessment of the 25 µg booster dose in children 6-11 years is 23 May 2022; the submission of the dossier happened in October 2022. Long-term safety data for the 25 µg booster dose given to children 6-11 years are not available. Moreover, a follow up safety assessment of 28 days or more is only available for approximately half of the participants enrolled in part 1 and part 2 (717 children taking Part 1 and Part 2 together). The sample size is not suitable to detect uncommon, rare or very rare events. Particularly the risk for MIS-C and myocarditis/pericarditis cannot be estimated and need to be followed within the safety surveillance after licensure. Children in good health and with stable chronic diseases (e.g., asthma, diabetes mellitus, cystic fibrosis, and human immunodeficiency virus [HIV] infection) were allowed to participate in trial P204. Stable diseases were defined as 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. A change in medication for dose optimisation (e.g., insulin dose changes), change within class of medication, or reduction in dose were not considered signs of instability. Safety data are only available for the administration of a 25 µg booster dose of mRNA-1273 the ancestral SARS-CoV-2 vaccine. No safety data are available for the variant-modified bivalent mRNA-1273.214 (Original + Omicron BA.1) vaccine for which the MAH seeks approval. The MAH claims an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine. The interval of the mRNA-1273 booster in P204 however is at least 6 months. The CHMP was of the view that a reduction of the interval to 3 months is acceptable based on extrapolation.

2.11. Effects Table

Table 34: Effects Table for Spikevax in the booster indication

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
NI	GMR mRNA-1273 NI in children 6-11 yoa vs. young adolescent	GMR	6-11yoa	18-25yoa	mRNA-1273 (Original)/ NI of booster vs. primary series met	
NI	SRR difference mRNA-1273 NI in children 6-11 yoa vs. young adolescent	SRR	6-11yoa	18-25yoa	mRNA-1273 (Original)/ NI of booster vs. primary series met	
Unfavourable Effects						
			6-11 yoa after 25 µg booster dose of mRNA-1273	6-11 yoa after any of 2 doses of 50 µg primary vaccination series with mRNA-1273		
	Any systemic solicited AR	N /n (%)	823/1280 (64.3)	2917/3386 (86.1)		
	Any local solicited AR	N /n (%)	1165/1280 (91.1)	3333/3386 (98.4)		

Abbreviations: N: number of subjects included in the analysis; n: number of subjects reporting an AR

2.12. Benefit-risk assessment and discussion

2.12.1. Importance of favourable and unfavourable effects and benefit-risk balance

Even though the course of COVID-19 in children is generally milder than in the older population, there are individuals that suffer considerably from the direct consequences of the infection. It is therefore important to have access to COVID-19 variant vaccines for this population.

No safety data are available for a 25 µg booster dose of mRNA-1273.214 for which the indication extension is sought for. The intention is therefore to extrapolate the safety and reactogenicity of mRNA-1273.214 given to children 6-11 from the safety and reactogenicity of a 25 µg booster dose of mRNA-1273 ancestral vaccine given to children 6-11 years together with the known safety profile of mRNA.1274.214 (Original + Omicron BA.1) in adults. A head-to-head-comparison of reactogenicity between children, adolescent and adults 18 years of age and older has methodological limitations, but does not suggest any clear trend or pattern of clinical meaningful different reactogenicity across age and vaccine groups. Moreover, the submitted safety data do not raise any concern with regard to a booster dose of 25 µg of mRNA-1273 given to children 6-11 years of age. The safety data base is not suitable to allow detection of uncommon, rare or very rare AEs, but could be acceptable taking the experience with the 2-dose primary vaccination into account. The reactogenicity after the booster dose was lower compared to after any dose of the 50 µg primary vaccination. The same was observed for

unsolicited AEs irrespective of causality and vaccine-related ones. The safety profile appears not to be different from what is described after the primary vaccination series in this age group. The risk for rare of very rare events like MIS-C or myocarditis/pericarditis cannot be estimated for this age group and need to be followed up within the safety surveillance after licensure. The MAH claims an interval of at least 3 months between administration of Spikevax bivalent Original/Omicron BA.1 and the last prior dose of a COVID-19 vaccine. The interval of the mRNA-1273 booster in P204 however is at least 6 months. The CHMP was of the view that a reduction of the interval to 3 months is acceptable based on extrapolation.

Based on the data submitted, the booster vaccination indication in children 6-11 years of age is also extended to the Spikevax (mRNA-1273) 0.1 mg/mL formulation, while noting that the administration of a 25 µg dose with the Spikevax (mRNA-1273) 0.2 mg/mL formulation is however not feasible.

2.12.2. Additional considerations on the benefit-risk balance

The benefit-risk balance for the administration of a booster dose of 25 µg mRNA-1273 to children 6-11 years is considered positive. The MAH applies for an extension of indication for Spikevax bivalent Original/Omicron BA.1 based on this data, which is considered acceptable as booster vaccination with the bivalent Original/Omicron BA.1 vaccine (mRNA-1273.214) demonstrated superiority in eliciting nABs against Omicron BA.1 and BA.4-5 regardless of prior SARS-CoV-2 infection as compared to mRNA-1273 (Original) in adults. The booster vaccination indication in children 6-11 years of age is also extended to the Spikevax (mRNA-1273) 0.1 mg/mL formulation, while noting that the administration of a 25 µg dose with the Spikevax (mRNA-1273) 0.2 mg/mL formulation is however not feasible.

It is also noted that the MAH intends to further extend the booster vaccination indication to the Spikevax bivalent Original/Omicron BA.4-5 vaccine (mRNA-1273-222) in a future, separate procedure.

2.13. Conclusions

The overall benefit-risk of Spikevax and of Spikevax bivalent Original/Omicron BA.1 as a booster dose in children 6 through to 11 years of age is considered positive.

3. Recommendations

Outcome

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

Variations 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
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	Type II	I and IIIB

Extension of indication to include a booster dose of Spikevax (25 µg elasomeran) and a booster dose of Spikevax bivalent Original/Omicron BA.1 (12.5 µg elasomeran/12.5 µg davesomeran) in children

aged 6 through 11 years of age, based on interim results from study P204; this is a Phase 2/3, Three-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; As a consequence, sections 2, 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC are updated. The Labelling and the Package Leaflet are updated in accordance. A revised RMP version 6.3 has been approved. In addition, the Marketing authorisation holder MAH took the opportunity to implement editorial changes.
To update sections 4.8 and 5.1 of the SmPC to include additional immunogenicity data for the paediatric population (6 to < 18 years) based on Real-World Safety studies.

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

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, IIIA 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/0256/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

4. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. 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-83-G’

5. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 15 December 2022